

# CLEVELAND CLINIC JOURNAL OF MEDICINE

**Celiac disease in the 'nonclassic' patient**

**Eruption of erythema after dieting**

**Finger nodules:  
The tip of the gouty iceberg**

**Acute pancreatitis: When to repeat serum lipase testing after the initial workup**

**Urine antigen testing for *Legionella pneumophila* in hospital patients with community-acquired pneumonia**

**Celiac disease: Who should be tested, and how?**

**Trigeminal neuralgia: The need for multidisciplinary management**

**Deadly drug rashes: Prompt recognition and action**

**Measuring exhaled nitric oxide in asthma diagnosis and management**



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## Celiac disease in the ‘nonclassic’ patient

Celiac disease (CD) is an immune disorder that is dependent upon the presence of ingested gluten to drive the disruption of mucosal integrity, resulting in manifestations of malabsorption. The expression of the disorder differs somewhat in childhood (greater degree of classic malabsorption) than in adulthood, where the attributed manifestations are far more heterogeneous, and some are controversial as to their direct relationship with the underlying pathophysiology. The classic characteristics of the disorder respond completely over time to prolonged complete abstinence from ingested gluten, although a true minority (< 2%) have “refractory” celiac disease, for which there is a clinically important differential diagnosis.<sup>1</sup> The dramatic efficacy of gluten avoidance in treating classic (autoimmune) gastrointestinal CD, coupled with increasing community awareness of the gut microbiome as a potential contributor to the pathophysiology of multiple disorders, has led to a cultlike acceptance of gluten avoidance as a potential panacea for all things autoimmune.

Patients who test convincingly positive for CD (although as noted by Nasser et al<sup>2</sup> in this issue of the *Journal*, there is no true gold standard for diagnosis) can expect relief of malabsorptive symptoms and normalization of their anti-tissue transglutaminase antibody test and duodenal histology if they maintain a strict gluten-free diet (GFD). Some extraintestinal manifestations of CD such as otherwise unexplained iron deficiency should also resolve, as iron deficiency may be a direct effect of the disrupted intestinal mucosa. Interestingly, CD has been offered as an explanation for nearly 4% of cryptogenic increases in level of aspartate aminotransferase or alanine aminotransferase, or both.<sup>3</sup> In 1 of several studies, after a thorough unrevealing evaluation for etiology, the unexplained aminotransferase elevation normalized in 4 out of 5 patients within 6 months of adherence to a GFD.<sup>4</sup>

As Nasser et al note, perhaps 1% of the general population may have CD, with most being untested and undiagnosed at least in part due to the absence of “classic” symptoms. They endorse consideration of testing of patients with several “nonclassical signs and symptoms of CD,” although they also note that “symptomatic improvement on a gluten-free diet has a diagnostic precision as low as 30%.”<sup>2</sup> I understand their perspective, and if a seemingly benign treatment option supported by the presence of positive laboratory test results provides an explanation and a therapeutic option for confusing and chronic symptoms, is there a downside? Many patients are trying some version of a GFD on their own initiative anyway, although meticulous adherence is likely rare.

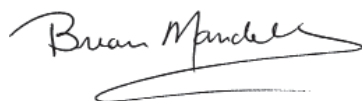
In my general rheumatology clinic, in patients with unexplained malaise, fatigue, and polyarthralgia, the only gastrointestinal issue as common as irritable bowel syndrome is concern for possible gluten sensitivity. If it were easy to accomplish, a trial of a GFD could be offered to all these patients, with or without minimal or full testing for CD. Some clinicians in my institution are seemingly taking this approach. But there are costs associated with both the testing and the treatment, in addition to the obvious financial costs of laboratory testing to the patient and to the health system at large.

On the other hand, adherence to a strict GFD is not easy and can be disruptive to families who share the kitchen and dinner table with patients following this diet. The diet can be uncomfortably constipating and should be guided by someone knowledgeable in nutrition. And since as

noted above even strict adherence does not guarantee relief of all symptoms, particularly those from associated conditions, there is the potential for additional anxiety from patient self-blame over treatment failure. Thus, the clinician should be as certain as possible that trying a GFD actually makes sense—and there, I believe, lies the real challenge. Despite significant advances in our understanding of CD, I am not yet convinced that there is a strong enough link between the nonclassical potential symptoms I hear from my patients (those in the “high clinical suspicion” box in the algorithm of Nasser et al<sup>2</sup>) to fully endorse adhering to an evidence-based testing algorithm for CD.

This challenge could be addressed in a pragmatically designed prospective trial placing all patients on a GFD, then blindly introducing gluten- or control-containing capsules, perhaps in a crossover design, to evaluate for a placebo effect of the GFD. Inclusion of masked testing for CD would permit delayed analysis of clinical responses stratified by test-positivity. There have been some preliminary efforts looking at dietary interventions, including GFD, in patients with fibromyalgia. But there is no answer yet,<sup>5</sup> and these are tough studies to conduct.

In the meantime, and with our patients’ assistance, many of us are informally utilizing N-of-1 empiric approaches in the clinic. Hopefully, the rigorous testing approach described by Nasser et al will at some point be more directly evaluated in our patients with nonclassic and associated symptoms, and be as useful as in patients with classic CD.



Brian F. Mandell, MD, PhD  
Editor in Chief

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## Chondrodermatitis nodularis helicis

**To the Editor:** In the May issue, Maggie So and Randall Edson<sup>1</sup> reported on an older man with a central crust over an ulcerated nodule on the left ear, diagnosed as chondrodermatitis nodularis helicis (CNH) based on the clinical findings. We have two suggestions for the diagnosis and management of CNH.

First, auricular granuloma annulare (AGA) should be considered in the differential diagnosis because it has a clinical presentation and location similar to CNH. AGA commonly presents as multiple, asymptomatic, unbroken nodules on unilateral or bilateral ears, although occasionally a solitary crusted nodule with mild tenderness may be present.<sup>2</sup> The main difference is that the pathological features of AGA show dermal collagen degeneration, mucin deposition, and either a palisaded or interstitial histiocytic infiltrate. Typical pathological findings include a nodule of degenerated homogeneous collagen surrounded by vascular granulation tissue with an overlying acanthotic epidermis, a central ulcer, inflammation and fibrosis of the underlying perichondrium, and degenerative cartilage.

Another concern is that some patients with CNH may have other associated chronic inflammatory and autoimmune diseases, such as polymyalgia rheumati-

ca, psoriasis, rheumatoid arthritis, CREST syndrome, vitiligo, and chronic dermatitis.<sup>3</sup> Therefore, careful history-taking, physical examination, and some targeted laboratory tests are still necessary for the patient with CNH.

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doi:10.3949/ccjm.90c.06001

**In Reply:** We thank Dr. Zhang and colleagues for their interest in our article and for their excellent queries. Although granuloma annulare can involve the external ear, it typically occurs on the antihelix, as noted in the excellent article published by Zhang et al.<sup>1</sup> The favorable response of relieving pressure to the external ear by sleeping on the unaffected side was more consistent with CNH. The patient described in our article had no evidence for any of the systemic inflammatory conditions mentioned by Dr. Zhang and colleagues.

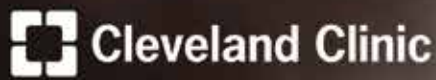
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# Eruption of erythema after dieting



**Figure 1.** Reticulate erythema with hyperpigmentation on the chest and neck, as well as on the back.

**A** 28-YEAR-OLD MAN PRESENTED to the dermatology clinic with a 1-week history of edematous erythema on his chest and neck. He complained of mild itching. He had received treatment with oral levocetirizine and topical 0.05% halometasone cream for 5 days, but the rash did not improve and actually worsened. He said that over the past 4 weeks he had been increasing his exercise and was on a strict diet for bodybuilding.

He had no significant past medical history and no history of drug or food allergies. Physical examination showed reticulate erythema with hyperpigmentation on the chest and neck (**Figure 1**), as well as the back. Laboratory testing revealed a high urinary ketone level of 2+ (reference range negative). The complete

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blood cell count, hepatic and renal function, fasting plasma glucose, glycosylated hemoglobin, blood lipid, and fungal microscopy examination were normal. We diagnosed prurigo pigmentosa based on the clinical presentation and results of laboratory testing.

### ■ PRURIGO PIGMENTOSA

Prurigo pigmentosa is an inflammatory dermatosis that usually occurs in young Asians and has a pronounced female predominance.<sup>1</sup> It is characterized by pruritic erythematous papules with a reticulate pattern on the back, chest, and neck, leaving behind hyperpigmentation after several days to weeks from the time of onset. The hyperpigmentation usually persists for several months.

Ketone bodies may play a key role in the pathogenesis. The proketogenic state results in an accumulation of ketone bodies around blood vessels that can further lead to dermal perivascular inflammation and contribute to the development of the condition.<sup>1,2</sup>

The most common risk factor is a change in diet including low-carbohydrate and ketogenic diets and anorexia nervosa.<sup>1</sup> Other potential triggers include friction from clothing,<sup>3</sup> sweat, ketonuria, hormonal changes, emotional stress, nutritional deficiency, atopic dermatitis, diabetes mellitus, adult-onset Still disease, acupuncture, pregnancy, and *Helicobacter pylori* infection.<sup>1,2</sup> As the ketogenic diet and dieting become increasingly popular, cases of prurigo pigmentosa seem to be on the rise<sup>4</sup> and may be underdiagnosed due to poor recognition.

### Differential diagnosis

The diagnosis of prurigo pigmentosa is primarily clinical. Biopsy is performed when the clinical presentation is atypical or the diagnosis is in doubt.

The differential diagnosis includes confluent and reticulated papillomatosis, seborrheic dermatitis, contact dermatitis, eczema, dermatitis herpetiformis, psoriasis vulgaris, systemic lupus erythematosus, urticaria,

and erythema multiforme. Confluent and reticulated papillomatosis is generally considered to only present reticulated hyperpigmentation without obvious inflammation and pruritus. However, it has been described along with pruritic inflammatory rash, and there is an opinion that confluent and reticulated papillomatosis and prurigo pigmentosa are different manifestations of the same disease spectrum because they have similar clinical and histologic findings and respond to similar therapies.<sup>5</sup>

### Therapy

Commonly, antihistamines and topical corticosteroids are ineffective for prurigo pigmentosa. The first-line treatment includes antibiotics such as minocycline, doxycycline, and dapsone.<sup>1</sup> Resuming a balanced diet can be useful to patients with ketosis or nutritional deficiencies.<sup>1</sup> A minority of patients experience a recurrence. Our patient was advised to resume a normal diet and was treated with oral doxycycline and topical tacrolimus for 2 weeks. The rash gradually resolved, leaving reticular hyperpigmentation. ■

### DISCLOSURES

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

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## THE CLINICAL PICTURE

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# Finger nodules: Tip of the gouty iceberg

**G**OUT IS CLINICALLY DEFINED by recurrent, dramatic, self-limited flares of inflammatory arthritis, bursitis, or tendonitis. Flares are the cardinal symptom of the gouty disease process, the deposition of uric acid in the soft tissues with a predilection to periarticular structures. The location of initial flares and uric acid deposits (tophi) is frequently in the extremities. This is attributed to the cooler temperatures in the hands and feet facilitating the deposition of uric acid in patients who have biologic hyperuricemia, defined as a serum urate level above its approximate saturation level of 6.8 mg/dL. However, some patients exhibit tophi detected on physical examination or deeper tophi detected by advanced imaging such as ultrasonography or dual-energy computed tomography in the absence of typical clinical flares or pain.

Uric acid deposition can be seen using dual-energy computed tomography or ultrasonography before the occurrence of flares. Deep-tissue periarticular and intra-articular tophi are usually clinically unrecognized until they are associated with a painful flare. Tophi in more superficial areas such as the ears, olecranon bursae, and skin may be noticed as asymptomatic nodules, often in patients who have experienced flares elsewhere. Some patients exhibit marked nodulosis due to undiagnosed tophi in the absence of typical gouty flares and thus may be undiagnosed as having gout and not treated. Two such patients are described below.

### ■ PATIENT 1

A 46-year-old male was referred to rheumatology for evaluation of hand stiffness. He had no history of acute painful flares. He had chronic kidney disease of unclear etiology, with a serum creatinine level 2.4 mg/dL (reference range 0.74–1.35) and a

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**Figure 1.** Tophi overlying the proximal interphalangeal and distal interphalangeal finger joints in a 46-year-old male patient.

serum urate 8.6 mg/dL (4.0–8.5). He had been told of osteoarthritis and possible gout but had never sought treatment.

The patient had tophi overlying the proximal interphalangeal (PIP) and distal interphalangeal (DIP) finger joints (**Figure 1**). While this presentation is often seen in postmenopausal women with osteoarthritic Heberden and Bouchard nodes and with tophi that may become acutely inflamed,<sup>1</sup> tophaceous deposition around the DIP and PIP joints is not limited to that demographic group and may be mischaracterized as inflammatory osteoarthritis.

On full examination, the patient also had a nodule on the helix of his left ear and small nodules palpable in the olecranon area bilaterally. The physical appearance, firm feel on palpation, and location of these asymptomatic nodules in conjunction with the





**Figure 2.** (A) Dermal and soft-tissue tophaceous nodules in the hands of a 70-year-old male patient. (B) After 6 months of aggressive urate-lowering therapy, there was dramatic resolution of his hand nodules.

significant hyperuricemia and chronic kidney disease supported the clinical diagnosis of gout. He did not have significant hyperlipidemia.

### Treatment

Due to the periarticular location of the significant tophaceous deposits, with resultant hand stiffness and difficulty in fully flexing the fingers, the suggested treatment regimen was aggressive urate-lowering therapy aiming for a very low serum urate level ( $< 3$  mg/dL), which would be expected to accomplish relatively rapid dissolution of the deposits. Depending on the patient's response to medication, this serum urate level might be attained using a dose-adjusted xanthine oxidase inhibitor with or without probenecid or pegloticase, followed by a xanthine oxidase inhibitor once significant tophi were dissolved and hand function normalized.

The patient was cautioned that rapid and intense lowering of the serum urate was likely to precipitate gout flares until the uric acid deposits had dissolved, and he was advised to have a plan in place to prevent flares and treat them if they should occur. As the

patient lived very far from the clinic, treatment was anticipated to be provided closer to his home.

### ■ PATIENT 2

A 70-year-old male presented with dermal and soft-tissue nodules in the hands (**Figure 2A**),<sup>2</sup> with no history of gout flares. He had been diagnosed with gout and previously had documented serum urate levels between 7.2 and 8 mg/dL, with a normal serum creatinine.

Experiencing minimal symptoms, he had never received urate-lowering therapy. He was otherwise healthy without any kidney, vascular, or metabolic disease. He described increasing hand stiffness causing difficulties in his avocational use of power tools and in driving industrial machinery. Interestingly, a large, hard mass adjacent to his right lateral malleolus led to him frequently being stopped and examined as he went through airport security screening procedures.

### Treatment

He was prescribed aggressive urate-lowering therapy utilizing uricase-replacement therapy with pegloticase,

and with serial testing of serum urate levels. After 6 months of therapy, with serum urate levels maintained below 0.2 mg/dL, there was dramatic resolution of his hand nodules (**Figure 2B**). After an additional 6 months of treatment, the malleolar tophus also regressed, allowing the patient to travel unimpeded through airport security screening. Pegloticase therapy was followed by treatment with allopurinol to maintain a serum urate of approximately 5.5 mg/dL.

## ■ NARROWING THE DIFFERENTIAL DIAGNOSIS

Chronic subcutaneous nodules can be found associated with a number of disorders, including rheumatoid arthritis, dyslipidemia, sarcoidosis, multicentric histiocytosis (periungual nodules), lipoma, systemic lupus erythematosus, dermatofibroma, calcinosis, metastatic carcinoma, and leukemia or lymphoma. However, only gouty tophi are likely to present in the anatomic locations with the appearance shown in these scenarios—especially in the absence of other systemic or laboratory features associated with an alternative underlying disorder.

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As shown in **Figure 1**, when the skin is pulled taut, there is a pearlescent yellow-white appearance to these firm, nontender nodules. If there is clinical uncertainty, or if the response to urate-lowering therapy is not as anticipated, needle aspiration of a nodule will reveal the presence of chalky material composed of monosodium urate crystals when viewed under polarized microscopy. Aspiration can be done with a 20- or 18-gauge needle by penetrating the nodule and twisting the needle, then wiping the bevel of the needle on a clean slide. Tophi, particularly if traumatized or repeatedly stretched due to location over a joint, may spontaneously perforate, drain uric acid crystal-containing material, and in rare cases, become infected. ■

## ■ EDITOR'S NOTE

Figure 2 was borrowed from reference 2, an editorial on the educational value of The Clinical Picture department in the *Cleveland Clinic Journal of Medicine*, published in February 2021.

## ■ DISCLOSURES

Dr. Mandell has disclosed consulting for Horizon Pharma.

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## Q: Serial serum lipase testing after the initial diagnostic workup for inpatients with acute pancreatitis: What is the evidence?

A 35-year-old male with no significant medical history presented to the hospital with acute epigastric pain radiating to his back. Workup revealed a serum lipase of 518 U/L (reference range 0–160 U/L), and computed tomography of the abdomen showed peripancreatic fat-stranding. He does not drink alcohol or take any medications, and the workup was negative for gallstones and hypertriglyceridemia. He was diagnosed with acute idiopathic pancreatitis and admitted to the hospital for management. He received early enteral feeding, intravenous fluid resuscitation, and opioid analgesia for pain control. His pain gradually improved and he was tolerating oral intake. A repeat serum lipase level on hospital day 3 was elevated at 609 U/L. Does this repeat serum lipase value have a role in guiding further clinical decisions?

**A:** Lipase testing should be ordered for the initial diagnostic workup of patients presenting with concern for acute pancreatitis. Once a diagnosis of acute pancreatitis is established, routine serial lipase testing is recommended against. Subsequent serum lipase testing should be reserved only for rare instances where there is concern for pancreatic duct blockage, pseudocyst formation, or lack of clinical improvement after 1 week, and should be performed in conjunction with repeat cross-sectional imaging.

Thus, for the 35-year-old male in the clinical vignette above, repeat lipase testing is not recommended, and clinically guided management should be utilized.

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### DEFINING THE PROBLEM

Acute pancreatitis occurs when the pancreas becomes suddenly inflamed, most commonly related to alcohol use and gallstones, but with a broad differential diagnosis. The condition leads to severe pain and extravasation of pancreatic enzymes, contributing to complications requiring thoughtful management. Acute pancreatitis affects 17 people per 100,000 in the United States annually and is among the most frequent indications for inpatient admission secondary to a gastrointestinal diagnosis.<sup>1,2</sup> There are roughly 280,000 patient admissions for acute pancreatitis annually, with a median cost of \$6,240 per patient per admission, totaling \$2.6 billion per year.<sup>3</sup>

### KEYS TO EVALUATION

Although upper abdominal pain is the main component of acute pancreatitis, confirmation by objective data is warranted to ensure an accurate diagnosis. Most commonly, the diagnosis is supported by a single measurement of a 3-fold elevation in serum pancreatic enzymes (amylase or lipase, or both) in the setting of characteristic epigastric pain. In the presence of abdominal pain and normal serum pancreatic enzymes or of elevated enzymes in the absence of abdominal pain, imaging is necessary for diagnosis.

The diagnosis of acute pancreatitis is based on the presence of 2 of the following 3 features according to the Atlanta classification: abdominal pain consistent with acute pancreatitis, serum lipase activity (or amylase activity) at least 3 times greater than the upper

limit of normal, and characteristic findings of acute pancreatitis on contrast-enhanced computed tomography, magnetic resonance imaging, or transabdominal ultrasonography.<sup>4</sup>

The lipase level increases within 4 to 8 hours after the onset of acute pancreatitis, peaks at 24 hours, and normalizes within 8 to 14 days, with the range encompassing the breadth of etiologies.<sup>5</sup> After the diagnosis is confirmed, serial lipase measurement has little value in gauging clinical progress or prognosis according to Choosing Wisely,<sup>6</sup> the American College of Gastroenterology,<sup>7</sup> and the American Gastroenterology Association.<sup>8</sup> The evidence for utilizing lipase as a prognostic marker is weak, and far stronger risk-stratification tools exist.<sup>7-9</sup>

### ■ SYMPTOMS AND CLINICAL CRITERIA SHOULD GUIDE MANAGEMENT

Symptom-guided and clinical criteria-guided management are the standard of care in acute pancreatitis to facilitate clinical decisions. The use of lipase, a diagnostic test, should not supersede clinical judgment. If there is concern that a patient is not clinically improving, reference to admission risk-stratification scores is recommended, along with consideration of cross-sectional imaging to provide more objective data.<sup>7,8</sup>

The most notable severity index scores—the Acute Physiology and Chronic Health Evaluation II,<sup>10</sup> the BISAP score,<sup>11</sup> and the Ranson criteria<sup>12</sup>—utilize laboratory and clinical data to appropriately predict morbidity at the time of admission. Importantly, none of these scores utilize serum lipase. Despite this knowledge, repeat lipase testing (RLT) is regularly inappropriately performed to guide clinical decisions such as initiation of enteral nutrition and appropriateness of patient discharge.<sup>13,14</sup>

### ■ MONETARY AND NON-MONETARY COSTS OF REPEAT LIPASE TESTING

In a retrospective review by Datta et al,<sup>13</sup> lipase testing was repeated in 203 adult inpatients an average of 2.88 times. In 81.2% of patients, the lipase decreased to below 3 times the upper limit of normal, and 63.6% of these patients had repeat testing despite the downward trend. Importantly, there was no difference in mortality in patients who underwent RLT vs those who did not (1.8% in RLT group vs 0.0% in non-RLT group,  $P = .450$ ), and there was no statistically significant difference in the severity of acute pancreatitis based on age, blood urea nitrogen, and

Systemic Inflammatory Response Syndrome criteria, all of which were surrogate markers of severity.<sup>13</sup>

A study by Ritter et al<sup>14</sup> showed that during an average inpatient stay of 3 days the mean number of lipase tests ordered per patient was  $2.4 \pm \text{SD } 2.5$  tests (range 1–25), and there was likewise no difference in disease severity in patients who had repeat testing and those who did not. This highlights that serum lipase was repeated in these patients not solely because they had severe disease, and thus, associated changes in costs cannot be attributed to disease severity. For example, if patients who had repeat serum lipase had more severe disease, then costs could be driven up by use of intensive care unit services. The same severity index for both groups of patients (ie, those who had repeat lipase testing and those who did not) thus reduces a degree of confounding in the cost analysis. While the actual cost of each lipase test was determined to be \$0.88 by bottom-up cost estimation, which approximates costs at the lowest level, the additional attributable cost per test, which reflects the non-value-added cost of an item, was \$3.41, bringing the total cost of each test to \$4.29.<sup>14</sup> Putting together these data, at an approximate total cost of \$4.29 attributed to each lipase test ordered, an excess of 1.4 to 1.88 additional lipase tests performed per patient, and 280,000 annual admissions for acute pancreatitis,<sup>3</sup> we estimate that a total range of \$1,681,680 to \$2,258,256 is spent annually as direct costs for RLT in the United States.

Several studies have also shown an association of RLT with increased length of stay and additional cost of admission, even with some statistical adjustment for pancreatitis severity.<sup>1,13</sup> These studies are limited due to their retrospective nature and may neglect to adjust for variables that may confound the relationship between RLT and reported outcomes. Nonetheless, RLT may add both direct and indirect costs and risks to hospital stays.

### ■ RISKS ASSOCIATED WITH REPEAT LIPASE TESTING

Although RLT has no diagnostic value, in certain situations when symptoms do not resolve by 1 week or if there is worsening abdominal pain beyond 1 week, RLT may help diagnose complications such as blockage of the pancreatic duct, acute peripancreatic collections, or development of a pseudocyst or necrosis. While all of these complications could cause elevations in lipase, cross-sectional imaging has a higher sensitivity than serum lipase levels for diagnosing locoregional complications of acute pancreatitis.<sup>15</sup>

Serum lipase testing should not be performed in the absence of clinical concern for complications, and if symptoms are concerning for such sequelae, imaging should be performed regardless of the serum lipase result.

Serial testing without regard to clinical status can lead to biased interpretation and unnecessary or even harmful downstream interventions. For example, when a patient who is otherwise clinically improving and has a lipase that is abnormal or at a higher level than at admission, this can create a situation where the clinicians caring for the patient incorrectly conclude that the patient is not improving, and such a conclusion can potentially prompt additional investigation.

Conversely, a patient with a normal lipase level or a level lower than at admission on serial testing who is clinically not showing signs of improvement is at risk for the incorrect conclusion that pancreatitis is getting better, and these interpretations may delay additional workup that the patient may actually need.

Overall, overutilization of RLT to monitor the disease course is common in nonselected groups of patients admitted with acute pancreatitis. It poses monetary and nonmonetary costs to the health system,<sup>14</sup> affords no mortality benefit, does not aid in prognostication, leads to unnecessary increased length of stay for patients in many cases, can potentially lead

to inaccurate interpretation of clinical status, and can potentially delay care in patients who otherwise show signs of unresolving pancreatitis.

## ■ TAKE-HOME MESSAGES

The evidence to support serum lipase testing beyond the initial diagnostic workup in patients presenting with suspicion of acute pancreatitis is weak, and the results of serial testing may be misleading and lead to adverse effects on patient care and increases in healthcare spending. Lipase testing should be ordered in the initial diagnostic workup, but serial or follow-up testing should be reserved for the rare instances where there is concern for pancreatic duct blockage, pseudocyst formation, or lack of clinical improvement after 1 week, and should be done in conjunction with repeat cross-sectional imaging, which is of higher diagnostic yield.

Routine serial testing of serum lipase in patients who are admitted to the hospital with acute pancreatitis contributes to increased monetary and nonmonetary costs to the health system and should be avoided. ■

## ■ DISCLOSURES

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

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# Q: Should urine antigen testing for *Legionella pneumophila* be ordered for all hospitalized patients with community-acquired pneumonia?

**A:** Urine antigen testing for *Legionella pneumophila* should not be ordered for all hospitalized patients admitted for community-acquired pneumonia (CAP), as a positive urine antigen test would not change guideline-recommended treatment of CAP. Empiric antibiotic treatment of CAP already ensures efficacy against *Legionella* infection.

There is no statistical difference in rates of death, clinical relapse, intensive care unit admission, length of hospital stay, or length of antibiotic therapy with pathogen-specific treatment vs empiric guideline-directed treatment of CAP.<sup>1</sup> Furthermore, there is a cost burden of urine antigen testing.

However, testing should be performed for severe cases of CAP, during legionnaires disease outbreaks, and in patients with a history of recent travel in an effort to optimize treatment or determine the source of an outbreak and have a positive environmental impact.

## ■ CLINICAL CHARACTERISTICS OF *LEGIONELLA* PNEUMONIA

CAP commonly presents with fever, cough (productive or nonproductive), and shortness of breath. Other common symptoms include but are not limited to fatigue, loss of appetite, pleuritic chest pain, and myalgias. CAP caused by *L pneumophila* can present with none, some, or all of these symptoms. *Legionella* pneumonia is commonly associated with altered level of mentation (11%–25% of cases), diarrhea (19%), and early-onset pleuritic chest pain (21%–24%).<sup>2</sup>

These findings may help distinguish *Legionella* CAP from CAP from other etiologic agents. Hyponatremia, hypophosphatemia, elevated transaminase levels, and highly elevated C-reactive protein and ferritin levels are nonspecific laboratory abnormalities that increase the diagnostic specificity for *Legionella* pneumonia in the right clinical context.<sup>3</sup> Interestingly, combining clinical symptoms and laboratory abnormalities also increases the diagnostic specificity for *Legionella* pneumonia.<sup>4</sup>

## ■ SEVERE COMMUNITY-ACQUIRED PNEUMONIA

Severe CAP is defined as CAP with 1 major criterion (septic shock with need for vasopressor support, or respiratory failure requiring mechanical ventilation) or 3 or more minor criteria. Minor criteria include respiratory rate greater than 30 breaths per minute, hypoxemia (ratio of partial pressure of oxygen to fraction of inspired oxygen  $\leq 250$ ), multilobular infiltrates, confusion, uremia (blood urea nitrogen  $> 20$  mg/dL), leukopenia, thrombocytopenia, hypothermia, and hypotension requiring aggressive fluid resuscitation.<sup>5</sup>

The mortality rate in patients with *Legionella* pneumonia who are admitted to an intensive care unit is between 9.1% and 41.7%.<sup>6–8</sup> Furthermore, there are certain patient populations (those with immunosuppression, chronic lung disease, history of smoking, or age over 50) that are more susceptible to severe CAP from *Legionella*.<sup>4</sup> For example, *Legionella* pneumonia patients with cancer can have a case-fatality rate as high as 31%.<sup>9</sup> Additionally, these patients at increased risk may experience relapse of *Legionella* pneumonia

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**TABLE 1**  
**Advantages and disadvantages of tests for *Legionella pneumophila***

Test	Sensitivity	Specificity	Advantages	Disadvantages
Culture	10%–80%	100%	Detects all serogroups	Results take several days, difficult technique
Urine antigen	70%–80%	> 99%	Results in less than 1 hour	Detects only <i>Legionella pneumophila</i> serogroup 1
Polymerase chain reaction	95%–99%	> 99%	Results in hours, detects all serogroups	Availability may be limited in some areas
Direct fluorescent antibody stain	25%–75%	> 95%	Results in hours, detects all serogroups	Difficult technique
Serology	80%–90%	> 99%	Detects all serogroups	Must test acute-phase and convalescent-phase sera, results take several weeks

Adapted from reference 13.

if it is not appropriately treated.<sup>10</sup> Thus, all patients with severe CAP and all patients considered more susceptible should undergo urine antigen testing for *L pneumophila*.

**TREATMENT CONSIDERATIONS**

The recommended empiric treatment for hospital inpatients with nonsevere CAP is combination therapy with a beta-lactam plus a macrolide antibiotic or monotherapy with a respiratory fluoroquinolone, either of which treats *Legionella* infection. A prospective, randomized study comparing targeted therapy based on results of urine antigen testing for *L pneumophila* vs empiric guideline-based treatment showed no statistically significant differences in outcomes of death, clinical relapse, intensive care unit admission, hospital length of stay, or length of antibiotic treatment.<sup>1</sup>

**EPIDEMIOLOGIC FACTORS**

Legionnaires disease is a water-borne illness, and a majority of community outbreaks arise from water sources contaminated with *Legionella*. Travel within 2 weeks of the initial presentation and possible or confirmed *Legionella* pneumonia outbreaks should prompt urine antigen testing. It is difficult to assess the number of cases of travel-related *Legionella* pneumonia owing to the dispersal of cases away from the environmental source of infection. Thus, it is imperative to inquire about recent travel when evaluating a patient. If the history is positive for any type of travel within 2 weeks of initial presentation, urine antigen testing for *L pneumophila* should be ordered.<sup>11</sup>

There should be a strong clinical suspicion for

a community or nosocomial outbreak of *Legionella* infection if there are 2 or more confirmed cases of *Legionella* pneumonia.<sup>12</sup> This may lead to increased urine antigen testing and to subsequent increased recognition and control of the source of the outbreak to prevent further cases.

**GAPS IN URINE ANTIGEN TESTING**

Methods to test for *Legionella* pneumonia include the urine antigen test, culture, and polymerase chain reaction (PCR) (Table 1).<sup>13</sup>

The benefits of urine antigen testing are its short time to results (less than 1 hour) and its high specificity (greater than 99%).<sup>14</sup> The test detects *L pneumophila* in the urine as early as 1 day after symptom onset but can remain positive for weeks.<sup>14</sup> However, the drawback of the urine antigen test is that it only tests for *L pneumophila* serogroup 1, the most common serotype in the United States, whereas culture and PCR detect all species and serogroups. The sensitivity of urine antigen testing is 70% to 80% and for culture it is 10% to 80%.<sup>15</sup> Culture carries a 100% specificity, while PCR carries a specificity greater than 99%.<sup>15</sup> The drawback of culture and PCR is the time to result, which is approximately 3 days for culture, and several hours for PCR. The sensitivity of PCR exceeds that of culture.<sup>15</sup> There are inherent limitations of each test. Thus, when testing for *Legionella* species, more than 1 method should be used.

**TAKE-HOME MESSAGES**

Urine antigen testing for *L pneumophila* should not be done for every patient hospitalized for CAP. If the

**TABLE 2**  
**Indications for *Legionella* testing**

Atypical symptoms including but not limited to altered mentation, pleuritic chest pain, and diarrhea
Admission to intensive care unit
High-risk patient features including immunosuppression, chronic lung disease, history of smoking, and age older than 50
Hypoxemia and increasing oxygen requirements
Recent travel (ie, within 2 weeks of initial presentation)
Concern for community or nosocomial pneumonia outbreak

appropriate empiric antibiotics are started, a positive urine antigen test will not change treatment strategies for patients with nonsevere CAP.

*Legionella* pneumonia may present with atypical symptoms such as altered mentation, pleuritic chest pain, and diarrhea, all of which point to severe CAP. More than 1 test (ie, urine antigen test, PCR) should be used for severe CAP.

Physicians must practice good clinical judgment when deciding whom and how to test for *Legionella* pneumonia (Table 2). Urine antigen testing for *L pneumophila*—when appropriately indicated as dis-

cussed here—can result in prompt and timely diagnosis of *Legionella* pneumonia, targeted antimicrobial therapy, and a potentially shorter duration of therapy compared with empiric therapy without a positive test. When appropriately used, urine antigen testing can lead to early recognition of a community outbreak and thus help to prevent spread of the 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.

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Guidelines

**BRIEF  
ANSWERS  
TO SPECIFIC  
CLINICAL  
QUESTIONS**

## Q: Celiac disease: Who should I test, and how?

**A:** Patients with chronic diarrhea or malabsorption (evidenced by weight loss, failure to thrive, or steatorrhea) should be tested for celiac disease (CD). To increase detection, testing is also recommended for patients with other symptoms or conditions that occur with CD, including bloating, constipation, abdominal pain, iron-deficiency anemia, elevated transaminase levels, neuropathy, ataxia, and infertility. Testing is also advisable for patients at increased risk of developing CD, including first-degree relatives of patients with CD, patients with dermatitis herpetiformis, and those who have autoimmune conditions such as type 1 diabetes mellitus and autoimmune thyroid disease.

The screening test of choice is tissue transglutaminase (TTG) immunoglobulin A (IgA) along with total IgA. Duodenal biopsy is indicated to confirm the diagnosis in patients with positive serology or high clinical suspicion.

### ■ WHAT IS CELIAC DISEASE?

CD is a chronic immune-mediated systemic disorder triggered in genetically susceptible people by the ingestion of gluten, a water-insoluble protein that is a constituent of wheat, rye, and barley. CD is characterized by inflammatory injury to the small bowel with gastrointestinal or systemic manifestations, or both. It can also exist with minimal or even no symptoms. Approximately 1% of the general population is affected<sup>1</sup>; most of those affected remain undiagnosed.

### ■ WHO SHOULD BE TESTED FOR CELIAC DISEASE?

The evidence that guides testing for CD continues to evolve. Classically thought to be only a syndrome of malabsorptive diarrhea, the disease is now recognized

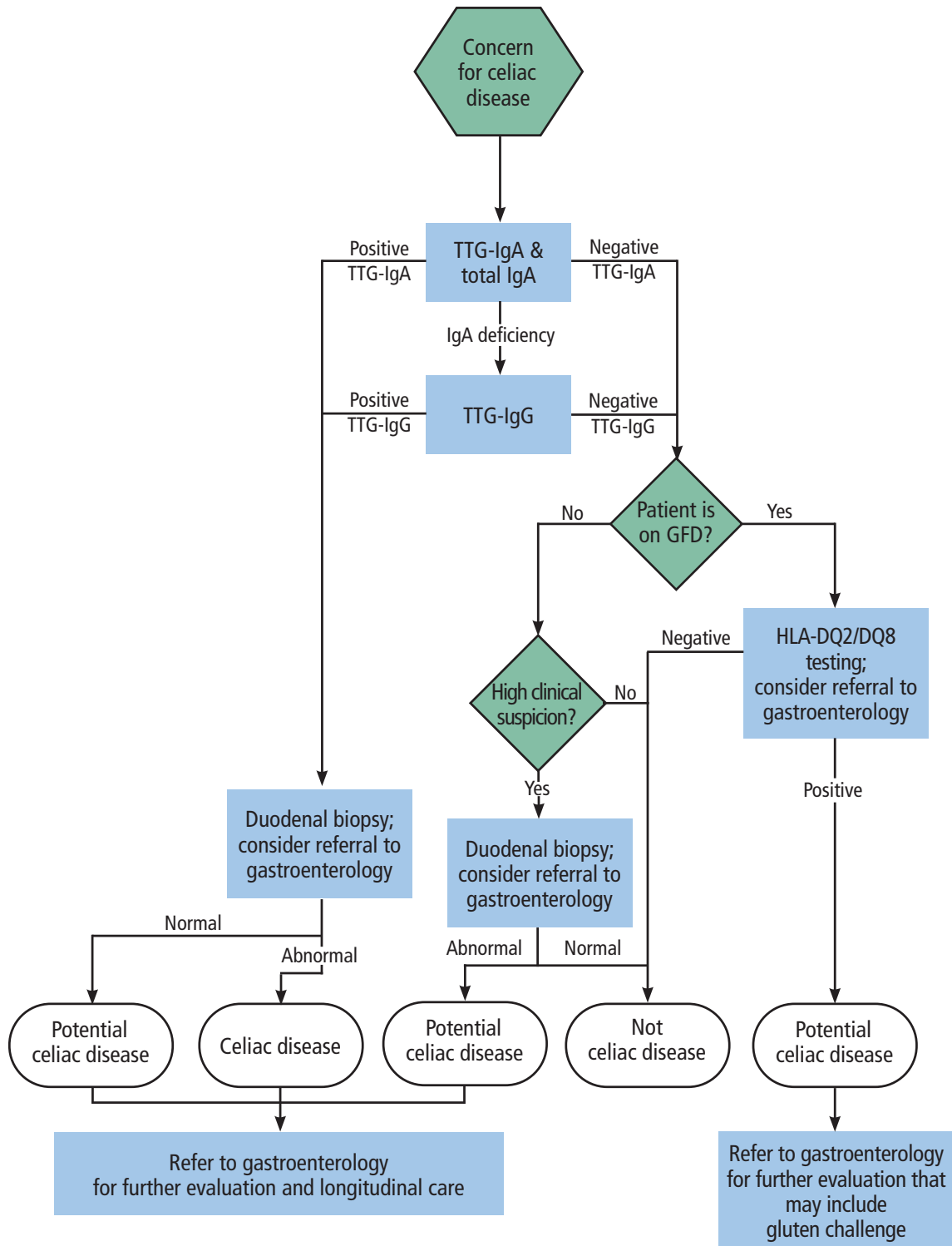
as having a myriad of nonclassical presentations. CD affects both men and women with a preponderance for women. It may occur at any age, with more than 20% of patients presenting after age 60.<sup>2</sup> Diarrhea is found in only 30% of newly diagnosed patients.<sup>3</sup> Despite the malabsorptive state, around 27% of CD patients in the United States are overweight.<sup>4</sup>

A 2017 US Preventive Services Task Force review found insufficient evidence to recommend screening the general asymptomatic population for CD.<sup>5</sup> Accordingly, mass screening is not recommended in clinical practice. Diagnosis relies on maintaining an appropriate index of suspicion and using a case-finding approach,<sup>6</sup> ie, actively screening patients who have signs or symptoms consistent with CD or belong to a high-risk group with an increased incidence of CD. Testing for CD in many of these conditions remains controversial, but it is advised and is proven to increase the identification of patients with CD.<sup>6</sup>

**Classical signs and symptoms of CD** that warrant testing include chronic diarrhea, particularly with evidence of malabsorption, steatorrhea, weight loss, and failure to thrive. Patients presenting with the classical dermatitis herpetiformis rash should also be tested.<sup>6,7</sup>

**Nonclassical signs and symptoms of CD** that warrant testing in the absence of a convincing alternative diagnosis or explanation include iron-deficiency anemia, chronically elevated serum transaminases with no alternative explanation, dyspepsia with postprandial abdominal discomfort and bloating, recurrent abdominal pain, chronic constipation, ataxia, epilepsy, peripheral neuropathy, infertility, recurrent miscarriages, delayed sexual maturity, short stature, early-onset osteoporosis, dental enamel hypoplasia, recurrent aphthous stomatitis, arthritis or arthralgia and myalgia, chronic fatigue, recurrent pancreatitis, and hypoplasia.<sup>6,8</sup>

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**Figure 1.** Diagnostic strategy for suspected celiac disease.

GFD = gluten-free diet; HLA = human leukocyte antigen; IgA = immunoglobulin A; IgG = immunoglobulin G; TTG = tissue transglutaminase

**High-risk groups with an increased incidence of CD** that warrant testing include first-degree relatives of patients with CD and patients with Down syndrome, Turner syndrome, or Williams syndrome. High-risk groups also include patients with autoimmune conditions such as type 1 diabetes mellitus, autoimmune thyroid disease, autoimmune hepatitis, lupus erythematosus, and psoriasis, as well as those with microscopic colitis and selective IgA deficiency.<sup>6,8</sup>

## ■ TESTING AND DIAGNOSTIC LIMITATIONS

There is no gold standard for the diagnosis of CD. The diagnostic process considers the clinical picture, serology, and histology together (**Figure 1**) because no symptom or sign is specific for CD. Even symptomatic improvement on a gluten-free diet has a diagnostic precision as low as 30%, and this outcome is common in other disorders such as nonceliac gluten sensitivity, food intolerance, and irritable bowel syndrome. Serology and histology also have limitations.

### Serology

Testing for CD should begin with a TTG-IgA antibody and a total IgA level. The TTG-IgA has about 95% sensitivity and specificity.<sup>6,9</sup> The higher the TTG-IgA titer, the more likely the result is a true positive. The total IgA level is valuable because patients with CD have an increased risk of having IgA deficiency and a falsely low TTG-IgA. If a patient is found to be IgA-deficient with a low TTG-IgA, then the sensitivity and specificity of TTG-IgG becomes excellent, making it the best antibody test to order next.<sup>10</sup>

A positive TTG-IgA or TTG-IgG result is an indication for upper endoscopy with multiple biopsies of the duodenum, specifically 1 or 2 from the bulb and 4 or more from the distal duodenum.<sup>6</sup> Use of comprehensive CD panels is discouraged as they sacrifice considerable specificity for minimal added sensitivity. Further, interpretation of mixed results poses a challenge that can result in overdiagnosis and unnecessary testing, including invasive and costly endoscopy.

Among the limitations of serologic testing, sensitivity decreases significantly in patients who are on a gluten-free diet.<sup>11</sup> Moreover, some patients have seronegative CD. If the index of suspicion for CD is sufficiently high, further evaluation is recommended despite negative serology.<sup>6</sup>

### Biopsy and histopathology

The best next step in patients with suspected CD is referral to a gastroenterologist for endoscopic small-bowel biopsy to establish the diagnosis and rule out

alternative diagnoses.<sup>6</sup> There has been impressive interest and success in validating the confirmation of CD diagnosis without biopsy, particularly in children with concordantly positive, high-titer antibodies (ie, > 10 times the upper limit of normal for TTG-IgA), but this strategy is not yet recommended for adults. Typical confirmatory biopsy results are notable for increased intraepithelial lymphocytes, crypt hyperplasia, and villous atrophy as described by the Marsh or the Corazza and Villanacci criteria.<sup>12-14</sup> Biopsy may be considered in a seronegative patient if the index of suspicion for CD remains high, as in patients with chronic diarrhea and evidence of malabsorption, in patients with gluten intolerance and other features of CD, or in symptomatic patients with a family history of CD.

Biopsy has limitations. Histologic abnormalities that correlate with CD can be patchy. There can be interprovider (gastroenterologist) variability in obtaining biopsies or in reading biopsies (pathologist) under a microscope. The results can also be equivocal in the presence of only 1 or 2 of the typical histologic features noted above: for example, CD is confirmed in only 10% of patients with isolated increased intraepithelial lymphocytes. The specificity of the biopsy increases if villous atrophy is identified, but it remains limited. Many enteropathies can mimic CD on biopsy, including autoimmune enteropathy, common variable immunodeficiency, and olmesartan-associated enteropathy.<sup>12</sup> As with serology, the sensitivity of the biopsy decreases significantly in patients already on a gluten-free diet. Lastly, endoscopic biopsy is an invasive procedure with procedure-related risks.

### Role of genetic testing

CD occurs only in individuals who are genetically predisposed. The genetic permissiveness for CD is human leukocyte antigen (HLA)-DQ2/DQ8. However, genetic testing has no role in the routine initial diagnosis of CD as it has little positive predictive value for CD. HLA-DQ2/DQ8 can be found in about 30% of the general population.<sup>15</sup> The utility of genetic testing is its high negative predictive value: if a patient is negative for HLA-DQ2/DQ8, then CD can be ruled out, with rare exceptions.<sup>15</sup> Genetic testing can be useful in patients who have discrepant clinical, serologic, and histologic findings. It can also be useful in patients on a gluten-free diet in whom the diagnosis of CD is questioned (**Figure 1**).

## ■ LONG-TERM FOLLOW-UP

CD is a chronic disorder with significant morbidity and mortality that can be obviated with gluten avoid-

ance. Treatment is a lifelong gluten-free diet with regular medical and dietitian follow-up. Ideally, patients are referred to a center that specializes in the care of CD with an integrated multidisciplinary team that includes gastroenterologists, gastrointestinal pathologists, and dietitians with expertise in the gluten-free diet. Patients should be monitored for dietary adherence, serologic and histologic improvement, symptom resolution, and early detection of associated complications over time. Monitoring for improvement beyond symptom resolution can be accomplished by checking

serology at 3 to 6 months, then every 6 months until seroconversion, and then annually.<sup>6</sup> Recent guidelines suggest considering intestinal healing as a goal that can be assessed by follow-up intestinal biopsy after 2 years on a gluten-free diet.<sup>6</sup> ■

### DISCLOSURES

Dr. Jansson-Knodell has disclosed ownership interest (stock, stock options in a publicly owned company) for ClearPoint Neuro, DarioHealth, Derm-Tech, DiaMedica Therapeutics, Exact Sciences, Inari Medical, Nano-X Imaging, Outset Medical, PAVmed, and Transmedics. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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# Guidelines for the management of trigeminal neuralgia

## ABSTRACT

Guidelines for the diagnosis and treatment of patients with trigeminal neuralgia (TN) advocate for a multidisciplinary team approach to improve the care of patients with acute and chronic TN. Evidence-based discussions and decisions are encouraged to establish care pathways for prompt diagnosis and treatment, and long-term outcomes data collection to improve care. The guidelines include summary materials for patients to inform them about their condition and available treatments.

## KEY POINTS

TN is a chronic pain disorder of the trigeminal nerve that causes sudden, intense facial pain.

TN may be caused by vascular contact with the trigeminal nerve (classic TN), an underlying pathology such as multiple sclerosis or tumor (secondary TN), or no known cause (idiopathic TN).

Once dental causes for facial pain are ruled out, prompt diagnosis of TN and initiation of first-line medications for rapid pain control are advised.

Imaging studies to determine the cause of TN and developing a care plan, including surgical options for some patients, should involve a multidisciplinary team.

**T**RIGEMINAL NEURALGIA (TN) IS A condition causing severe, unilateral, episodic facial pain. The diagnosis of TN is clinical, and patients typically report brief, lancinating attacks triggered by eating, drinking, talking, touching the face, or even a puff of wind. There is a distinction between typical TN paroxysms where there is no pain between episodic attacks and TN with concomitant pain where there is background pain between attacks.

Key symptoms and differential diagnosis for TN are summarized in **Table 1**. The lifetime prevalence of TN is estimated to be 0.3% (95% confidence interval [CI] 0.1%–0.5%),<sup>1</sup> but this has not been validated, and it may be more frequent. TN is more common in persons ages 50 to 60, with a slight predominance in women.<sup>2,3</sup> There are 3 etiologic classifications for TN<sup>4</sup>:

- Classic—vascular contact on the trigeminal nerve
- Secondary—possible underlying pathology such as schwannoma or multiple sclerosis
- Idiopathic—no apparent structural cause (**Table 2**).<sup>4</sup>

Secondary TN, due to multiple sclerosis or tumors (mostly benign), can present in a very similar way to classic TN, and these patients can also have periods of remission. It is important to evaluate if there are any auditory symptoms or signs, as these may indicate a tumor, which will require a different management approach. TN can be the primary diagnostic factor in 7% of patients with multiple sclerosis.<sup>5</sup>

Although symptoms of TN may stop spontaneously, the pain is severe and distressing. It was reported that patients with TN experienced a 3-fold higher risk of anxiety and

**TABLE 1**

## Key symptoms of trigeminal neuralgia and differential diagnosis

Key symptoms	Other possible symptoms	Differential diagnosis
Paroxysmal pain <ul style="list-style-type: none"> <li>• Sharp and shooting</li> <li>• Lasts seconds to minutes</li> <li>• Provoked by light touch</li> </ul>	Burning, prickling, dull tender constant background pain	Trigeminal neuralgia with concomitant, continuous pain
Trigeminal nerve innervation area	Interparoxysmal pain	Temporomandibular disorder
Pain cannot be evoked between attacks (refractory period)	Autonomic symptoms <sup>a</sup>	SUNCT and SUNA
Periods of remission or relapse	Sensory change <sup>b</sup>	Painful trigeminal neuropathy
Abrupt onset	After eating	Dental, cracked tooth

<sup>a</sup>Some facial reddening and tearing, sometimes on both sides, may be seen during acute pain paroxysms. If more pronounced with strictly unilateral conjunctival reddening, eyelid droop, nasal blockage, then consider SUNCT and SUNA.

<sup>b</sup>During a relapse of trigeminal neuralgia and especially just after paroxysms of pain, there may be subtle transient unilateral sensory change in the area innervated by the trigeminal nerve. The presence of permanent sensory alterations and atypical features such as absent refractory period and no pain remission raise the possibility of trigeminal nerve damage and painful trigeminal neuropathy.

SUNA = short-lasting unilateral neuralgiform headache attacks with autonomic features; SUNCT = short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing

depression compared with a control group.<sup>6</sup> Another study estimated that 45% (89 of 198) of patients with TN reported more than 15 days of interference in daily activity in the last 6 months, 35.7% (75 of 210) had mild to severe depression, and half had anxiety symptoms.<sup>7</sup> The fear of an attack was reported to lead 30% (30 of 103) of patients with TN to experience symptoms consistent with posttraumatic stress disorder.<sup>8</sup>

### GUIDELINES INCLUDING ALL STAKEHOLDERS

The care pathways for patients with TN are extremely variable, partly due to the wide range of specialists consulted. There is therefore a need to establish evidence-based care plans for the management of both acute and chronic TN, using a multidisciplinary approach endorsed by all stakeholders. It is with this in mind that the Royal College of Surgeons of England issued TN national guidelines for the United Kingdom (UK).<sup>9</sup> These were based on the recently published European Academy of Neurology guidelines.<sup>10</sup> The discussion of guidelines here refers to the UK guidelines unless otherwise noted.

### CLINICAL SETTING: OUTPATIENT AND INPATIENT

These guidelines apply to all patients with TN as outpatients or inpatients in both primary care and secondary care settings.

### INTENDED AUDIENCE: SPECIALIST, GENERAL PRACTICE

The intended audience is primary care, medical, and dental practitioners as well as all specialists who manage patients with TN. Appendix A of the guidelines provides a plain-language summary for patients with TN to inform them of the current care recommendations and help them make informed choices.

### WHO WROTE THE GUIDELINES

The guidelines were written by a multidisciplinary team representing the following organizations:

- Association of British Academic Oral and Maxillofacial Surgeons
- British & Irish Society for Oral Medicine
- British Association for the Study of Headache
- British Association of Oral and Maxillofacial Surgeons
- Faculty of Pain Medicine of the Royal College of Anaesthetists
- Royal College of General Practitioners
- Society of British Neurological Surgeons
- The Faculty of General Dental Practice UK
- The Trigeminal Neuralgia Association UK, a patient support group.

The guidelines were prepared under the auspices of the Faculty of Dental Surgery of the Royal College of

**TABLE 2**  
**Classification of trigeminal neuralgia**

Type	Subtypes
Classic trigeminal neuralgia (neurovascular compression present)	<ul style="list-style-type: none"> <li>• Purely paroxysmal</li> <li>• Concomitant continuous pain</li> </ul>
Secondary trigeminal neuralgia (underlying pathology present)	<ul style="list-style-type: none"> <li>• Attributed to multiple sclerosis</li> <li>• Attributed to space-occupying lesion</li> <li>• Attributed to other causes</li> </ul>
Idiopathic trigeminal neuralgia (no underlying cause found)	<ul style="list-style-type: none"> <li>• Purely paroxysmal</li> <li>• Concomitant continuous pain</li> </ul>

Based on data from reference 4.

Surgeons England using their guideline-development process encompassing literature search, peer review, public engagement, and approval by the Faculty. The guidelines are available on the Royal College of Surgeons of England website (<https://www.rcseng.ac.uk/dental-faculties/fds/publications-guidelines/clinical-guidelines>), with the expectation that there will be timely review and updates.<sup>9</sup>

## ■ WHAT ARE THE MAIN RECOMMENDATIONS?

The guidelines recommend the diagnosis and phenotyping of TN by multidisciplinary teams, especially the early contribution from a qualified dental specialist to exclude local intraoral causes of pain.

### Approach to diagnosis

The diagnosis of TN is noted to be complex and should also include the measurement of patient-related outcomes such as the Brief Pain Inventory, Penn Facial Pain Scale-Revised, and the Hospital Anxiety and Depression Scale. In primary care, documenting the intensity and frequency of symptoms and the impact on quality of life using a rating of mild, moderate, or severe could provide useful data on treatment outcomes after the use of medications. Patients should be provided with written information such as the Brain and Spine Foundation Facial Pain Booklet (<https://www.brainandspine.org.uk/our-publications/booklets/face-pain>).

Use of magnetic resonance imaging (MRI) to investigate the underlying cause of TN is advocated and, if MRI is contraindicated, use brain computed tomography and angiography and neurophysiologic tests such as brainstem auditory evoked potentials. Our standard request is for thin-slice MRI of the brain and internal auditory meatus, and enhancement is not usually required. The images should be reported by experienced

neuroradiologists and reviewed with the treating clinicians. High-quality thin-slice MRI provides high sensitivity (88%; 95% confidence interval 80%–93%) and specificity (94%; 95% confidence interval 91%–96%) of potential nerve compression or distortion.<sup>10</sup>

### Drug therapy

The guidelines summarize the data for recommending pharmacotherapy with the best evidence for carbamazepine, but also includes the use of oxcarbazepine, lamotrigine, baclofen, gabapentin, and botulinum toxin. The recommendation for primary care physicians to start patients with TN on first-line medication before referral to a specialist is pragmatic and avoids treatment delays. First-line and second-line medications, dosage, and side effects are outlined in Table 3. Individuals of Han Chinese or Thai origin are at risk of Stevens-Johnson syndrome when using carbamazepine or oxcarbazepine.<sup>10</sup>

In practice, individualized pharmacotherapy plans are needed, balancing the benefits and side effects experienced by each patient. Because TN is a paroxysmal disorder, it is difficult to judge when to reduce and withdraw treatment. Many patients choose to continue medications even when in remission. Careful guidance and counseling may be needed to help patients de-escalate and withdraw from treatment. These drugs are generally safe, and some primary care physicians may have previously prescribed them for treating epilepsy or other neuropathic pain conditions. Rapid pain control should be the main aim, and there is no reason why primary care physicians cannot initiate second-line therapy depending on their knowledge and experience. Some patients with TN may be adequately managed outside specialist centers, though these guidelines provide a framework for multidisciplinary care.

**TABLE 3**  
**Evidence-based pharmacotherapy for trigeminal neuralgia**

Drug	Dosage regimen	Usual dose range	Common side effects
First-line therapy Carbamazepine <sup>a</sup>	100 mg twice daily; double after 3 days to 200 mg twice daily; increase by 100–200 mg twice daily every 3 days, then 200 mg 4 times daily	800–1,200 mg daily	Sedation, dizziness, blurred vision, nausea, unsteady lethargy, double vision, headache May cause hyponatremia, skin rashes, pancytopenia Risk of osteoporosis with long-term use May reduce oral contraception efficacy
Oxcarbazepine <sup>a</sup>	150 mg twice daily, double to 300 mg twice daily after 3 days; increase by 150–300 mg twice daily every 3 days, then 300 mg 4 times daily	1,200–1,800 mg daily	Drowsiness, dizziness, diplopia, confusion, nausea, abdominal pain, headache, depression, diarrhea High risk of hyponatremia Chronic use risks osteoporosis May reduce oral contraception efficacy
Second-line therapy Lamotrigine	Start 25 mg a day for 7 days, then 25 mg twice daily for 7 days, then 50 mg twice daily for another week; subsequent dose increments of 50 mg every 7 days, up to 10 weeks	200 mg twice daily	Blurred vision, agitation, aggression, unsteadiness, dizziness, nausea, dry mouth, insomnia, joint pains Risk of skin rashes and Stevens-Johnson syndrome with rapid dose escalation Probably safe for pregnant women at a dose of 100 mg twice daily
Baclofen	5 mg 3 times daily for 3 days, then increase to 10 mg 3 times daily for 3 days; increase by 10 mg 3 times daily every 3 days until maximum dose	40–80 mg daily	Anxiety, depression, agitation, unsteadiness, headache, sedation, tremor, skin rash, blurred vision, dry mouth, abdominal pain, withdrawal symptoms if stopped too rapidly
Gabapentin	100 mg 3 times daily day 1, 200 mg 3 times daily day 2 and 300 mg 3 times daily day 3. Increase by 1–300 mg 3 times daily every 3 days to maximum dose; start 100 mg 3 times daily or 300 mg at bedtime; can increase dose up to 300 to 600 mg 3 daily	900–3,600 mg daily	Amnesia, confusion, dizziness, vertigo, drowsiness, depression, nausea, blurred vision, peripheral edema, constipation, abdominal bloating, weight gain
Pregabalin	25 mg twice daily; increase by 25–50 mg twice daily every 3 days	600 mg daily	Confusion, drowsiness, constipation, blurred vision, dizziness, nausea, peripheral edema, increased appetite, weight gain

<sup>a</sup>Carbamazepine and oxcarbazepine are available in liquid form. Dosage ranges vary due to lack of high-quality trials.

**Management of acute relapses**

Although few papers in the medical literature address managing acute TN relapses, the guidelines summarize the current literature. The experts advised that lidocaine can be administered in 3 different ways to manage TN, ie, nasal spray, local nerve block, and intravenous infusion. There is some evidence for the use of botulinum toxin, and also a recommendation

for a trial of subcutaneous sumatriptan to alleviate an acute TN attack. Intravenous lidocaine, phenytoin, and fosphenytoin are also suggested for inpatient treatment (Table 4).<sup>9,11</sup>

**Neurosurgical management**

The guidelines recommend involvement of neurosurgeons who are experienced in managing TN

**TABLE 4**  
**Treatments for acute episodes of trigeminal neuralgia based on a systematic review**

Provider	Treatment
All clinicians (dentist, general practitioner, specialist)	Lidocaine <ul style="list-style-type: none"> <li>• 10-mg nasal spray, 2 sprays into nostril on affected side; can be used intraorally, but spit out after 1 minute</li> <li>• 5% ointment to trigger area</li> <li>• 2% 1:80,000 adrenaline local infiltration to nerve block trigger area</li> </ul>
General practitioner, specialist	Sumatriptan 6 mg subcutaneous injection, followed by oral sumatriptan 50 mg twice daily for 1 week
Specialist only	Botulinum toxin type A injection, 3 mg in 1 mL
Specialist, inpatient basis	Intravenous Infusions <ul style="list-style-type: none"> <li>• Lidocaine 1.5 mg/kg over 1 hour, up to 5 mg/kg in a randomized clinical trial</li> <li>• Phenytoin 10 mg/kg</li> <li>• Fosphenytoin 15 mg/kg</li> </ul>

Based on data from references 9 and 11.

when pharmacotherapy is ineffective or causes intrusive side effects. To better support informed decision-making, a neurosurgical consult is best done when a patient’s pain is in remission. Patients should be aware that invasive procedures are only expected to reduce brief lancinating pain but have unpredictable effects on the interparoxysmal pain, or can even make it worse. The guidelines state that 25% to 40% of patients with TN choose surgery within 2 years of symptom onset.<sup>9</sup>

Surgical treatments for TN include posterior fossa microvascular decompression (MVD) and neuroablative therapies such as stereotactic radiosurgery, radiofrequency thermocoagulation, balloon compression, glycerol rhizolysis, and internal neurolysis. For patients with classic TN (ie, arterial contact on the trigeminal nerve), MVD has the best surgical results for medication-free, long-term pain relief, with 62% to 89% of 5,149 patients reportedly pain-free at follow-up of 3 to 10.9 years.<sup>9,10</sup>

In posterior fossa MVD, any vessels or arachnoid tissue compressing the trigeminal nerve in the root entry zone is moved away. If no compressions are found, internal neurolysis may be performed to separate (or “comb”) the fascicles of the trigeminal nerve. Patients need to be medically fit to undergo MVD, and there is a 0.3% mortality rate and a risk of complications such as cerebrospinal fluid leak, infection, and stroke, but a lower risk of sensory changes.<sup>10</sup>

Neuroablative therapies (ie, stereotactic radiosurgery, radiofrequency rhizotomy, balloon compression, glycerol rhizolysis) involve controlled damage to the

trigeminal nerve and have a lower mortality risk but are more likely than MVD to increase the chance of altered sensation including the loss of corneal reflex.<sup>10</sup> Neuroablative treatments have varying levels of success, with an average of 2 to 4 years.<sup>10</sup>

Stereotactic radiosurgery, compared with all other procedures, may have the lowest risk of short-term complications, but it has an increased probability of causing facial numbness and dysesthesia,<sup>10</sup> as well as a long postprocedure duration before expected pain relief or complications. Glycerol rhizolysis (denervation using a chemical) offers the lowest chance for both,<sup>10</sup> while radiofrequency thermocoagulation (denervation using heat) is reported to have a higher chance of success but also a greater risk of sensory loss than with all other procedures.<sup>10</sup>

**Efficacy of surgical procedures**

The guidelines include the efficacy of surgical procedures for TN as reported by Bendtsen et al<sup>10</sup> but it is important to emphasize that the results are from single-intervention, nonrandomized studies among select patients in specialized centers.<sup>10</sup> Individual patients may not achieve the same level or duration of pain relief. Patients with interparoxysmal pain need to be cautioned before choosing neuroablative treatments such as glycerol rhizolysis, balloon compression, and radiofrequency rhizotomy. Pain between lancinating exacerbations may indicate existing nerve damage, and further iatrogenic destruction may lead to anesthesia dolorosa (a feeling of pain in an area that is completely numb to the touch).

### Timing and selection of surgical treatment

The guidelines are not proscriptive about when or which surgical operation should be offered, and any such decision must be made jointly between well-informed patients and their clinicians from multiple disciplines. Neuroablative procedures for TN may require an overnight hospital stay and can be performed in patients who have other comorbidities. Surgical complications should be balanced against the side effects of long-term pharmacotherapy.

### Referral for pain management

The guidelines recommend patient referral to pain management programs with access to clinical psychologists and physiotherapists because the pain severity, disruption of daily life, and associated psychological impact of TN can adversely affect a patient's mental health. The fear of a relapse cannot be underestimated. Pain psychologists and pain management nurse specialists can help patients alleviate some of these fears. Patients should be encouraged to join a trigeminal neuralgia support group such as Trigeminal Neuralgia Association UK ([www.tna.org.uk](http://www.tna.org.uk)), which has a multidisciplinary clinician panel offering advice.

### Need for long-term follow-up and outcomes evaluation

A key recommendation of the guidelines is to urge clinicians managing patients with TN to follow up and gather long-term patient outcomes data to evaluate treatment efficacy and results. TN is a relapsing-remitting condition, and initial pain improvement may not always be due to treatment. This is true especially for invasive procedures, where initial good response may be followed by treatment complications and relapses.

### ■ WHAT IS DIFFERENT FROM PREVIOUS GUIDELINES?

Previous guidelines have been developed solely by experts in the field, whereas for the UK guidelines, all potential caregivers were consulted. A patient representative from the Trigeminal Neuralgia Support Group was included, as well as representatives from the Brain and Spine Foundation, a charity specializing in producing booklets for the general public on neurologic conditions. The new guidelines also recommend aids such as the Ottawa Personal Decision Guide (<https://decisionaid.ohri.ca/decguide.html>) to help patients make informed choices.

Pharmacotherapy and surgical treatments are recommended according to the best available evidence, similarly to other published guidelines.<sup>10</sup> The UK guidelines include the use of botulinum toxin injections and emphasize early discussion of neurosurgical

options to inform patients of the full array of possible treatments. There is also strong emphasis on the need for TN care to be delivered by a multidisciplinary team.

### ■ WHAT IS THE EXPECTED CLINICAL IMPACT?

The guidelines encourage primary care physicians to promptly diagnosis TN and initiate pharmacotherapy after ruling out dental causes of facial pain. All patients should be evaluated to rule out secondary causes of facial pain, even if the pain is in remission. If relapses occur, patient referral to a multidisciplinary specialist team is advised to inform patients about the most appropriate treatment for their condition.

The coalescence of interested clinicians can prompt the collection and evaluation of long-term outcomes data to improve TN care. One example of this was an audit of 129 patients with TN evaluating treatment efficacy by choosing outcome measures meaningful to patients.<sup>12</sup> Using the Patient Global Impression of Change score, 79% (102 of 129) of patients reported their condition was better since starting treatment in a specialist center. Notably, even in this study in a multidisciplinary specialist center, 20% of patients did not experience improvement in their condition,<sup>12</sup> a finding that should prompt further research to bridge this management gap.

The data also revealed that the long period of inadequate pain control between symptom onset and specialist referral contributes to patients' perception of treatment failure. A review of outcomes over an 11-year period in 285 patients without prior surgery for TN reported that 54% (153 of 285) had a surgical procedure and 46% (132 of 285) were medically managed.<sup>13</sup> Of the 334 patients included in the study, 93 (28%) were pain-free and off medication. The largest group that was pain-free and off medication were those who had undergone first-time surgery (84 patients, or 55%). Of the 49 patients undergoing surgery for a second time, only 11 (22%) were pain-free and off medication, and the 132 who remained on medication alone (18 patients, or 16%) were pain-free and off medication due to remissions.<sup>13</sup>

### ■ DO OTHER SOCIETIES AGREE OR DISAGREE?

These guidelines are based on other documents first published by the American Academy of Neurology and the European Federation of Neurological Sciences in 2008,<sup>14</sup> which was further updated by the European Academy of Neurology in 2019.<sup>10</sup> They are also in line with the care pathways published by a Danish group in 2015<sup>15</sup> and a UK group in 2020.<sup>12,16</sup> All agree on the need for more research.

■ HOW WILL THIS CHANGE DAILY PRACTICE?

These guidelines help patients to choose and clinicians to develop the optimal care pathway using available evidence. If the appropriate expertise is available, some patients with TN should be managed in a multidisciplinary primary care setting. When such services are not available or adequate, access to specialist management may be delayed and fragmented.<sup>17</sup> Streamlining this process should allow faster access to the most appropriate services for individual patients. There is also the recommendation for all clinicians managing this condition to collect long-term outcomes data and disseminate best practices to improve the quality of care.

■ WHEN WOULD THE GUIDELINES NOT APPLY?

The guidelines depend on accurate phenotyping of TN. As there are no specific diagnostic tests, clinical assessment is crucial and must be undertaken by experienced clinicians. Many conditions can mimic TN, especially painful trigeminal neuropathy. The pathophysiology and management of trigeminal neuropathy is different, though it may coexist with TN, especially after failed surgery.

Another condition that often coexists with TN is temporomandibular disorder. This is a nociceptive pain condition but may have elements of sharp, shooting pain triggered by eating, talking, or brushing teeth.<sup>18</sup> It

is important to correctly identify the causes triggering pain even in patients known to have TN.

TN may be on the same spectrum of trigeminal autonomic cephalalgias, a group of disorders in which autonomic features such as conjunctival redness, tearing, meiosis, eyelid-dropping, and nasal congestion are noted. These include short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and short-lasting unilateral neuralgiform headache attacks with autonomic features (SUNA).<sup>19</sup> In some patients, one condition may evolve into another over time. The drug treatment of these conditions may overlap, although the role for surgery is less well defined for trigeminal autonomic cephalalgias, and occipital nerve blocks that may alleviate SUNCT or SUNA do not work for TN.<sup>20</sup>

In the UK, many patients do not reach specialist centers for 4 to 10 years after symptom onset, and this increases the risk of developing anxiety, depression, and sleep disorder.<sup>5</sup> These psychologically traumatized patients with TN have increased suicide risk, and it is important to recognize this so that they are offered additional support not previously mentioned in these guidelines.<sup>21,22</sup>

■ DISCLOSURES

Dr. Bahra has disclosed consulting for Pfizer. Dr. Zakrzewska has disclosed consulting for Biogen and Noema Pharma. The other authors report no relevant financial relationships, which in the context of their contributions, could be perceived as a potential conflict of interest.

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# Measuring exhaled nitric oxide when diagnosing and managing asthma

## ABSTRACT

Measuring the concentration of nitric oxide in the exhaled breath may have several roles in patients with suspected or confirmed asthma: as an adjunctive test for the disease, as a test to determine whether patients with asthma are likely to respond to inhaled corticosteroids, as a way to monitor and adjust this therapy, and as a way to estimate the likelihood of exacerbations. However, it is not very sensitive or specific and should not be used by itself, but rather in conjunction with clinical signs and symptoms. The authors address the role of measuring exhaled nitric oxide in the diagnosis and management of asthma and provide guidance for its appropriate use.

## KEY POINTS

Nitric oxide is produced in the airways of patients with type 2 inflammation.

The fractional concentration of exhaled nitric oxide (FeNO) can be used as an adjunctive test for asthma, but it can be raised or lowered by many extrinsic and intrinsic factors other than asthma and should not be used by itself.

Patients with asthma and high FeNO values are more likely to benefit from inhaled corticosteroid and biologic therapy.

Measuring the FeNO may be useful in adjusting the daily dose of inhaled corticosteroids in adults with asthma, both up-titration and weaning. However, data conflict on how much value this adds compared with using clinical signs alone.

**A**STHMA IS A HETEROGENEOUS pulmonary disease characterized by inflammation of the lower airways. In recent years, specific endotyping through biomarkers of airway inflammation has helped in guiding evaluation and assessment of the severity of asthma and in deciding on treatment.

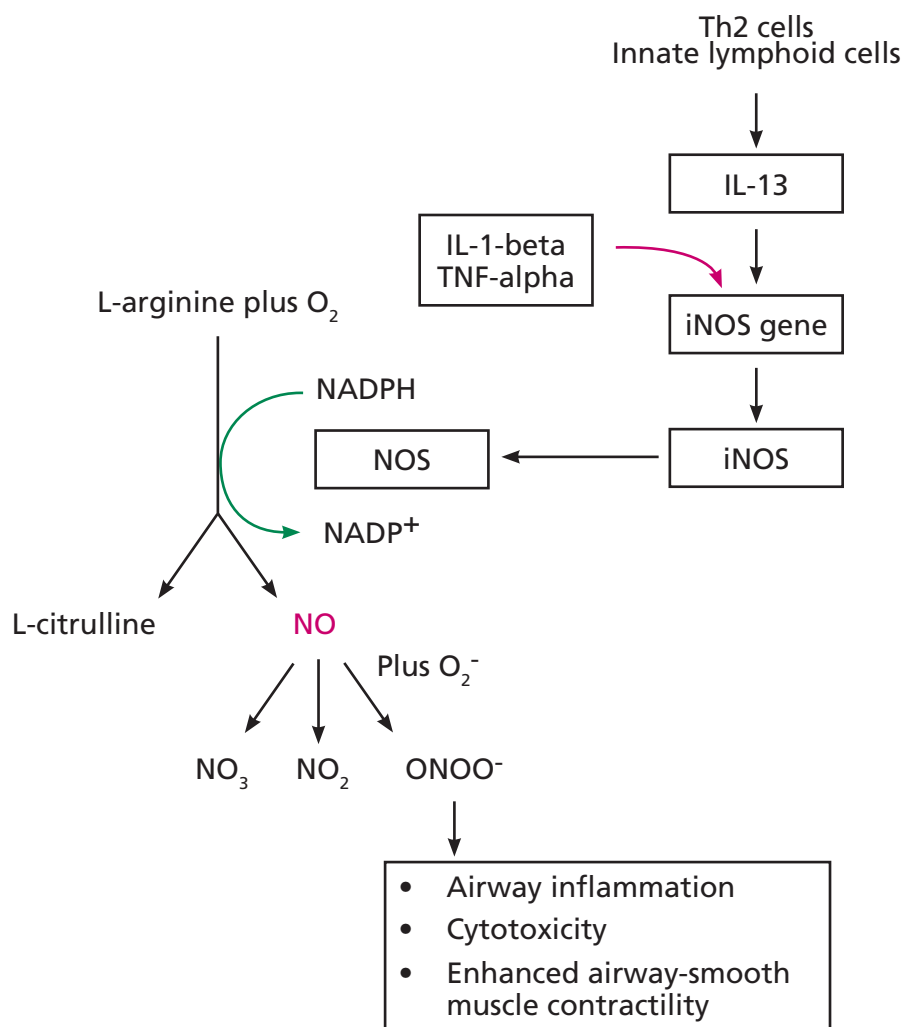
One of the biomarkers is exhaled nitric oxide, which can now be measured in parts per billion (ppb). In this review, we discuss current care guidelines regarding the role of measuring exhaled nitric oxide in the evaluation and management of asthma.

## ■ TYPES OF ASTHMA

Asthma is a chronic inflammatory disorder of the airways that results physiologically in bronchial hyperreactivity, and clinically in recurrent episodes of wheezing, chest tightness, or coughing. It is a heterogeneous disease with distinct mechanistic pathways (endotypes) and variable clinical presentations (phenotypes). Regarding endotypes, we can classify cases of asthma according to levels of type 2 (T2) inflammation:

- T2-high, with high levels of interleukin (IL)-4, IL-5, and IL-13, inflammation, and exhaled nitric oxide; it tends to respond to treatment with inhaled corticosteroids
- T2-low, with lower levels of the above, but higher levels of IL-1-beta and IL-6; it tends to resist treatment with inhaled corticosteroids.

This dichotomy has shaped our thinking about the pathobiology and biochemistry of asthma. Type 2 cytokines (IL-4, IL-5, and



**Figure 1.** Inflammatory cytokines interleukin (IL)-13, IL-1-beta, and tumor necrosis factor alpha (TNF-alpha) are upregulated in response to tissue damage and induce expression of the inducible nitric oxide synthase (iNOS) gene, leading to a more sustained release of nitric oxide (NO).

NADP = nicotinamide adenine dinucleotide phosphate; NADPH = reduced form of NADP; NO<sub>2</sub> = nitrite; NO<sub>3</sub> = nitrate; ONOO = peroxynitrite; Th2 = T helper cell type 2

IL-13) are produced by CD4-positive T cells; IL-5 is also produced by CD8-positive T cells and natural killer cells, and IL-13 is also produced by innate lymphoid cells.<sup>1</sup> IL-4 also increases IL-13 production, which contributes to the physiologic features of asthma such as mucus production and airway fibrosis and hyperresponsiveness.<sup>2</sup>

**■ NITRIC OXIDE IS A PRODUCT OF TYPE 2 INFLAMMATION**

Nitric oxide in exhaled breath is produced in the airways by nitric oxide synthase. The inducible isoform of nitric oxide synthase is a mediator of eosinophilic

airway inflammation. In T2-high asthma, IL-13 upregulates inducible nitric oxide synthase, leading to increased nitric oxide production. This increased nitric oxide production worsens type 2 inflammation and contributes to airway remodeling and narrowing.<sup>3</sup> In people with asthma, the amount of nitric oxide in the breath is proportionate to the number of eosinophils in the sputum, peak flow variability, and hyperresponsiveness to methacholine, and it is reduced by both inhaled and oral corticosteroids.<sup>4,5</sup>

In 2007, Suresh et al<sup>6</sup> performed the first known direct measurement of nitric oxide released from human bronchial epithelial cells. They demonstrated that stimulation with IL-13 results in a significant increase

in nitric oxide production by inducing inducible nitric oxide synthase and alters nitric oxide metabolism, resulting in an increase in the amount of nitrate relative to nitrite (**Figure 1**). They concluded that the bronchial epithelium is the likely source of nitric oxide in the exhaled breath, and that increased levels observed in inflammatory diseases such as asthma are likely due to inducible nitric oxide synthase upregulation.<sup>6</sup> Notably, other inflammatory cytokines such as IL-1-beta and tumor necrosis factor alpha can also upregulate inducible nitric oxide synthase and subsequently increase exhaled nitric oxide, reducing the specificity of nitric oxide for type 2 cytokines such as IL-13.<sup>7</sup>

In 1998, Dweik et al<sup>8</sup> showed that oxygen regulates nitric oxide levels through effects on the kinetics of nitric oxide synthase and proposed that nitric oxide synthase is a mediator of the vascular response to oxygen in the lung.

### ■ NITRIC OXIDE AS AN ADJUNCTIVE DIAGNOSTIC TEST FOR ASTHMA

Asthma is typically diagnosed clinically, but this can sometimes be challenging because asthma is episodic and lacks a gold standard diagnostic test. Numerous studies have evaluated the diagnostic accuracy of measuring exhaled nitric oxide compared with established diagnostic standards such as bronchial provocation, postbronchodilator forced expiratory volume in 1 second, peak-flow variability, or a combination of these.<sup>9</sup>

Karrasch and colleagues<sup>9</sup> performed a systematic review and meta-analysis of 26 such studies and reported that nitric oxide testing had an overall 65% sensitivity (95% confidence interval 58%–72%) and 82% specificity (95% confidence interval 76%–86%) for diagnosing asthma. Higher cutoff values were more specific, while there was no association with sensitivity.

However, confounding factors that increase or decrease nitric oxide need to be considered. Values can be elevated by chronic rhinosinusitis, nasal polyposis, atopy without other features of asthma, rhinovirus respiratory infections, exposure to air pollution, or in patients who are male, older, or taller.<sup>10,11</sup> Conversely, factors that can reduce exhaled nitric oxide include cigarette smoking, inhaled corticosteroid use, alcohol use, strenuous exercise, and drugs such as leukotriene receptor antagonists and prostaglandins (**Table 1**).<sup>11</sup>

Nitric oxide testing increases the accuracy of asthma diagnosis and is most reliable in patients who are not taking corticosteroids.<sup>12</sup> Elevated nitric oxide levels may complement the clinical history and spirometry testing to support the diagnosis of asthma, particularly when clinical suspicion is high. Conversely, low levels

can help exclude asthma in the setting of normal spirometry and no suggestive symptoms.

A systematic review of 32 studies (24 in adults, 8 in children) concluded that nitric oxide measurement, bronchodilator reversibility, blood eosinophils, or immunoglobulin E should not be used individually to diagnose asthma, since using them as stand-alone tests has limited accuracy.<sup>13</sup> Therefore, expert opinion is that nitric oxide measurement should be used in conjunction with testing for variable airflow limitation to support the diagnosis of asthma.<sup>14</sup>

### Expert society recommendations

**The National Asthma Education and Prevention Program**<sup>15</sup> recommends that if nitric oxide is measured, it should be done as part of an ongoing monitoring and management strategy. This group also makes a conditional recommendation that if the diagnosis of asthma is uncertain, one can measure nitric oxide as an adjunct to the evaluation. Although there is limited evidence for an exact cutoff point, this group notes that a fractional concentration of exhaled nitric oxide (FeNO) higher than 50 ppb is consistent with type 2 inflammation<sup>15</sup> and supports a diagnosis of asthma (other guidelines use a cutoff point of 40 ppb),<sup>16,17</sup> whereas a concentration lower than 25 ppb suggests a diagnosis other than asthma.

**The British Thoracic Society and the Global Initiative for Asthma** favor measuring nitric oxide as an adjunctive tool to diagnose type 2 inflammation<sup>18</sup> or to support starting an inhaled corticosteroid.<sup>19</sup> The Global Initiative for Asthma highlights the limitation of confounding features of testing—ie, exhaled nitric oxide can be elevated in nonasthmatic conditions like eosinophilic bronchitis, atopy, allergic rhinitis, and eczema and may be normal in T2-low asthma.

**The European Respiratory Society**<sup>20</sup> recommends that if the diagnosis is not clear based on initial bronchodilator reversibility testing, nitric oxide should be measured as part of the diagnostic workup in adults over age 18. A cutoff point of 50 ppb has a high specificity (> 90%) and supports a diagnosis of asthma, but high exhaled nitric oxide levels themselves do not define asthma, and conversely, a value lower than 40 ppb does not rule out asthma.<sup>20</sup> FeNO is also low during bronchoconstriction and the early phases of the allergic response and can be variable during viral respiratory infections.

In conclusion, exhaled nitric oxide measurement should not be used in isolation, and current guidelines emphasize the importance of incorporating clinical history, physical examination, and spirom-

**TABLE 1**  
**Factors other than asthma that raise or lower the fractional concentration of exhaled nitric oxide (FeNO)**

Factors that increase FeNO	Factors that decrease FeNO
<p><b>Chronic rhinosinusitis, nasal polyposis, or both:</b> FeNO is increased in patients with allergic rhinitis or nasal polyposis even in the absence of a concomitant asthma diagnosis. Patients with allergic rhinitis have higher FeNO levels than patients with nonallergic rhinitis. Perennial sensitization leads to higher FeNO than seasonal allergens.</p> <p><b>Atopy:</b> Acute exposure to allergens can increase FeNO by up to 50%.</p> <p><b>Rhinovirus respiratory infections</b> can increase FeNO by 50% to 150% through inducible nitric oxide synthase upregulation. However, not all viral infections increase FeNO—respiratory syncytial virus and influenza reduce FeNO, and bacterial infections of the respiratory tract do not affect FeNO.</p> <p><b>Nitrate-containing foods</b> such as beetroot can increase FeNO levels by 20% to 60%.</p> <p><b>Air pollution (particulate matter and ozone),</b> possibly because of oxidative potential, even in the absence of asthma.</p> <p><b>Male sex:</b> association is consistent after adjustment for height.</p> <p><b>HIV infection</b> is associated independently with raised FeNO after adjusting for use of airway medication, blood eosinophil counts, and immunoglobulin E.</p> <p><b>Increasing age:</b> Effect is greater in people over age 60 or 64, but data conflict in adults and are more consistent in children.</p> <p><b>Increased height,</b> because of increases in airway mucosal surface area.</p>	<p><b>Cigarette smoking</b> decreases FeNO by 40% to 60%. Magnitude of reduction correlates with the cumulative lifetime cigarette consumption. The effect of cigarette smoking may be reversible, but has not been reported consistently. Smokers with asthma have higher FeNO levels than healthy smokers. In clinical practice, look for intraindividual changes.</p> <p><b>Inhaled steroid use.</b> FeNO generally is sensitive to inhaled steroids and therefore will be low in most patients who are adherent to treatment.</p> <p><b>Alcohol ingestion</b>—Avoid before testing.</p> <p><b>Spirometry</b> may cause a marginal decrease. The effect is of minor importance in clinical practice, but one preferably should measure FeNO before spirometry.</p> <p><b>Certain drugs</b></p> <ul style="list-style-type: none"> <li>• Leukotriene receptor antagonists</li> <li>• Prostaglandins: inhaled prostaglandin E2 and iloprost downregulate inducible nitric oxide synthase expression.</li> </ul> <p><b>Physical exercise</b>—Avoid strenuous exercise before testing.</p> <p><b>UNCERTAIN EFFECT</b></p> <p><b>Menstrual cycle</b>  FeNO levels may vary, but this is not a consistent finding.</p>

Reprinted from Chest 2022; 161(4):906-917, Rupani H, Kent BD. Using fractional exhaled nitric oxide measurement in clinical asthma management, with permission from Elsevier.

etry testing when it is used.<sup>12</sup> Its overall specificity is higher than its sensitivity, which indicates it is more useful for ruling in than for ruling out the diagnosis of asthma.

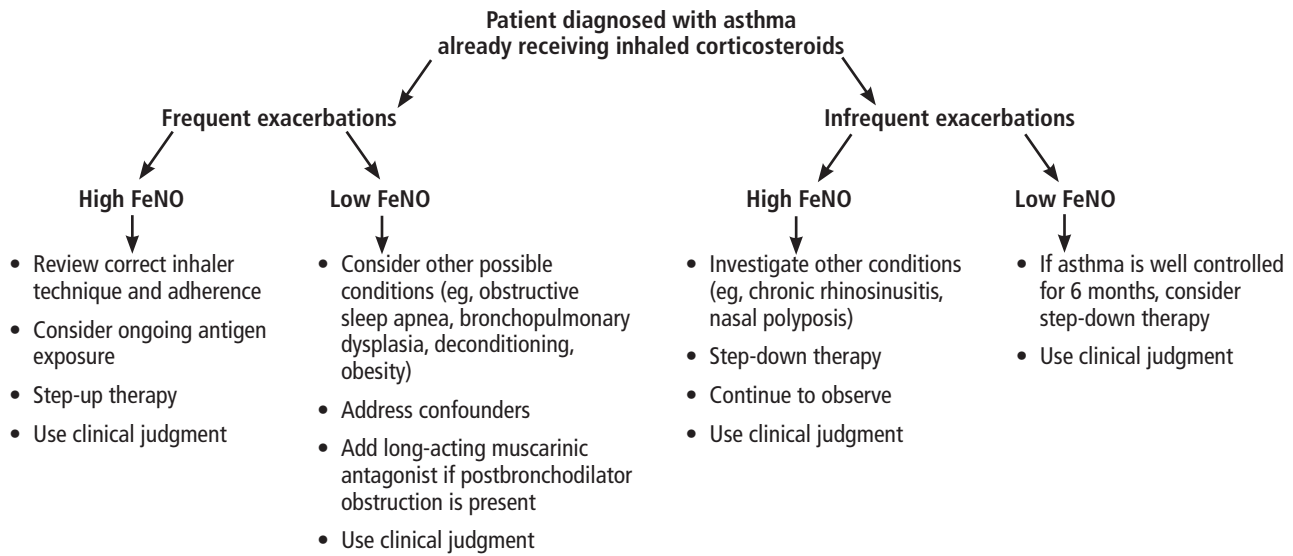
**■ HIGH NITRIC OXIDE PREDICTS RESPONSE TO STEROIDS**

Managing asthma requires addressing environmental factors, ensuring adherence and understanding of the disorder in patients, and partnering with them on goals of care and quality of life. Guidelines recommend increasing the dose of corticosteroids as needed to control symptoms and reduce exacerbations. However, this approach can often lead to patients being on a high dose of corticosteroids without completely attaining benefits.

Like eosinophils in the sputum, nitric oxide in the breath is a good predictor of response to corticosteroid treatment.<sup>21</sup> Smith et al<sup>21</sup> showed that in patients with respiratory symptoms, especially asthma, those with values higher than 47 ppb had a higher likelihood of responding to steroids. High nitric oxide is a better predictor of steroid responsiveness than bronchodilator reversibility, peak flow variability, or airway hyperresponsiveness.<sup>21-23</sup> Patients with high nitric oxide levels who have never taken steroids have a better clinical response to them, manifested as improved symptoms and lung function.<sup>21</sup>

Exhaled nitric oxide is reduced by inhaled corticosteroid therapy, but the magnitude of reduction does not necessarily correlate with clinical response.<sup>24</sup>

Nitric oxide levels can also help to guide step-down treatment with inhaled corticosteroids. A meta-analy-



**Figure 2.** Algorithm for clinical use of measurements of the fractional concentration of exhaled nitric oxide (FeNO).

Adapted from reference 11.

sis revealed that in patients on an inhaled corticosteroid and with FeNO levels less than 50 ppb, reducing the dose gradually did not lead to increased exacerbations. However, reducing the dosage in patients with an FeNO of 50 ppb or higher did lead to increased exacerbations.<sup>25</sup> Generally speaking, for those on inhaled corticosteroids, a high FeNO does not necessarily suggest a benefit from inhaled corticosteroids, but a low FeNO suggests that increasing the inhaled corticosteroid dose may not be useful (Figure 2).<sup>11,26</sup>

### ■ NITRIC OXIDE PREDICTS EXACERBATIONS

The risk of exacerbations also seems to correlate with a higher FeNO in patients with severe asthma. Kupczyk et al<sup>27</sup> found that patients with a baseline FeNO higher than 45 ppb had a rate of exacerbations per year nearly 6 times higher than those with a lower FeNO.<sup>27</sup> Lehtimäki et al<sup>26</sup> performed a systematic review and reported that patients with lower FeNO values while on inhaled corticosteroid therapy “probably” have a low risk of subsequent exacerbations.

The risk of exacerbations can be predicted more accurately by taking peripheral blood eosinophilia into account along with the nitric oxide level. Soma et al<sup>28</sup> found that patients with eosinophil counts of  $0.3 \times 10^9/L$  or higher and FeNO of 25 ppb or higher were more likely to have an exacerbation compared with those with low levels of both.

Data conflict on exactly how useful nitric oxide testing is in predicting exacerbations in patients with severe asthma. Studies in the United Kingdom showed the Asthma Control Questionnaire was a better predictor of exacerbations than nitric oxide.<sup>29</sup> The Liberty Asthma Quest trial<sup>30</sup> and a study in a Japanese cohort<sup>28</sup> with severe asthma showed that the combination of high blood eosinophil counts and a high FeNO could identify patients prone to frequent exacerbations.

In short, measuring nitric oxide has both prognostic and therapeutic value. The National Asthma Education and Prevention Program<sup>15</sup> emphasizes that although nitric oxide measurement can be used in choosing, monitoring, and adjusting steroid therapy, it should be an adjunct to other management and monitoring strategies.

### ■ NITRIC OXIDE SUPPRESSION AS A TEST OF TREATMENT ADHERENCE

In 2014, the definition of severe asthma was updated to distinguish between difficult-to-treat asthma and severe asthma.<sup>31</sup> Asthma is called “difficult to treat” if it remains uncontrolled despite treatment with high-dose inhaled corticosteroids or other controller medications, or requires this level of treatment to remain well controlled. It is called “severe” if it requires treatment with high doses of an inhaled corticosteroid plus

a second controller, systemic corticosteroids, or both to prevent it from becoming uncontrolled, or if it remains uncontrolled despite this therapy. Up to 17% of asthma cases are classified as difficult to treat, and 4% to 8% are considered severe.<sup>32</sup>

Some asthma patients who are prescribed appropriate inhaler therapy and still experience frequent exacerbations are not using their inhalers or are not using them properly. Failure to recognize nonadherence or improper inhaler technique can lead to a vicious cycle of dose escalation and systemic steroid prescriptions, thus leading to potentially avoidable adverse effects of steroid therapy.

Nonadherence to inhaled corticosteroid therapy can contribute to poor asthma control but is sometimes challenging to prove. Measuring nitric oxide after directly observed inhaled corticosteroid administration can serve as an objective method to find out whether patients with difficult-to-treat asthma are adhering to treatment.

In a study in 28 patients with mild asthma, Kharitonov et al<sup>33</sup> found that nitric oxide levels decreased within a few days of starting inhaled corticosteroid therapy, and increased again after steroid withdrawal.

McNicholl et al<sup>34</sup> recruited 22 patients with difficult-to-treat asthma and an FeNO higher than 45 ppb and classified them as adherent or nonadherent based on whether they had filled more than 80% or less than 50% of their prescriptions. After 7 days of directly observed inhaled corticosteroid therapy, the nonadherent patients had a greater reduction in FeNO, to 47% vs 79% of their baseline values ( $P = .003$ ). However, the authors calculated that a 5-day test would work nearly as well as a 7-day test (area under the receiver-operating curve 0.86 vs 0.88). They validated the 5-day test in a larger group of 40 patients using a 42% or greater drop in FeNO as the number to detect nonadherence. Compared with prescription-filling records and plasma steroid levels, the nitric oxide test demonstrated reasonable discriminatory ability (sensitivity 0.67 [95% CI 0.44–0.84] and specificity 0.95 [95% CI 0.78–0.99]).<sup>34</sup>

Therefore, nitric oxide suppression testing may have a role in identifying patients who are not adhering to inhaled corticosteroid therapy and, in particular, those who fill their prescriptions but do not actually take the medication.<sup>35,36</sup>

Devices for measuring FeNO at home have been developed, such as the Niox VERO. A study by Heaney et al<sup>37</sup> showed that using these devices during maintenance inhaled corticosteroid therapy resulted in significant reductions in FeNO and blood eosin-

ophil counts and increases in forced expiratory volume in 1 second and asthma-control questionnaire scores.<sup>37</sup>

Thus, nitric oxide suppression testing may identify patients who may have been labeled as having difficult-to-control asthma but who were not receiving inhaled corticosteroid therapy (due to either nonadherence or poor inhaler technique). These patients may thus be spared escalating steroid doses and subsequent side effects. However, since evidence is sparse in patients without severe asthma, the National Asthma Education and Prevention Program recommends against using nitric oxide as a measure of adherence in them, and the role of nitric oxide suppression for checking adherence is limited to patients with severe asthma.<sup>15</sup>

### ■ NITRIC OXIDE MAY PREDICT RESPONSE TO BIOLOGIC THERAPY

Most studies have used peripheral eosinophilia to characterize the T2-high asthma endotype, but elevated exhaled nitric oxide can also serve as an indicator of a T2-high endotype. Consistent with this, elevated nitric oxide has been shown to predict a favorable response to biologic therapies, and low nitric oxide has been shown to predict less improvement with biologic therapy.<sup>38</sup> This ability to predict response may confer a cost-saving benefit.<sup>39</sup>

Notably, in a post hoc analysis, patients with elevated nitric oxide (FeNO  $\leq 25$  ppb) and peripheral eosinophilia (eosinophil counts  $> 0.150 \times 10^9/L$ ) had a greater reduction in exacerbations with mepolizumab than those with peripheral eosinophilia alone.<sup>40</sup> Patients with high FeNO also derived greater benefit from tezepelumab, although those with an FeNO lower than 25 ppb did have a reduction in exacerbations.<sup>41</sup> McDowell et al,<sup>42</sup> in a prospective observational study, showed that the exhaled nitric oxide level during an exacerbation is useful in discriminating between eosinophilic and noneosinophilic exacerbations in patients treated with mepolizumab. They suggested that nitric oxide be measured during exacerbations and that if FeNO is low ( $\leq 20$  ppb), oral steroids may be of limited utility and antibiotics alone should be considered. Conversely, a high FeNO ( $\geq 50$  ppb) provides support for giving oral steroids.<sup>42</sup>

### ■ ANOTHER TOOL, BUT NOT THE ONLY TOOL

The level of exhaled nitric oxide should be combined with other measures to assess asthma control and should be interpreted within the context of the pretest

**TABLE 2**  
**How is measuring exhaled nitric oxide useful in asthma?**

Elevated fractional concentration of exhaled nitric oxide (FeNO) serves as an adjunct to history, physical examination, and spirometry testing to help with the diagnosis of asthma and is most reliable in patients who have never received steroids.

Conversely, low FeNO can help exclude asthma in the setting of normal spirometry and no suggestive symptoms.

High FeNO is an indicator of a T2-high phenotype and can predict response to inhaled corticosteroids and biologic therapies.

High FeNO is a predictor of increased exacerbation risks and accelerated decline in lung function.

FeNO can be used to monitor adherence and compliance with treatment.

Low FeNO can help to step down asthma treatment with inhaled corticosteroids.

#### Factors limiting the interpretation of FeNO

FeNO should not be used in isolation, and clinical history, physical examination, and spirometry testing should be incorporated.

Many factors other than asthma can raise or lower FeNO (See Table 1).

FeNO is also lower during bronchoconstriction and in the early phases of allergic response.

FeNO can be variable during viral respiratory infections.

probability.<sup>43,44</sup> If there are no confounding factors, a low level of exhaled nitric oxide suggests that a response to corticosteroids is unlikely, whereas a high level suggests that a response to corticosteroids is likely. Ultimately, however, it is the individual clinician who identifies persistent inflammation and decides on initiating or stepping down corticosteroid therapy.

In summary, exhaled nitric oxide should not be the sole tool used to diagnose asthma, although when used

in the right clinical context, it can support the diagnosis of asthma, predict the response to inhaled corticosteroid therapy, monitor compliance, and predict the prognosis of asthma (Table 2). ■

#### DISCLOSURES

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

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# Deadly drug rashes: Early recognition and multidisciplinary care

## ABSTRACT

Potentially deadly drug rashes include Stevens-Johnson syndrome/toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, acute generalized exanthematous pustulosis, and drug-induced vasculitis. Differentiating them can be a challenge. Factors to consider include timing of rash to drug exposure, rash distribution and clinical appearance, and the presence of systemic features such as mucosal involvement, organ failure, or eosinophilia. Various scoring systems aid in the diagnosis, but skin biopsy is the gold standard. Prompt identification and withdrawal of the suspected offending agent are the crucial first steps in management.

## KEY POINTS

Differentiating severe drug rashes involves consideration of timing of drug exposure, clinical appearance of the rash, presence of systemic features, and often skin biopsy.

Early recognition and immediate withdrawal of offending agents is critical to minimize debilitating and potentially life-threatening consequences of severe drug rashes.

Pharmacologic treatment depends on the rash and is controversial, with inconsistent published outcomes. A multidisciplinary approach with supportive measures is key to reducing morbidity and mortality.

**A**DVERSE DRUG REACTIONS (ADRs) are the fifth leading cause of death among all diseases and account for 5% to 10% of hospitalizations worldwide.<sup>1</sup> They remain a challenge in modern healthcare, particularly with increasing complexity of comorbidities and therapeutics.

By definition, ADRs are unintended harmful events attributed to the use of medicines in clinical practice. They are associated with prolonged hospital courses, increased rates of readmission and costs of patient care, and death, and 30% to 45% involve the skin.<sup>1</sup> Risk factors include female sex, older age, higher numbers of drugs, immunocompromised status, and autoimmune disorders.<sup>1</sup>

Identifying the type of drug rash is a challenge. Clinicians are familiar with the clinical features of the 2 most common drug-induced cutaneous reactions, morbilliform drug rash and urticarial rash<sup>2</sup>:

- Morbilliform drug rash, also called exanthematous or maculopapular drug eruption, is the most common, classically presenting with an erythematous maculopapular rash 1 to 2 weeks after a drug exposure
- Urticarial rash, the second most common, presents as annular, pruritic, migratory plaques usually within hours of initial drug exposure.<sup>2</sup>

Cutaneous reaction rates are highest with penicillins, sulfonamides, anticonvulsants, and nonsteroidal anti-inflammatory drugs (NSAIDs), and NSAIDs and salicylates are more commonly associated with urticarial than with morbilliform drug rash.<sup>3</sup> Severe drug rashes are less common but can be life-threat-

**TABLE 1**  
**Characteristics of selected high-risk drug rashes<sup>a</sup>**

Disease	Onset	Skin findings	Hallmarks	Drug triggers	Diagnosis <sup>b</sup>
SJS/TEN	1–3 weeks	Red/purple macules progressing to vesicles, erosions, and ulcerations	Mucous membrane involvement; Nikolsky sign	Allopurinol, antibiotics (particularly sulfonamide), antiepileptics, NSAIDs	SCORTEN
DRESS	2–6 weeks	Generalized maculopapular erythematous rash	Facial edema and redness, eosinophilia, elevated transaminases	Allopurinol, antibiotics, antiepileptics, antiretrovirals, isoniazid, NSAIDs	RegiSCAR
AGEP	48 hours	Generalized maculopapular erythematous rash with pinpoint pustules	Face, trunk, and intertriginous area; tiny pustules often difficult to see	Antibiotics, antimycotics, diltiazem, hydroxychloroquine	EuroSCAR; consider dermatoscopy
Drug-induced vasculitis	1–3 weeks	Palpable purpura	Dependent areas, reverse koebnerization	Allopurinol, amiodarone, antibiotics, beta-blockers, diuretics, metformin, NSAIDs, SSRIs	Evaluate for alternative causes of systemic vasculitis

<sup>a</sup> Treatment starts with immediate identification and cessation of the offending drug.

<sup>b</sup> Consider skin biopsy to further support diagnosis for all these rashes.

AGEP = acute generalized exanthematous pustulosis; DRESS = drug reaction with eosinophilia and systemic symptoms; EuroSCAR = European Study of Severe Cutaneous Adverse Reactions; NSAIDs = nonsteroidal anti-inflammatory drugs; RegiSCAR = Registry of Severe Cutaneous Adverse Reactions; SCORTEN = Severity-of-Illness Score for Toxic Epidermal Necrolysis; SJS/TEN = Stevens-Johnson syndrome/toxic epidermal necrolysis; SSRIs = selective serotonin reuptake inhibitors

ening. Early recognition and prompt immediate withdrawal of the suspected drug is crucial.

This article reviews the distinguishing features of 4 severe drug rashes, summarized in **Table 1**: Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), and drug-induced vasculitis.

**■ STEVENS-JOHNSON SYNDROME/TOXIC EPIDERMAL NECROLYSIS**

SJS and TEN are overlapping conditions characterized by mucocutaneous reactions with epidermal necrosis and detachment. The conditions are classified into 3 categories of severity based on the percentage of body surface involved:

- SJS: lesion area is less than 10%
- SJS/TEN overlap: lesion area is 10% to 30%
- TEN: lesion area is greater than 30%.

The estimated overall incidence of SJS/TEN in Europe and the United States is up to 6 cases per million person-years. The rates are higher in adults, females, and people of Asian or Black ethnicity. The

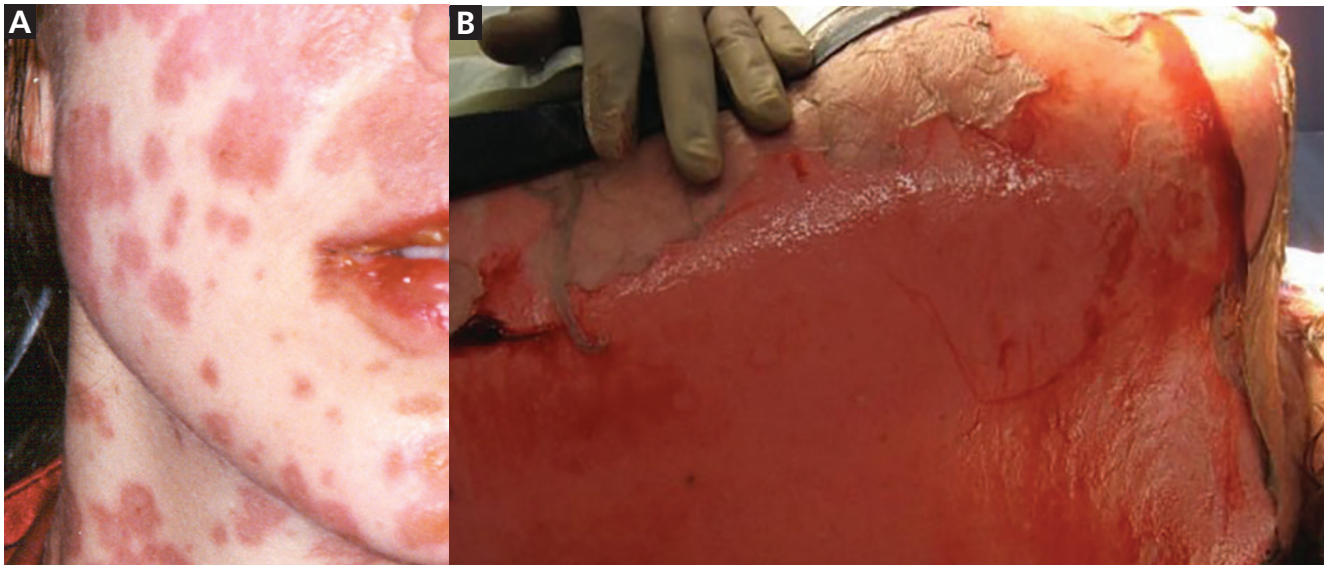
most common inciting drugs are allopurinol, antibiotics (particularly sulfonamide antibiotics), antiepileptics, and NSAIDs.<sup>4</sup> Immune checkpoint inhibitors, which are increasingly prescribed for malignancy, are associated with severe cutaneous drug eruptions, including SJS/TEN.<sup>5</sup>

**Symptom onset after 1 to 3 weeks**

Rash onset is usually 1 to 3 weeks after drug introduction. Typically, lesions appear first on the face and thorax before spreading symmetrically. They start as macules and target-like lesions with erythema and dark necrotic centers and develop into vesicles, erosions, or ulcerations with epidermal detachment. They often have a positive Nikolsky sign, ie, where traction pressure causes epidermal shearing and erosion (**Figure 1**).<sup>6</sup>

**Systemic manifestations**

Systemic manifestations are common and include flu-like symptoms, fever, lymphadenopathy, and mucosal involvement (conjunctival, oropharyngeal, esophageal, and genital). Mucosal involvement occurs in up to 90% of patients, and mouth ulcers, grittiness in the eyes, odynophagia, and dysuria are common.<sup>4,6</sup>



**Figure 1.** (A) Macules and target-like lesions with erythema and dark necrotic centers in Stevens-Johnson syndrome. (B) Positive Nikolsky sign with epidermal shearing in Stevens-Johnson syndrome.

The most clinically significant elements of mucosal involvement are the sequelae of mucosal ulceration that result in scarring and stricture, which affect several organ systems—namely, the cornea, urethra, esophagus, and pulmonary tract. Severe complications of SJS/TEN include respiratory failure, shock, functional volume depletion, and infections. The average mortality rate is 1% to 5% in SJS and 25% to 35% in TEN.<sup>4,7</sup>

### Diagnosis

The diagnosis of SJS/TEN is based on a history of drug exposure along with clinical evidence of classic mucocutaneous lesions. The gold standard for diagnosis is skin biopsy with routine histopathology and direct immunofluorescence studies. Biopsy can be helpful even in early stages if the diagnosis is uncertain, but it is more definitive in later stages with the hallmark manifestations of full-thickness necrosis and subepidermal detachment. Biopsy at this later stage helps exclude diagnoses that mimic SJS/TEN. These include staphylococcal scaled-skin syndrome and other generalized rashes with blisters, such as exfoliative erythroderma, bullous pemphigoid, pemphigus vulgaris, and linear immunoglobulin A dermatosis.<sup>8</sup>

### Supportive care and prompt referrals are essential

The first and most important step in management of a patient with SJS/TEN is immediate identification and withdrawal of the suspected offending medications.

Prompt withdrawal of the causative agent before erosions and blisters develop significantly reduces the risk of death.<sup>9</sup> The SCORTEN tool (Severity-of-Illness Score for Toxic Epidermal Necrolysis) includes prognostic indicators such as heart rate, age, and renal function and can be used to determine a patient's risk of death with SJS/TEN (Table 2).<sup>4,10</sup>

The mainstay of treatment is supportive care: intravenous fluids, electrolyte replacement, nutritional support, pain control, and prevention of infection. Interval skin cultures and blood cultures can aid in early detection and treatment of superinfection.<sup>11</sup> Prompt referral to burn units and specialists (eg, ophthalmology, urology) based on organ involvement is indicated.

Treatment with corticosteroids is controversial, but intravenous immunoglobulin (IVIG) therapy alone or in combination with corticosteroids has shown varying degrees of success.<sup>12,13</sup> Other options include plasmapheresis, immunosuppressive agents (cyclosporin, cyclophosphamide, thalidomide), or various combinations of these options and any of the above treatments.<sup>14</sup> Prophylactic systemic antibiotics should be avoided unless a workup for infection raises concern for bacterial superinfection.<sup>15</sup>

### ■ DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS

DRESS is a delayed-onset multiorgan reaction. The onset is usually 2 to 6 weeks after initiation of medi-

**TABLE 2**  
**Severity-of-illness Score**  
**for Toxic Epidermal Necrolysis (SCORTEN)**

SCORTEN parameter	Point
Age ≥ 40	1
Malignancy	1
Heart rate ≥ 120 beats per minute	1
Initial surface of epidermal detachment > 10%	1
Serum urea > 10 mmol/L	1
Serum glucose > 14 mmol/L	1
Bicarbonate ≤ 20 mmol/L	1
Total score	Predicted mortality risk (%)
0–1	3.2
2	12.1
3	35.8
4	58.3
> 5	90

Adapted from information in references 4 and 10.

cation, although a rash can be seen earlier with medications such as antibiotics.<sup>16</sup> The incidence is 1 in 1,000 to 10,000 drug exposures, and it is responsible for about 18% of inpatient adverse drug reactions that affect the skin.<sup>17,18</sup> The most common offending drugs include antiepileptics (carbamazepine, phenytoin, lamotrigine, phenobarbital), allopurinol, sulfonamides (sulfasalazine, dapsone, trimethoprim-sulfamethoxazole), minocycline, vancomycin, and antituberculosis agents (isoniazid, rifampicin, ethambutol, pyrazinamide).<sup>19</sup>

**Fever, rash, facial edema, eosinophilia**

DRESS often starts with fever and a rash, characterized as a nonspecific severe pruritic skin eruption affecting more than 50% of the body surface area. Patients often develop severe facial edema that is central with peri-orbital sparing. The rash is usually maculopapular, but lesions are polymorphous and can present as plaques, blisters, target-like lesions, urticaria, exfoliation, eczema, or, rarely, lichenoid eruptions (Figure 2).

In addition to rash and fever, other manifestations may include lymphadenopathy, hematologic abnormalities, and internal organ involvement (most commonly liver, kidney, lung, and cardiac injury). Up to 95% of patients with DRESS have eosinophilia.<sup>20</sup> With a prolonged clinical course, sequential reactivation of various human herpesviruses (particularly type 6 and type 7) and, less frequently, Epstein-Barr virus and cytomegalovirus infections, may be seen.<sup>21</sup>

The course can wax and wane with multiple flares. The average mortality rate is 4% to 10% from multi-organ failure (most commonly hepatic necrosis),<sup>22</sup> with long-term complications that include exfoliative dermatitis,<sup>23</sup> acute necrotizing eosinophilic myocarditis, and autoimmune sequelae such as thyroid disease, vitiligo, alopecia areata, lupus erythematosus, autoimmune hemolytic anemia, and fulminant type 1 diabetes mellitus.<sup>22–25</sup>

**RegiSCAR: Resource for diagnostic criteria**

The clinical presentation of rash, eosinophilia, and internal organ involvement should prompt an evaluation for possible DRESS. The RegiSCAR criteria (Registry of Severe Cutaneous Adverse Reactions) are the most detailed and frequently used diagnostic criteria (Table 3).<sup>21</sup> Follow-up bloodwork should be obtained based on suspected organ involvement. Histopathology for DRESS is nonspecific and includes spongiosis, basal vacuolization, necrotic keratinocytes, dermal-epidermal infiltrates, dermal edema, and perivascular infiltrates of lymphocytes with or without eosinophils.<sup>7,21</sup>

Identifying the causative agent may be a challenge because of the delayed presentation after drug exposure. Lymphocyte transformation testing is the most reliable in vitro method to confirm the causative drug, and is particularly useful for confirming anticonvulsant and antituberculosis therapies. It assesses activation of drug-specific T cells with 73% sensitivity and 82% specificity, but must be performed 2 to 6 months after the acute phase.<sup>21,26</sup> In vivo skin testing, particularly patch testing and delayed intradermal testing, can also be useful in identifying the causative drug.<sup>21,26</sup>

**Multidisciplinary management**

Management of DRESS requires a multidisciplinary approach based on organ involvement and severity. If the patient has mild disease with a modestly elevated transaminase (< 3 times upper limit of normal), treatment is symptomatic with topical corticosteroids.<sup>27</sup> Moderate- to high-dose systemic corticosteroid therapy is the treatment of choice for severe disease. For corticosteroid-resistant patients, IVIG and Janus kinase inhibition have shown some success. Other alternatives include immunosuppressive agents (cyclophosphamide, cyclosporine, interferons, mycophenolate mofetil, rituximab), antivirals, and plasmapheresis. Antibiotics and antipyretics should be avoided unless there is definite evidence of infection.<sup>21</sup>



**Figure 2.** (A) A maculopapular rash in a drug reaction with eosinophilia and systemic symptoms. (B) Lesions may also present as plaques, blisters, or target-like lesions.

### ■ ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS

AGEP is a severe rapid cutaneous pustular reaction that usually occurs within 48 hours of drug exposure. Its incidence is 1 to 5 cases per million person-years, and common causative drugs are antibiotics, antimycotics, hydroxychloroquine, and diltiazem.<sup>28</sup>

#### Abrupt presentation

AGEP presents abruptly with hundreds of pinhead-size pustules on a background of diffuse edematous erythema (Figure 3). It usually starts in the intertriginous folds or on the face, or both, and later spreads to the trunk and extremities. Lesions can cause burning and pruritus, and mucosal involvement is rare.

The rash is associated with fever, leukocytosis (predominantly neutrophilia), elevated C-reactive protein level, and in 20% of patients, multiorgan involvement.<sup>29</sup> Pustules resolve spontaneously within a few weeks and are followed by postpustular pinpoint desquamation described as collarette-shaped. The overall mortality rate is less than 5%, mostly from complications such as skin superinfection, multiorgan dysfunction, and disseminated intravascular coagulation.<sup>7,29</sup>

#### Dermoscopy enhances early diagnosis

The EuroSCAR diagnostic score (European Study of Severe Cutaneous Adverse Reactions) can be used to define clinical and diagnostic criteria (Table 4).<sup>30</sup> Pustules are often difficult to visualize, but dermoscopy with a magnifier and polarized light can enhance early diagnosis with detection of pustules at an early stage.

Skin biopsy usually reveals intracorneal, subcorneal, and intraepidermal pustules with papillary dermal edema and infiltrates with neutrophils and eosinophils, occasionally including epidermal changes such as spongiosis with necrotic keratinocytes. When the cause of AGEP is unclear, patch testing after resolution of the symptoms may be an option.<sup>29</sup>

Prevention of infection with moist dressings and antiseptic solutions is recommended during the pustular phase. In prolonged cases, topical corticosteroids may help relieve symptoms and decrease duration of hospitalization. Antibiotics should be avoided in the absence of superinfection.<sup>29</sup>

### ■ DRUG-INDUCED VASCULITIS

Drug-induced vasculitis is typically a small-vessel vasculitis related to the immune complex-mediated reaction of the dermal capillaries and venules. Drug-induced vasculitis is usually limited to cutaneous vasculitis and arthralgia but, rarely, it can present as severe multiorgan involvement that can mimic primary systemic vasculitis.<sup>31</sup> Drug-induced vasculitis typically presents 1 to 3 weeks after drug initiation and is usually self-limited. The most common causative drugs are antibiotics, sulfonamides, diuretics, allopurinol, NSAIDs, amiodarone, beta-blockers, selective serotonin reuptake inhibitors, and metformin.<sup>32</sup>

The usual presentation is nonblanching palpable petechiae and purpura (Figure 4). The rash is commonly bilateral on dependent areas of the body and sometimes develops into hemorrhagic vesicles and



**TABLE 3**  
**Registry of Severe Cutaneous Adverse Reactions diagnostic criteria for drug reaction with eosinophilia and systemic symptoms**

Criteria <sup>a</sup>	Score <sup>b</sup>		
	No	Yes	Unknown
1) Acute skin eruption			
a) More than 50% body surface area affected	0	+1	0
b) Rash characteristic of DRESS	-1	+1	0
c) Biopsy suggesting DRESS	-1	0	0
2) Fever > 38.5°C	-1	0	-1
3) Lymphadenopathy (> 1 site, > 1 cm)	0	+1	0
4) Internal organ involvement <sup>c</sup>	0	+1	0
5) Eosinophilia			
a) Eosinophils 700–1,499, or 10%–19.9% if leukocytes < 4.0 x 10 <sup>9</sup> L		+1	
b) Eosinophils > 1,500 or > 20% if leukocytes < 4.0 x10 <sup>9</sup> L		+2	
6) Atypical lymphocytes	0	+1	0
7) Thrombocytopenia			
<b>Additional parameters</b>			
Resolution in > 15 days	-1	0	-1
Exclusion of: antinuclear antibodies, blood culture, serology for hepatitis A, B, and C, chlamydia, or mycoplasma		+1	

<sup>a</sup>Diagnosis requires 3 or more criteria.

<sup>b</sup>Likelihood of diagnosis based on total score: < 2 = no; 2–3 = possible; score 4–5 = probable; score > 5 = definite.

<sup>c</sup>Maximum of 2 points.

DRESS = drug reaction with eosinophilia and systemic symptoms

Adapted from information in reference 21.

bullae, pustules, nodules, crusted ulcers, or livedo reticularis. Koebnerization, the appearance of lesions at areas of trauma, is uncommon, but reverse koebnerization has been described with the disappearance of the lesions with pressure bandaging following the skin biopsy.<sup>32</sup>

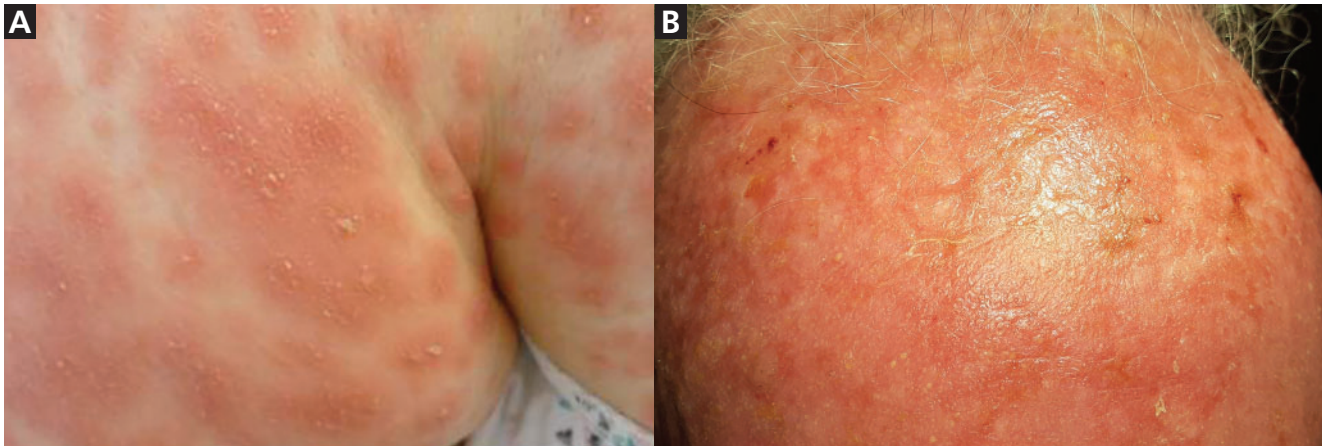
Approximately 30% of patients present with extracutaneous involvement such as arthralgias or renal, gastrointestinal, pulmonary, or neurologic symptoms.<sup>32</sup> The mortality rate, about 2%, is usually related to systemic involvement.<sup>32</sup>

**Consider alternative causes**

Diagnosis of a drug-induced vasculitis should be guided by the clinical presentation with consideration of alternative causes of systemic vasculitis. A reasonable workup includes basic laboratory testing, infectious serologies

(hepatitis B and C, human immunodeficiency virus), serum protein electrophoresis, direct immunofluorescence studies with immunoglobulins (IgG, IgA, IgM), antinuclear antibodies, rheumatoid factor, serum complement levels, antineutrophil cytoplasmic antibodies, and cryoglobulins. Definitive diagnosis can be confirmed with skin biopsy that typically shows any of the following:

- Evidence of neutrophilic infiltration within and around the vessel wall with the signs of “clear dust” or leukocytoclasia (disintegration of neutrophil nuclei into fragments)
- Fibrinoid necrosis or fibrin deposition within and around the vessel wall
- Signs of damage to the vessel wall and surrounding tissue such as damaged endothelial cells or extravasated red blood cells.



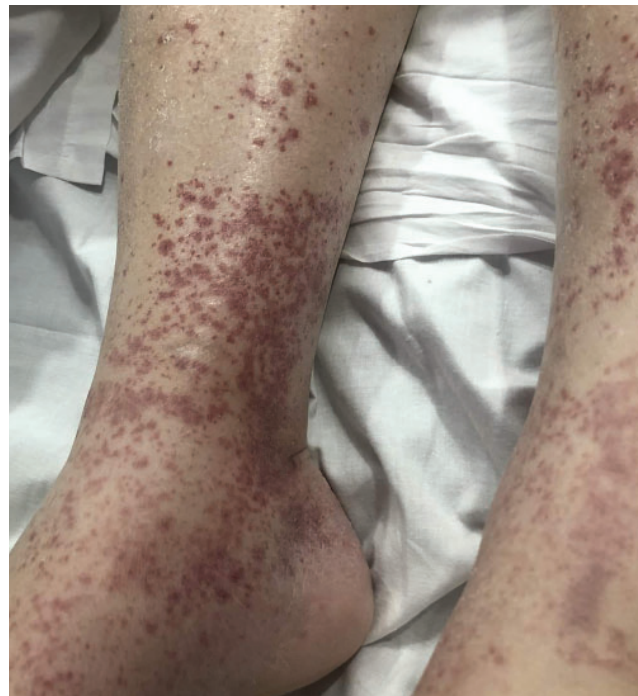
**Figure 3.** (A) Pustules and diffuse edematous erythema in a patient with acute generalized exanthematous pustulosis affecting intertriginous folds and, (B) a patient's forehead.

When drug-induced vasculitis is suspected, the causative agent should be discontinued immediately. In most cases, the condition is self-limited and responds to supportive care and symptomatic relief including rest, elevation if a dependent extremity is affected, and use of compression stockings. In severe cases, corticosteroids usually bring a rapid response. Other options are colchicine, dapsone, hydroxychloroquine, and NSAIDs. In patients with underlying systemic vasculitis, immunosuppressive medications (azathioprine, methotrexate, mycophenolate mofetil), biologics, or plasma exchange can be considered.<sup>33</sup>

#### ■ GENERAL APPROACH: IDENTIFY, CONFIRM, GIVE SUPPORTIVE CARE

The most important clues for identifying and differentiating among deadly drug rashes are in the history, timing of exposure, and the bedside physical examination. While there is overlap, severe drug rashes have distinguishing features and characteristics, reviewed in **Table 1**.

Generally, when a severe drug rash is suspected, immediate identification and withdrawal of the suspected offending medication is indicated. To aid and support the diagnosis, especially in cases of uncertainty, a definitive diagnosis is often confirmed with skin biopsy. Because of the potential for life-threatening complications and sequelae, management starts immediately with supportive measures: intravenous maintenance fluid, nutritional supplementation, and consultations with burn units or other specialists to minimize long-term sequelae such as ocular, renal, lung, liver, or genitourinary involvement. Specific medical management is complicated and varies depending on the patient and the specific rash.



**Figure 4.** Rash associated with drug-induced vasculitis. Bilateral presentation on dependent areas of the body is common.

#### ■ PREVENTION IS A CHALLENGE

Preventing severe drug rashes is challenging, although gathering a thorough history of past severe adverse drug reactions can help decrease risk of future harm.

There may be a role for human leukocyte antigen testing in prevention of severe adverse drug reactions, as shown in the following 2 examples:

**TABLE 4**  
**European Study of Severe Cutaneous Adverse Reactions scoring system for acute generalized exanthematous pustulosis<sup>a</sup>**

Rash	Typical	Compatible	Insufficient	Clinical course	Yes	No
Pustules	+2	+1	0	Mucosal involvement	-2	0
Erythema	+2	+1	0	Acute onset < 10 days	0	-2
Distribution/pattern	+2	+1	0	Resolution < 15 days	0	-4
				Fever > 38.75 °C	+1	0
Postpustular desquamation	If yes, +1	If no, 0		Polymorphonuclear neutrophils > 7,000/mm <sup>3</sup>	+1	0
<b>Histology</b>						
Other disease					-10	
Not representative, or no histology					0	
Exocytosis of polymorphonuclear cells					+1	
Subcorneal and/or intraepidermal nonspongiform pustule(s) or pustule(s) not otherwise specified (NOS) with papillary edema; or subcorneal and/or intraepidermal spongiform or NOS pustule(s) without papillary edema					+2	
Spongiform subcorneal and/or intraepidermal pustule(s) with papillary edema					+3	

<sup>a</sup> Likelihood of acute generalized exanthematous pustulosis based on total score: ≤ 0 = no; 1–4 = possible; 5–7 = probable; ≥ 8 = definite.

Adapted from information in reference 30.

The HLA-B\*5801 allele is associated with a markedly elevated risk of allopurinol hypersensitivity syndrome. The prevalence of this allele is highest among persons of Han Chinese, Korean, and Thai descent (7.4%) and African Americans (3.8%).<sup>34</sup> The American College of Rheumatology conditionally recommends testing for the HLA-B\*5801 allele in these higher risk populations before starting allopurinol.<sup>34</sup>

The HLA-B\*1502 allele is almost exclusively seen in patients with Asian ancestry, and these patients have a higher risk of SJS and DRESS with antiepi-

leptic agents.<sup>35</sup> The US Food and Drug Administration recommends screening these at-risk populations before starting carbamazepine, oxcarbazepine, and possibly phenytoin. Future studies are likely to identify other genetic testing that could limit provocation of serious cutaneous adverse drug reactions. ■

**DISCLOSURES**

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

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