Hailey-Hailey disease is an autosomal dominant blistering dermatosis due to a mutation in the ATP2C1 gene (OMIM 604384). This gene encodes a calcium ATPase present on the Golgi apparatus contributing to the formation of intercellular adhesions. Disruption of this enzyme results in acantholysis, which is most clinically pronounced in intertriginous areas that are subject to heat, friction, sweating, and bacterial colonization. Hailey-Hailey disease can have spontaneous periods of clinical improvement; however, the disease often has a long-term course and treatment can be challenging. Because there is currently no cure for this condition, most therapies aim to minimize the influence of exacerbating factors.

Report of a Case
A man in his 50s presented with a 30-year history of intermittent flares of pruritic and painful intertriginous lesions. On physical examination, the patient had erythematous, macerated plaques with superficial erosions on the bilateral axillae, inguinal, and crural folds and a few smaller papules on the lateral neck (Figure, A). The patient’s medical history was notable for atrial fibrillation, which was well controlled with digoxin. A skin biopsy revealed acanthosis with elongation of rete ridges and overlying focal parakeratosis. Areas of full and partial thickness acantholysis were noted. The clinical and histopathologic features were consistent with a diagnosis of Hailey-Hailey disease.

Therapeutic Challenge
The patient had been prescribed various topical corticosteroid and antifungal creams as well as oral antibiotics in the past with minimal improvement.

Solution
The patient was started on a combination regimen of topical mometasone ointment, 0.1%, once daily, oral minocycline, 50 mg twice daily, and a trial of oral glycopyrrolate, 1 mg daily, with approval from the patient’s cardiologist. After 1 month of this course of therapy, the patient demonstrated moderate improvement of his lesions but requested a simplified treatment plan. At this point, therapies with minocycline and the topical corticosteroid were discontinued, but glycopyrrolate monotherapy was maintained. Over the next month, the patient’s condition fully cleared, and he has remained symptom-free for 6 months (Figure, B). Prior to this, the patient’s disease course involved numerous flares throughout the year; this relatively long symptom-free period was a substantial improvement. While he did note some mild xerostomia, he has otherwise tolerated glycopyrrolate without any significant adverse effects.

Discussion
The mutation in the ATP2C1 gene in Hailey-Hailey disease produces an abnormal calcium pump on the Golgi bodies of keratinocytes. This
calcium pump leads to increased intracellular calcium, which has been demonstrated to cause an adenosine triphosphate (ATP) depletion. Actin polymerization, an ATP-dependent process, is important in the formation of adherens junctions between keratinocytes; therefore, intracellular calcium dysregulation and ATP depletion can lead to weak cell-to-cell interactions resulting in characteristic bullous lesions. Lesions typically present in puberty but may manifest later. The eruption has a predilection for intertriginous areas, and known factors (ie, heat, friction, secondary infections) exacerbate the disease. Meditations and therapeutic interventions, which can mitigate the effects of these precipitants, have been used to reduce disease activity.

Nonpharmacologic therapies have demonstrated some benefit in the treatment of Hailey-Hailey disease. Hamada et al observed significant clinical improvement in a patient with refractory disease, who was treated with narrow-band UV-B therapy. The use of nonablative lasers such as the long-pulsed alexandrite laser for anti-inflammatory effects and ablative carbon dioxide laser for resurfacing have also demonstrated benefit in recalcitrant cases. While long-term control can be achieved with laser procedures, multiple sessions may be required for optimal efficacy.

Treatment with tetracyclines, namely doxycycline, is helpful in the management of lesions in Hailey-Hailey disease. Because of antibacterial and anti-inflammatory properties, tetracyclines can help limit disease exacerbations. This class of antibiotics is especially useful in the control of macerated lesions in intertriginous areas, which are presumed to have an increased bacterial load.

Topical corticosteroids are also frequently used in the treatment of Hailey-Hailey disease owing to their anti-inflammatory properties. They have been shown to decrease protease activity; however, the application of topical steroids is limited by potential adverse effects associated with long-term use.

Bessa et al, Koeyers et al, and Lapiere et al reported on the beneficial effects of intralesional botulinum toxin type A as a means of decreasing sweat secretion and reducing active lesions. Reduction in sweating by neuromodulators is achieved by inhibition of the sympathetic stimulus to the eccrine gland. Botulinum toxin type A causes degradation of proteins required for the release of acetylcholine and stimulation of perspiration. The postulated mode of improvement in Hailey-Hailey disease in response to botulinum toxin type A involves decreased microorganism colonization and friction as a result of less moisture in the areas of involvement. While efficacious, numerous injections are required at each affected site and treatments are expensive.

Hyperhidrosis is more traditionally managed with the use of topical preparations and systemic anticholinergic medications. Glycopyrrolate (glycopyrronium bromide [Robinul; Shionogi Inc]) is a systemic anticholinergic with a short half-life (0.8 hours) that inhibits the sympathetic stimulation of eccrine sweat glands by blocking the M3 muscarinic receptors on glandular tissue. These receptors are the site of action of acetylcholine after release from the presynaptic terminal. Glycopyrrolate has been shown to be a safe and effective treatment of hyperhidrosis and exhibits less central nervous system adverse effects than other anticholinergic medications because of its inability to cross the blood-brain barrier. However, glycopyrrolate can cause other systemic adverse effects such as dry mouth, mydriasis, increased intraocular pressure, tachycardia, decreased gastric motility and secretion, constipation, and urinary retention, and it is contraindicated for patients with myasthenia gravis, paralytic ileus, and pyloric stenosis.

Patients with cardiovascular disease, gastroesophageal reflux, bladder obstructions, and glaucoma can use glycopyrrolate but should proceed with treatment cautiously. Glycopyrrolate is also relatively inexpensive and on most drug formularies. In our patient, a trial of low-dose glycopyrrolate, 1 mg daily, was initially instituted as part of a combination regimen and was continued as a single agent. Systemic glycopyrrolate was an effective, affordable, and well-tolerated medication, which produced significant improvement and sustained clearance of Hailey-Hailey disease in our patient. While dosing should be titrated to the individual needs of the patient, the currently recommended daily maximum dose of glycopyrrolate is 8 mg. In the future, trials may include the use of topical glycopyrrolate as maintenance therapy, which could provide similar therapeutic benefit with an even milder adverse effect profile. This case demonstrates a novel application for oral glycopyrrolate as a potential adjuvant or single agent maintenance therapy in the management of Hailey-Hailey disease.

REFERENCES