

JAMA Dermatology

Research

Original Investigation

265 Purse-String Suture vs Second Intention Healing: Results of a Randomized, Blind Clinical Trial
J Joo and Coauthors

271 Multicenter Prospective Cohort Study of the Incidence of Adverse Events Associated With Cosmetic Dermatologic Procedures: Lasers, Energy Devices, and Injectable Neurotoxins and Fillers
M Alam and Coauthors

278 Use of a Picosecond Pulse Duration Laser With Specialized Optic for Treatment of Facial Acne Scarring
JA Brauer and Coauthors

285 Cellular Basis of Secondary Infections and Impaired Desquamation in Certain Inherited Ichthyoses
A Chan and Coauthors

293 Learning to Detect, Categorize, and Identify Skin Lesions: A Meta-analysis
L Rourke and Coauthors

302 Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: Ear, Nose, and Throat Description at Acute Stage and After Remission
E Baquignon and Coauthors

Case Report/Case Series

308 Newly Described Features Resulting From High-Magnification Dermoscopy of Tinea Capitis
F Lacarrubba and Coauthors

311 Acute Generalized Exanthematous Pustulosis Caused by Dihydrocodeine Phosphate in a Patient With Psoriasis Vulgaris and a Heterozygous *IL36RN* Mutation
N Nakai and Coauthors

316 Gadolinium-Associated Plaques: A New, Distinctive Clinical Entity
RM Gathings and Coauthors

Opinion

Viewpoint

257 Chikungunya: Emerging Threat to the United States
LV Stamm

Editorial

259 Experience vs Experiments With the Purse-String Closure: Unexpected Results
IA Maher and Coauthors

Invited Commentary

327 Enhancing the Role of Physical Therapy in Venous Leg Ulcer Management
J McCulloch and Coauthors

Clinical Review & Education

Review

320 Effect of Physical Therapy on Wound Healing and Quality of Life in Patients With Venous Leg Ulcers: A Systematic Review
E Yim and Coauthors

The Cutting Edge

328 Oral Glycopyrrolate for the Treatment of Halley-Halley Disease
M Kantszewska and Coauthors

JAMA Dermatology Clinicopathological Challenge

331 Chronic Ulceration and Fibrosis of the Forearm
E Rozas-Muñoz and Coauthors

333 Nonhealing Tongue Ulcer in an Indian Man
K Maharaja and Coauthors

335 Eroded and Pedunculated Buttock Nodule
KI Mosejane and Coauthors

Continuing Medical Education

355 Online CME Quiz Questions

JAMA Dermatology Patient Page

356 Lichen Planus

LETTERS

Research Letter

339 Teledermatology Perception Differences Between Urban Primary Care Physicians and Dermatologists
OA Ogbachie and Coauthors

340 Standardized Patient-Based Assessment of Dermatology Resident Communication and Interpersonal Skills
S Wang and Coauthors

342 Family Risk Discussions After Feedback on Genetic Risk of Melanoma
JL Hay and Coauthors

Observation

343 Coexistence of Staphylococcal Scalded Skin Syndrome and Acute Graft-vs-Host Disease
C Thomas and Coauthors

345 Cyclosporine in the Management of Poststreptococcal Pustulosis
P Fleming and JC Shaw

346 In Vivo Imaging of Miliaria Profunda Using High-Definition Optical Coherence Tomography: Diagnosis, Pathogenesis, and Treatment
HL Tey and Coauthors

348 Birt-Hogg-Dubé Syndrome in an African Patient and a Novel Mutation in the *FLCN* Gene
EN Pritchett and Coauthors

Comment & Response

349 Indications and Limitations of Afamelanotide for Treating Vitiligo

Issue Highlights and Continued Contents on page 245



K⁺larity for Spironolactone At Last!

Emmy M. Graber, MD, MBA

Spironolactone was approved by the US Food and Drug Administration (FDA) 30 years ago for several noncutaneous conditions, such as congestive heart failure. It acts as an



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aldosterone antagonist and thereby promotes diuresis, reduces blood pressure, and retains potassium.¹ Aside from these mechanisms of action, spironolactone also exerts several antiandrogenic effects in the skin. Spironolactone decreases sebum production by competing with both dihydrotestosterone (DHT) and testosterone for the androgen receptors and also halts the conversion of testosterone to the more potent sebum producer DHT. In addition, spironolactone decreases type 2 17 β -hydroxysteroid dehydrogenase and thereby inhibits androgen synthesis.² These antiandrogenic actions make spironolactone well suited to treat androgen-driven cutaneous disorders, such as acne.

Although spironolactone is not FDA approved to treat acne, there are many of us who regularly prescribe spironolactone for acne with great success. Adult female acne, which is hormonally driven, is particularly pronounced on the lower face, jawline, and neck. Such hormonal acne is often described as flaring in a cyclical nature—either just before or just after menses. For patients who may fit into this clinical picture, spironolactone can be especially useful.

Studies evaluating the efficacy for spironolactone are sparse, but those that exist are compelling. One prospective study³ of 64 women prescribed spironolactone found that in all, acne improved to some degree and over half of them were clear after spironolactone use. Another smaller study⁴ followed 27 women with severe acne and found that 85% were entirely clear or had “excellent” results (>75% clearance) at 6 months. Because of the paucity of data, the efficacy of spironolactone for acne treatment is considered indeterminate by the Cochrane Database.⁵

Because some studies suggest superb results with spironolactone, and with the push to limit oral antibiotic use, why would dermatologists not prescribe spironolactone for adult hormonal acne? I suspect that many physicians balk at giving spironolactone owing to fear of adverse effects. The potential adverse effects include breast tenderness, menstrual irregularities, hypotension, and the oft-feared hyperkalemia. Concomitant oral contraceptive use can offset any breast tenderness and menstrual irregularities. Hypotension is rare and minimal—only an average 5% drop in blood pressure may be noted in otherwise healthy individuals.⁶ Hyperkalemia from any etiology, when severe enough, can cause cardiac arrhythmias and death.

Wait...What? Cardiac arrhythmias and death? Is spironolactone prescribing not for the faint at heart? Is this fear of hyperkalemia with spironolactone use founded on evidence, or is this concern unjustified?

Prior to the report by Plovianich et al⁷ in this issue of *JAMA Dermatology*, only a few studies supported the safety of spironolactone in otherwise healthy patients. Shaw et al⁶ found a clinically insignificant increase in potassium in 10% of 85 patients. In another study, no hyperkalemia was seen in 35 patients, all of whom were prescribed spironolactone at a dosage 100 mg per day.⁸

Many patients prescribed spironolactone concomitantly take an oral contraceptive pill. The newer generation of oral contraceptives containing the progestin drospirenone may theoretically increase the risk of hyperkalemia because they are also aldosterone antagonists. A study⁴ looking at 27 patients prescribed both spironolactone and drospirenone-containing oral contraceptives found no cases of hyperkalemia. Despite the intriguing results of this study⁴ and others, their small sample size undermines the findings.

Finally, Plovianich et al⁷ provide us with a large, well-designed study to assuage our fears of hyperkalemia. Their results showing no increased risk of hyperkalemia in patients with acne prescribed spironolactone will surely change the way many clinicians practice. However, it should be noted that the patients with acne in their study⁷ included only “young healthy females,” and those with cardiac disease, renal disease, or prescribed medications potentiating the risk of hyperkalemia were excluded. While the physician may feel reassured that he or she does not need to check potassium levels in otherwise healthy individuals, one should do a thorough review of a patient’s medications and medical history to ensure safety with spironolactone use.

Still, some dermatologists may not feel comfortable prescribing spironolactone despite the now-palliated fears of hyperkalemia. What about spironolactone’s potential to cause feminization of male fetus genitalia, and what about the black box warning on spironolactone? In a study⁹ in which pregnant rats were treated with 5 times the human dose of spironolactone, male offspring showed evidence of genital feminization, yet no human studies support this risk. MicroMedex,¹⁰ a collection of different drug databases, finds the “magnitude of teratogenic risk to a child born after spironolactone exposure during gestation to be undetermined.” MicroMedex does comment that the quality and quantity of data on which this risk estimate is based is “very limited.” In regard to the black box warning, the manufacturer recommends avoiding

“unnecessary use” as spironolactone has been shown to induce endocrine tumors in rats.¹¹ However, such studies may not be comparable with human use. Rats given spironolactone for 2 years at 10 to 500 times the human dose showed increased risk of tumors (although many were benign adenomas) of the breast, liver, and myeloid leukocytes.¹² Although extrapolated from exorbitantly high dosages in rats, these results led manufacturers to include a black box warning recommending avoidance of long-term spironolactone use. Despite suggestions that there may be an increased risk of some endocrine tumors, there exists no association between spironolactone use and breast cancer.¹³

As supported by the findings in this study,⁷ there is great intervariability among physicians’ frequency of potassium monitoring. Studies such as this one are important in that they standardize care and thereby reduce unnecessary

spending. More frequently, employers and third-party insurers are relying on the “value” of a clinician’s care to determine reimbursement. Our value is calculated by care quality divided by cost. If our costs increase, the value of our care is lessened. This has important implications because the strength of our specialty will be diminished if we are deemed less valuable.¹⁴

Fears of adverse effects of medication amplify like an urban legend among prescribers. Because of studies like that of Plovanič et al,⁷ we can elucidate fact from fiction and better serve our patients while calming our own fears. Furthermore, understanding the safety of medications prevents unnecessary laboratory monitoring and results in drastic cost savings. The authors should be commended for providing clarity about spironolactone monitoring and thereby improving our patient care.

ARTICLE INFORMATION

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