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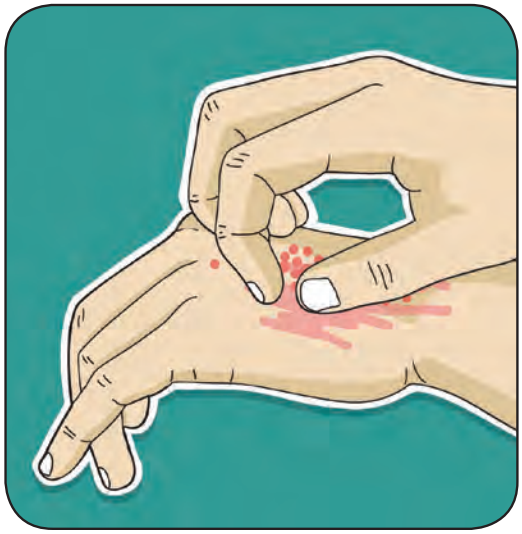
JDPA

Journal of Dermatology for Physician Assistants



Official Journal of the Society of Dermatology Physician Assistants

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THE ONE-OF-A-KIND
TOPICAL JAK INHIBITOR

NEW for uncontrolled, mild to moderate atopic dermatitis in non-immunocompromised patients aged ≥12 years[1]

- **Clear or almost clear skin** (IGA 0/1)* in >50% of patients at week 8 (53.8% vs 15.1% and 51.3% vs 7.6% vehicle†; $P<0.0001$)[1,2]
- **Meaningful itch relief** (Itch NRS4) in >50% of patients at week 8 (52.2% vs 15.4% and 50.7% vs 16.3% vehicle†; $P<0.0001$)[1,2‡]
  - **Itch NRS4 response seen as early as day 3** (18.4% OPZELURA vs 4.2% vehicle and 13.2% OPZELURA vs 0% vehicle†)[3]

OPZELURA was studied in 1249 adult and adolescent patients ≥12 years of age in 2 identically designed double-blind, randomized, vehicle-controlled trials (TRuE-AD1 and TRuE-AD2). In both studies, patients had an affected BSA of 3%-20% and an IGA score of 2 or 3 on a severity scale of 0-4. Patients were randomized to monotherapy with OPZELURA or vehicle BID for 8 weeks.[1,2]

*With a ≥2-grade improvement from baseline.[1]

†In TRuE-AD1 and TRuE-AD2, respectively.[1,2]

‡≥4-point improvement in NRS among patients with a score of ≥4 at baseline.[1]

BID=twice daily; BSA=body surface area; IGA=Investigator's Global Assessment; JAK=Janus kinase; NRS=numeric rating scale.

Discover the difference at OpzeluraHCP.com

Incyte Dermatology

INDICATION

OPZELURA is indicated for the topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Limitation of Use:

Use of OPZELURA in combination with therapeutic biologics, other JAK inhibitors or potent immunosuppressants such as azathioprine or cyclosporine is not recommended.

IMPORTANT SAFETY INFORMATION

SERIOUS INFECTIONS

Patients treated with oral Janus kinase inhibitors for inflammatory conditions are at risk for developing serious infections that may lead to hospitalization or death. Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease.**
- **Invasive fungal infections, including candidiasis and pneumocystosis.**
- **Bacterial, viral, and other infections due to opportunistic pathogens.**

Avoid use of OPZELURA in patients with an active, serious infection, including localized infections.

If a serious infection develops, interrupt OPZELURA until the infection is controlled. Carefully consider the benefits and risks of treatment prior to initiating OPZELURA in patients with chronic or recurrent infection. Closely monitor patients for the development of signs and symptoms of infection during and after treatment with OPZELURA.

No cases of active tuberculosis (TB) were reported in clinical trials with OPZELURA. Cases of active TB were reported in clinical trials of oral Janus kinase inhibitors used to treat inflammatory conditions. Consider evaluating patients for latent and active TB infection prior to administration of OPZELURA. During OPZELURA use, monitor patients for the development of signs and symptoms of TB.

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were reported in clinical trials with Janus kinase inhibitors used to treat inflammatory conditions including OPZELURA. If a patient develops herpes zoster, consider interrupting OPZELURA treatment until the episode resolves.

Please see additional Important Safety Information on following page.

Please see Brief Summary of Full Prescribing Information on following pages.

Opzelura™
(ruxolitinib) cream 1.5%

IMPORTANT SAFETY INFORMATION for OPZELURA™ (ruxolitinib) cream 1.5% (continued)

SERIOUS INFECTIONS (continued)

Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking oral ruxolitinib. OPZELURA initiation is not recommended in patients with active hepatitis B or hepatitis C.

MORTALITY

Higher rate of all-cause mortality, including sudden cardiovascular death, has been observed in patients treated with oral Janus kinase inhibitors for inflammatory conditions.

MALIGNANCIES

Lymphoma and other malignancies have been observed in patients treated with Janus kinase inhibitors for inflammatory conditions. Patients who are current or past smokers are at additional increased risk. Non-melanoma skin cancers, including basal cell and squamous cell carcinoma, have occurred in patients treated with OPZELURA. Perform periodic skin examinations during OPZELURA treatment and following treatment as appropriate.

MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)

Higher rate of MACE (including cardiovascular death, myocardial infarction, and stroke) has been observed in patients treated with Janus kinase inhibitors for inflammatory conditions. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if these symptoms occur.

THROMBOSIS

Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis has been observed in patients treated with oral Janus kinase inhibitors for inflammatory conditions. Many of these adverse reactions were serious and some resulted in death. Patients with symptoms of thrombosis should be promptly evaluated.

Thromboembolic events were observed in clinical trials with OPZELURA. There was no clear relationship between platelet count elevations and thrombotic events. OPZELURA should be used with caution in patients who may be at increased risk of thrombosis.

Thrombocytopenia, Anemia and Neutropenia

Thrombocytopenia, anemia and neutropenia were reported in the clinical trials with OPZELURA. Consider the benefits and risks for individual patients who have a known history of these events prior to initiating therapy with OPZELURA. Perform CBC monitoring as clinically indicated. If signs and/or symptoms of clinically significant thrombocytopenia, anemia, and neutropenia occur, patients should discontinue OPZELURA.

Lipid Elevations

Treatment with oral ruxolitinib has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides.

Adverse Reactions

The most common adverse reactions (≥1%) are nasopharyngitis (3%), diarrhea (1%), bronchitis (1%), ear infection (1%), eosinophil count increased (1%), urticaria (1%), folliculitis (1%), tonsillitis (1%), and rhinorrhea (1%).

Pregnancy

There will be a pregnancy registry that monitors pregnancy outcomes in pregnant persons exposed to OPZELURA during pregnancy. Pregnant persons exposed to OPZELURA and healthcare providers should report OPZELURA exposure by calling 855-4MEDINFO or 855-463-3463.

Lactation

Advise women not to breastfeed during treatment with OPZELURA and for four weeks after the last dose (approximately 5 elimination half-lives).

Please see Brief Summary of Full Prescribing Information on following pages.

References: 1. Opzelura. Prescribing Information. Incyte Corporation; 2021. **2.** Papp K, Szepietowski JC, Kircik L, et al. Efficacy and safety of ruxolitinib cream for the treatment of atopic dermatitis: results from 2 phase 3, randomized, double-blind studies. *J Am Acad Dermatol.* Published online May 3, 2021. doi:10.1016/j.jaad.2021.04.085. **3.** Data on file. Incyte Corporation. 2021.

Incyte Dermatology

Opzelura™ (ruxolitinib) cream 1.5%

Opzelura™ (ruxolitinib) cream 1.5%

OPZELURA™ (ruxolitinib) cream, for topical use

Brief Summary of FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE: OPZELURA is indicated for the topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Limitation of Use: Use of OPZELURA in combination with therapeutic biologics, other JAK inhibitors or potent immunosuppressants such as azathioprine or cyclosporine is not recommended.

WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS, AND THROMBOSIS

SERIOUS INFECTIONS
Patients treated with oral Janus kinase inhibitors for inflammatory conditions are at risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions and Adverse Reactions]*.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease.**
- **Invasive fungal infections, including candidiasis and pneumocystosis.**
- **Bacterial, viral, and other infections due to opportunistic pathogens.**

Avoid use of OPZELURA in patients with an active, serious infection, including localized infections. If a serious infection develops, interrupt OPZELURA until the infection is controlled.

The risks and benefits of treatment with OPZELURA should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with OPZELURA *[see Warnings and Precautions]*.

MORTALITY
Higher rate of all-cause mortality, including sudden cardiovascular death have been observed in patients treated with oral Janus kinase inhibitors for inflammatory conditions *[see Warnings and Precautions]*.

MALIGNANCIES
Lymphoma and other malignancies have been observed in patients treated with Janus kinase inhibitors for inflammatory conditions *[see Warnings and Precautions]*.

MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)
Higher rate of MACE (including cardiovascular death, myocardial infarction, and stroke) has been observed in patients treated with Janus kinase inhibitors for inflammatory conditions *[see Warnings and Precautions]*.

THROMBOSIS
Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis has been observed at an increased incidence in patients treated with oral Janus kinase inhibitors for inflammatory conditions compared to placebo. Many of these adverse reactions were serious and some resulted in death. Patients with symptoms of thrombosis should be promptly evaluated *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS

Serious Infections: Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving oral janus kinase inhibitors. Serious lower respiratory tract infections were reported in the clinical development program with topical ruxolitinib. Avoid use of OPZELURA in patients with an active, serious infection, including localized infections. Consider the risks and benefits of treatment prior to initiating OPZELURA in patients: with chronic or recurrent infection; with a history of a serious or an opportunistic infection; who have been exposed to tuberculosis; who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or with underlying conditions that may predispose them to infection. Closely monitor patients for the development of signs and symptoms of infection during and after treatment with OPZELURA. Interrupt OPZELURA if a patient develops a serious infection, an opportunistic infection, or sepsis. Do not resume OPZELURA until the infection is controlled.

Tuberculosis: No cases of active tuberculosis (TB) were reported in clinical trials with OPZELURA. Cases of active TB were reported in clinical trials of oral Janus kinase inhibitors used to treat inflammatory conditions. Consider evaluating patients for latent and active TB infection prior to administration of OPZELURA. During OPZELURA use, monitor patients for the development of signs and symptoms of TB.

Viral Reactivation: Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were reported in clinical trials with Janus kinase inhibitors used to treat inflammatory conditions including OPZELURA. If a patient develops herpes zoster, consider interrupting OPZELURA treatment until the episode resolves.

Hepatitis B and C: The impact of Janus kinase inhibitors used to treat inflammatory conditions including OPZELURA on chronic viral hepatitis reactivation is unknown. Patients with a history of hepatitis B or C infection were excluded from clinical trials.

Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking oral ruxolitinib. OPZELURA initiation is not recommended in patients with active hepatitis B or hepatitis C.

Mortality: A higher rate of all-cause mortality, including sudden cardiovascular death was observed in clinical trials of oral Janus kinase inhibitors used to treat inflammatory conditions. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA.

Malignancy and Lymphoproliferative Disorders: Malignancies, including lymphomas, were observed in clinical trials of oral Janus kinase inhibitors used to treat inflammatory conditions. Patients who are current or past smokers are at additional increased risk. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA, particularly in patients with a known malignancy (other than successfully treated non-melanoma skin cancers), patients who develop a malignancy, and patients who are current or past smokers.

Non-melanoma Skin Cancers: Non-melanoma skin cancers including basal cell and squamous cell carcinoma have occurred in patients treated with OPZELURA. Perform periodic skin examinations during OPZELURA treatment and following treatment as appropriate.

Major Adverse Cardiovascular Events (MACE): Major adverse cardiovascular events (MACE) defined as cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke were observed in clinical trials of Janus kinase inhibitors used to treat inflammatory conditions. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if these symptoms occur.

Thrombosis: Thrombosis, including deep venous thrombosis (DVT), pulmonary embolism (PE) and arterial thrombosis, has been observed at an increased incidence in patients treated with oral Janus kinase inhibitors for inflammatory conditions compared to patients treated with placebo. Many of these adverse reactions were serious and some resulted in death. Thromboembolic events were observed in clinical trials with OPZELURA. There was no clear relationship between platelet count elevations and thrombotic events. OPZELURA should be used with caution in patients who may be at increased risk of thrombosis.

Thrombocytopenia, Anemia and Neutropenia: Thrombocytopenia, anemia and neutropenia were reported in the clinical trials with OPZELURA. Consider the benefits and risks for individual patients who have a known history of these events prior to initiating therapy with OPZELURA. Perform CBC monitoring as clinically indicated. If signs and/or symptoms of clinically significant thrombocytopenia, anemia, and neutropenia occur, patients should discontinue OPZELURA.

Lipid Elevations: Treatment with oral ruxolitinib has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides.

ADVERSE REACTIONS

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In two double-blind, vehicle-controlled clinical trials (Trials 1 and 2), 499 subjects 12 years of age and older with atopic dermatitis were treated with OPZELURA twice daily for 8 weeks. In the OPZELURA group, 62% of subjects were females, and 71% of subjects were White, 23% were Black, and 4% were Asian. The adverse reactions reported by ≥ 1% of OPZELURA-treated subjects and at a greater incidence than in the vehicle arm through week 8 are as follows for OPZELURA (N=499) vs Vehicle (N=250), respectively: Subjects with any treatment emergent adverse event (TEAE) 132 (27%) vs 83 (33%), Nasopharyngitis 13 (3%) vs 2 (1%), Bronchitis 4 (1%) vs 0 (0%), Ear infection 4 (1%) vs 0 (0%), Eosinophil count increased 4 (1%) vs 0 (0%), Urticaria 4 (1%) vs 0 (0%), Diarrhea 3 (1%) vs 1 (<1%), Folliculitis 3 (1%) vs 0 (0%), Tonsillitis 3 (1%) vs 0 (0%), and Rhinorrhea 3 (1%) vs 1 (<1%).

Adverse reactions that occurred in Trials 1 and 2 in < 1% of subjects in the OPZELURA group and none in the vehicle group were: neutropenia, allergic conjunctivitis, pyrexia, seasonal allergy, herpes zoster, otitis externa, Staphylococcal infection, and acneiform dermatitis.

DRUG INTERACTIONS

Drug interaction studies with OPZELURA have not been conducted. Ruxolitinib is known to be a substrate for cytochrome P450 3A4 (CYP3A4). Inhibitors of CYP3A4 may increase ruxolitinib systemic concentrations whereas inducers of CYP3A4 may decrease ruxolitinib systemic concentrations.

Strong Inhibitors of CYP3A4: Avoid concomitant use of OPZELURA with strong inhibitors of CYP3A4 as there is a potential to increase the systemic exposure of ruxolitinib and could increase the risk of OPZELURA adverse reactions.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry: There will be a pregnancy registry that monitors pregnancy outcomes in pregnant persons exposed to OPZELURA during pregnancy. Pregnant persons exposed to OPZELURA and healthcare providers should report OPZELURA exposure by calling 1-855-463-3463.

Risk Summary: Available data from pregnancies reported in clinical trials with OPZELURA are not sufficient to evaluate a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of ruxolitinib to pregnant rats and rabbits during the period of organogenesis resulted in adverse developmental outcomes at doses associated with maternal toxicity.

The background risks of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies carry some risk of birth defects, loss, or other adverse outcomes. The background risk in the U.S. general population of major birth defects and miscarriage is 2-4% and 15-20%, respectively.

Data

Animal Data: Ruxolitinib was administered orally to pregnant rats or rabbits during the period of organogenesis, at doses of 15, 30 or 60 mg/kg/day in rats and 10, 30 or 60 mg/kg/day in rabbits. There were no treatment-related malformations at any dose. A decrease in fetal weight of approximately 9% was noted in rats at the highest and maternally toxic dose of 60 mg/kg/day. This dose resulted in systemic exposure approximately 22 times the clinical systemic exposure at the maximum recommended human dose (MRHD); the clinical systemic exposure from ruxolitinib cream, 1.5% applied twice daily to 25-40% body surface area is used for calculation of multiples of human exposure. In rabbits, lower fetal weights of approximately 8% and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day. This dose resulted in systemic exposure approximately 70% the MRHD clinical systemic exposure. In a pre-and post-natal development study in rats, pregnant animals were dosed with ruxolitinib from implantation through lactation at doses up to 30 mg/kg/day. There were no drug-related adverse effects on embryofetal survival, postnatal growth, development parameters or offspring reproductive function at the highest dose evaluated (3.1 times the MRHD clinical systemic exposure).

Lactation

Risk Summary: There are no data on the presence of ruxolitinib in human milk, the effects on the breastfed child, or the effects on milk production. Ruxolitinib was present in the milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the serious adverse findings in adults, including risks of serious infections, thrombocytopenia, anemia, and neutropenia, advise women not to breastfeed during treatment with OPZELURA and for approximately four weeks after the last dose (approximately 5 elimination half-lives).

Data: Lactating rats were administered a single dose of [14C]-labeled ruxolitinib (30 mg/kg) on postnatal Day 10, after which plasma and milk samples were collected for up to 24 hours. The AUC for total radioactivity in milk was approximately 13 times the maternal plasma AUC. Additional analysis showed the presence of ruxolitinib and several of its metabolites in milk, all at levels higher than those in maternal plasma.

Pediatric Use: The safety and effectiveness of OPZELURA for the topical treatment of atopic dermatitis have been established in pediatric patients aged 12 to 17 years of age with mild-to-moderate atopic dermatitis. Use of OPZELURA in this age group is supported by evidence from Trials 1 and 2 which included 92 subjects aged 12 to 17 years. No clinically meaningful differences in safety or effectiveness were observed between adult and pediatric subjects. The safety and effectiveness of OPZELURA in pediatric patients younger than 12 years of age have not been established.

Juvenile Animal Toxicity Data: Oral administration of ruxolitinib to juvenile rats resulted in effects on growth and bone measures. When administered starting at postnatal day 7 (the equivalent of a human newborn) at doses of 1.5 to 75 mg/kg/day, evidence of fractures occurred at doses ≥ 30 mg/kg/day, and effects on body weight and other bone measures [e.g., bone mineral content, peripheral quantitative computed tomography, and x-ray analysis] occurred at doses ≥ 5 mg/kg/day. When administered starting at postnatal day 21 (the equivalent of a human 2-3 years of age) at doses of 5 to 60 mg/kg/day, effects on body weight and bone occurred at doses ≥ 15 mg/kg/day, which were considered adverse at 60 mg/kg/day. Males were more severely affected than females in all age groups, and effects were generally more severe when administration was initiated earlier in the postnatal period. These findings were observed at systemic exposures that are at least 40% the MRHD clinical systemic exposure.

Geriatric Use: Of the 1249 total subjects with atopic dermatitis in clinical trials with OPZELURA, 115 were 65 years of age and older. No clinically meaningful differences in safety or effectiveness were observed between patients less than 65 years and patients 65 years and older.

PATIENT COUNSELING INFORMATION

Advise the patient or caregivers to read the FDA-approved patient labeling (Medication Guide).

Infections: Inform patients that they may be at increased risk for developing infections, including serious infections, when taking Janus kinase inhibitors. Instruct patients to tell their healthcare provider if they develop any signs or symptoms of an infection. Advise patients that Janus kinase inhibitors increase the risk of herpes zoster, and some cases can be serious.

Malignancies and Lymphoproliferative Disorders: Inform patients that Janus kinase inhibitors may increase the risk for developing lymphomas and other malignancies including skin cancer. Instruct patients to inform their health care provider if they have ever had any type of cancer. Inform patients that periodic skin examinations should be performed while using OPZELURA.

Major Adverse Cardiovascular Events: Advise patients that events of major adverse cardiovascular events (MACE) including non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, have been reported in clinical studies with Janus kinase inhibitors used to treat inflammatory conditions. Instruct all patients, especially current or past smokers or patients with other cardiovascular risk factors, to be alert for the development of signs and symptoms of cardiovascular events.

Thrombosis: Advise patients that events of DVT and PE have been reported in clinical studies with Janus kinase inhibitors used to treat inflammatory conditions. Instruct patients to tell their healthcare provider if they develop any signs or symptoms of a DVT or PE.

Thrombocytopenia, Anemia and Neutropenia: Advise patients of the risk of thrombocytopenia, anemia, and neutropenia with OPZELURA. Instruct patients to tell their healthcare provider if they develop any signs or symptoms of thrombocytopenia, anemia or neutropenia *[see Warnings and Precautions]*.

Administration Instructions: Advise patients or caregivers that OPZELURA is for topical use only *[see Dosage and Administration]*.

Advise patients to limit treatment to 60 grams per week.

Pregnancy: Inform patients to report their pregnancy to Incyte Corporation at 1-855-463-3463 *[see Use in Specific Populations]*.

Lactation: Advise a patient not to breastfeed during treatment with OPZELURA and for four weeks after the last dose *[see Use in Specific Populations]*.

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EDITORIAL & JOURNAL STAFF

JDPA
Journal of Dermatology for Physician Assistants

The official journal of the Society of Dermatology Physician Assistants

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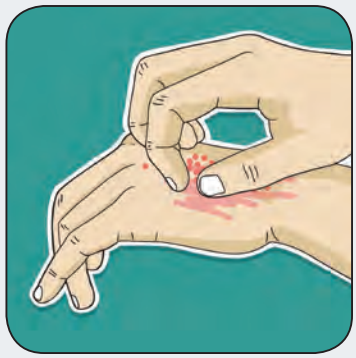
TABLE OF **CONTENTS**



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SDPA Annual Summer Dermatology Conference

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SDPA 2022

SDPA conferences are recognized as the premier educational and networking venues for Dermatology PAs.

EDITOR'S **MESSAGE**

New Beginnings

Here we are at the start of a new year. I think we are all happy to turn the page of the calendar and look forward with hope to the year ahead. The COVID pandemic continues to be a stressor as I write this, but as we continue to live and work in this historic time, I am grateful to have this community of intelligent and hardworking dermatology PAs as my colleagues. Our daily work efforts alleviate suffering and make this world a better place. So, let us raise a glass to commemorate the past and celebrate as we look forward to the future.

Speaking of the future in 2022, the *JDPA* will continue to have original research, clinically relevant case reports, and other timely features on issues important to the Derm PA. Another initiative of the *JDPA* is to foster collaboration and be a resource for our SDPA members who wish to continue their professional development by publishing. I would encourage you to email me if you have more questions or an interest in publishing a case report, editorial, continuing education article, or your doctoral dissertation or other original writing in *JDPA*. Another way to get involved and give back to the Derm PA community is by becoming a peer reviewer for *JDPA*. Use your clinical expertise to read and provide constructive comments for a fellow Derm PA's manuscript. This time reading, editing, and using your critical thinking makes others' articles better and makes you a better writer and clinician. Being a peer reviewer is not a large time commitment, and we can help you through the process. If you are interested, please email me. And a heartfelt thank you to those Derm PA colleagues who have recently become peer reviewers. Your volunteerism improves this journal.

As you turn the pages in this issue, we have a CME-accredited article on chronic pruritus, which is very appropriate for winter. Our Dermatology Grand Rounds feature this month discusses a case of isotretinoin-induced acne fulminans. This case is a nice reminder of the uncommon complication. Speaking of isotretinoin, I hope that everyone enjoyed iPLEDGE's gift to us and our patient's this past holiday season when they updated their IPLEDGE system Dec 13, 2021, resulting in treatment delays and hours of time working to access the new updated system to obtain prescriptions for our patients. As I worked through this, I found the SDPA's coverage of this helpful.[1] I appreciate all the PAs who contributed their experience to help us all work through the iPLEDGE system update.

In this Winter issue, we are also pleased to feature two insightful commentaries. First, Roderick S. Hooker, PhD, MBA, PA, Adjunct Professor of Health Policy at Northern Arizona University, addresses a question that has arisen in several situations involving PAs in various settings and roles, "Are physician assistants cost-effective in their employment?" The editorial calls for additional dermatology specific workforce research to answer this question. Reading the editorial, I thought of this study of SDPA members that found that in 2013, the median annual productivity of a Derm PA was $500,000 and median income at $100,000.[2] I agree with the authors of the study who said, "PAs in dermatology appear to generate adequate revenue to be profitable to a dermatology practice."[2] Although research like this seems fundamental to the practicing Dermatology PA who knows their worth, publications like this help inform economists and healthcare administrators of the value of the work we do and should continue to be done to show up-to-date information.

Our second commentary featured in this issue is, "The evolution will be peer-reviewed," by Peter Young, MPAS, PA-C. In his editorial, he references an article by Laura K. Ferris. Ferris and her coauthors, all from the University of Pittsburgh Medical Center in Pittsburgh, Pennsylvania, were studying computer aided classification of lesions but happened to find that in their study PAs required less biopsies to diagnose melanoma than physician colleagues.[3]

I was delighted to see this study as I was not aware of it! Good job, Mr. Young, proving your point that a side effect of writing is you become more familiar with current medical literature.

Enjoy the issue and thank you for continuing to fight the good fight every day for your patients. However, as we go forward into the new year, I encourage you to prioritize your health and "recharge" in whatever way you find meaningful, whether going for a chilly run or snuggling up with a book and your loved ones by a fire. Here is to 2022 and us.

Cynthia F. Griffith, MPAS, PA-C
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March 25-29, 2022
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An Educational Symposium for the Future of Physician Assistants
April 28, 2022 - May 1, 2022
Biltmore Hotel
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https://fsdpa.org/event/2022-new-wave-dermatology-conference/

SDPA Annual Summer Dermatology Conference
June 16–19, 2022
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November 17-20, 2022
InterContinental Miami
Miami, Florida
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FROM THE PRESIDENT'S DESK:

SDPA, PA Profession Poised for Growth and Success in 2022

As we begin the new year and strive toward new goals, I cannot help but reflect on what the SDPA has accomplished over the past six months. First, the Society of Dermatology Physician Assistants (SDPA) and its membership continue to grow. We now have the highest number of members, volunteers, and staff personnel to date, with new members stepping up into leadership, which is beyond exciting for me. Second, the *Journal of Dermatology for Physician Assistants (JDPA)* has welcomed a new Editor-in-Chief, Ms. Cynthia Faires Griffith, MPAS, PA-C and more than 30 new peer reviewers for the journal. Their team has so much passion and drive that will undoubtedly take the journal to new heights in 2022. Finally, SDPA has exciting plans for all Dermatology PAs in 2022 to revamp the Dermatology PA Foundation (DPAF), take conferences to the next level, and provide more CME to make everything bigger, better, and focused on the profession in its entirety.

Even though the SDPA is a trade association with members, I feel that it truly represents all Dermatology PAs because, in the end, we educate, support, and defend individual Dermatology PAs whether member or nonmember. SDPA members, I applaud you for supporting the only organization that gives back to the entire Dermatology PA profession. If you are not a member, I encourage you to join and be part of the movement that takes us higher because together, we are stronger.

The PA profession is a top career choice in healthcare (again), but we already knew that. For the fifth year in a row, PA has been named one of the top two healthcare jobs in the country by U.S. News & World Report in its annual Best Jobs List. PA was runner up this year to Nurse Practitioner on the Best Healthcare Jobs List and placed third on Best Jobs Overall. I would argue we take it a step further and say the Dermatology PA profession is even better, although I acknowledge that, as a practicing Derm PA, I'm a little biased! PA positions, especially in Dermatology, are highly sought after, as we know. So, this year, we continue to highlight members' accomplishments to share with our colleagues and the public. Please keep them coming! Also, don't forget to pay it forward to an aspiring Dermatology PA by offering your time and guidance through mentorship.

I get asked by many strangers about becoming a Dermatology PA, and I never hesitate to tell them my story. I also emphasize the importance of becoming involved outside the scope of the practice. Whether a pre-PA student, a current PA student, or a PA practicing in a different specialty, I am always available to share my wisdom. Though these conversations are hardly ever done in person, it is a pleasure to connect with these

individuals and take the journey throughout their careers. Nothing feels better than to finally meet with those connections in person at an SDPA conference.

The positive vibes within the organization keep the momentum going. It takes a team to move the ball but only one person to get that ball rolling. Could you be that person? Absolutely! Be the change and remember that change is imperative for any company or organization to grow and become successful. New thoughts and ideas brought in are what evolves the status quo. Though it can be frightening at first, it is the only way to move forward! So, I challenge you to step out of your comfort zone and "go-for-it!"

Warm regards,

Renata Block

Renata Block, MMS, PA-C
President SDPA

Cost-Effectiveness of PA Employment in Dermatology

By Roderick S. Hooker, PhD, MBA, PA

"Are physician associates/assistants (PAs) cost-effective in their employment?" This question has arisen in several situations involving PAs and nurse practitioners (NPs) in various settings and roles. Based on the literature, it seems clear they are cost-effective in primary care and surgery. The list of PA and NP activities in various disciplines and areas of healthcare provision that are cost-effective is long, and each peer-reviewed publication seems to put to rest the question of their value to employers. This is especially true in primary care.[1,2] The existing body of evidence strongly supports PAs and NPs in general medicine/family medicine as not only cost-effective, but also "cost-beneficial." PAs and NPs are considered cost-beneficial when they do not negate their wage differential by ordering more tests, incurring more liability, or taking longer in an encounter than a physician, on average. Instead, they produce the same outcome as a physician in the same setting and under the same circumstances but with less than one-half the annual compensation.[3] Sometimes the outcome of care by the PA is better than the physician-matched cohort.[4] The literature on team use involving PAs and NPs is even more striking. While "team" has many definitions, all teams have, at a minimum, two or more members working interdependently towards a common goal.[5] In contemporary studies, it appears that teams that include PAs and NPs can produce even better outcomes than traditional physician-only practices.[6]

> *"Are physician associates/assistants (PAs) cost-effective in their employment?"*

The literature on PA cost-effectiveness has been summarized in a comprehensive systematic review. In works gathered across various settings, spanning five countries, and of many medical and surgical specialties, the result was that PAs are cost-effective employees.[7] In total, 42 papers met review criteria and were extensively evaluated. Remarkably, few displayed significant risks of bias (an exclusion criterion). The bottom line is that PAs are cost-effective, in general, and in a dozen specialties. Although the dermatology literature was scanned for PAs and many publications reviewed, no labor input or cost-effectiveness study emerged. Some differentiation on melanoma diagnoses by PAs and MDs was reported, which implicated scope of practice and supervision issues of dermoscopy.[8,9]

Are dermatology PAs cost-effective to their employers? Are they in roles of substitution or as complements? Do they return more revenue than their wages to the private practice entrepreneur, or are they used to improve care throughput in a practice like Kaiser Permanente? In 2012, results from a membership survey conducted by the Society of Dermatology Physician Assistants (SDPA) reported the return on investment is positive.[10] Self-reported value aside, other questions linger. When employed in the same setting, is there a division of labor between a dermatology MD/DO, PA, or NP? Organizational efficiency experts and managers want to know these fundamental questions for staffing purposes. At the same time, why are PAs and NPs being employed in dermatology practices when the American Academy of Dermatology seems unbracing?

While the answer to this labor economic question remains open, some compelling evidence points in a positive direction. Clearly, after a half century of utilization, if PAs and NPs were not useful to dermatologists, they would not be employed.[11] If they produced greater liability than physicians, their role would be checked. On the other hand, if demand is outstripping the supply, contemporary adjustments need to be made to meet this demand. What is clear to this observer is that dermatology services are increasing because of PAs and NPs working in this domain.[12] Whether this growth will catch up with the theoretical demand of the next decade remains for more granular data.

How productive are dermatology PAs? Are they taking undifferentiated patients as the next dermatology

request, or are they managing what is handed to them (referred to as a 'hand-maiden' role)?[13] Which type of provider is producing the best 'compensation to production ratio'? How satisfied are patients with dermatology PAs? Are there differences in outcomes of care when each type of dermatology provider is compared? Does a PA or NP certified by any agency improve compensation or serve as a requirement of employment when the longitudinal outcomes of care by these three providers of dermatology have not been quantified?

Americans sit on a rich tranche of data to answer many fundamental medical questions. Countrywide, the records reside in large databanks at the National Center for Health Statistics (https://www.cdc.gov/nchs/index.htm), Medical Group Management Association, Kaiser Permanente, and others. Locally, each practice produces an electronic record that characterizes the clinician, the patient, ICD code, CPT code, prescription, RVUs, and length of visit. An individual in a small practice or an administrator in a large setting like the Veterans Health Administration could easily download these data. Questions to ask include, *"What is the annual productivity of a dermatology PA, and how does he or she compare to a physician? Are there statistical differences in out-comes of care?"*

The value of publishing such data is it serves as a historical marker on the development and evolution of PAs and their benefit to society. One of the more critical outcomes of the investigation of PAs has been that they are cost-effective in many roles. In general, they produce a social good that would not be served given a scarcity of physicians. To this end, I believe the role of dermatology PAs should be more than superficially known if they are to be valued by all parties and masters of their societal role.

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The Evolution Will be Peer-Reviewed

By Peter A. Young, MPAS, PA-C

ABSTRACT

Physician assistants participate in peer-reviewed publications less than other health professionals. The history of osteopathic physicians and podiatrists demonstrate how important journal participation is for successful professional evolution. Various non-dermatologists have contributed novel information to the dermatology literature, including some dermatology physician assistants. The practice of research and authorship positions physician assistants to advocate more effectively for their profession, by cultivating deeper understanding of easily misconstrued scientific literature. A shift is needed in the dermatology physician assistant profession, toward more authorship in peer-reviewed scientific publications.

KEYWORDS

Your PA can; your dermatology PA can handle it; dermatology literature and advanced practice providers; history of medicine; dermatology history

> *"Every great movement must experience three stages; ridicule, discussion, and adoption."*
>
> *- John Stuart Mill*

Advocacy campaigns to promote physician assistants (PAs) are ever-present on social media platforms, such as "Your PA Can" and "Your Dermatology PA Can Handle It".[1,2] These efforts are noble, but there is also need for organized effort on another front: more participation in peer-reviewed journals. Research led by PAs is sparse compared to other health professions,[3] and scholarship among PA educators has dropped over the last decade (50.6% report having no publications).[4] As the number of dermatology PAs has grown, positive sentiment toward PAs in peer-reviewed dermatology journals has steadily declined.[5]

It takes decades for new medical professions to fully earn the status quo's recognition, and these transformations always involve production of science's only universal currency: peer-reviewed publications. The history of osteopathic physicians (DOs) demonstrates this well; within the past century they evolved from subjects of widespread derision to fully licensed practitioners.

A survey of laypersons in 1936 examined the perceived social status of various health professionals, in which osteopaths ranked 18th overall, below dietitians. In 1937, DOs had privileges equivalent to MDs in only 26 states. The official stance of the American Medical Association (AMA) was that DOs were non-physician "cultists" with whom it was unethical for MDs to associate. But from its inception, the American Osteopathic Association (AOA) actively pursued professional recognition for DOs, including by supporting their publications. By 1902, the AOA had its own Committee on Publication to improve the quality of osteopathic case reports, knowing this was necessary for the *Journal of the AOA* to become respected. Between 1941 to 1943, Stedman Denslow, DO, published four articles in two prominent non-osteopathic journals. This paved the way for federal support of DO-led research and was of great importance to osteopathic physicians because it showed they could conduct reputable research accepted by the greater scientific community. In the mid-1960s, the AMA dropped the "cultist" label and allowed MD members to associate with DOs. In 2020, approximately 25 percent of United States medical school graduates were DOs.[6]

The history of podiatrists similarly underscores this theme. By 1960 they had earned surgical privileges in 47 states, after decades of legislative efforts. But their success met backlash from the American Academy of Orthopedic Surgeons (AAOS), which asserted podiatrists should be physically supervised by MDs and barred from performing bone surgery (soft tissue only). Podiatrists responded with a "publish or perish" stance, increasing peer-reviewed journal participation to support their claim that legislative changes were appropriate for their level of training. After years of rejection, the *Journal of Foot and Ankle Surgery* was finally accepted into Index Medicus in 1977. Peer-reviewed articles demonstrating the responsibility, safety, and efficacy of podiatrists became the profession's ticket to gradually being tolerated by the AMA and AAOS, who slowly toned back opposition.[7] Podiatrists' abilities to serve patients gradually flourished, and more recognition naturally followed. There is more to the stories of podiatrists and DOs (both were multifactorial, involving marketing campaigns and legislative efforts), but scientific publications were critical for each.

You don't have to be a dermatologist to contribute novel information to the field of dermatology. Captain John Smith had no medical training when he wrote the first account of rhus dermatitis in 1609. The inventor of Mohs micrographic surgery, Frederic Mohs, was not a dermatologist but rather a general surgeon.[8] Nurse practitioner Margaret Oliviero routinely co-authors articles with dermatologists in high-impact journals.[9]

Continued on page 18...

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Dermatology PA Bethany Grubb has authored work in the *Journal of the American Academy of Dermatology,*[10] as have several other PAs.

If you fear rejection of your work, rest assured that even experts get turned down. A written description of the first hair transplant in America was rejected by a well-known dermatology journal, the editor's response being "Can't be done." The method is now practiced in offices worldwide.[8] My first submission to a peer-reviewed journal was outright rejected, but after revision and resubmission, was accepted.[11] With practice, you may even grow to savor rejections for the lessons they render.

By authoring your own manuscripts, you grow more in touch with existing literature, which better positions you to speak up if your profession is unfairly criticized. For example, a 2018 study concluded that "the diagnostic accuracy of PAs may be lower than that of dermatologists" for melanoma in-situ.[12] Experts have highlighted issues with the article, most notably its lack of risk factor analysis (including personal history of melanoma, the malignancy's greatest risk factor).[13] But buried in another article from the same institution and corresponding author are related findings that garnered little public attention. In a study of eight PAs and 12 dermatologists who analyzed 173 skin lesion images, the PAs were 15.9 percent more sensitive than the dermatologists for detection of melanoma (a finding that was statistically significant).[14] Comparing these two articles of common origin may help some people to consider possible unintentional blind spots to the positive qualities of dermatology PAs.

Several outstanding articles are available on how to write for peer-reviewed journals.[15-17] There is also now an author group of dermatology professionals offering free mentorship to those interested in writing for peer-reviewed publications, the Collaboratory for Interprofessional Authorship in Dermatology.[18] I hope you'll use these resources to join this great tradition, and in doing so improve PA participation in the greater dermatology community. We each have the power to co-author the future.

The author's opinions are his own and not representative of any organization.

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Dermatology Grand Rounds

Recognizing and Managing Isotretinoin-Induced Acne Fulminans without Systemic Symptoms

By M. Bryn Marsh, MPAS, PA-C

ABSTRACT

This report describes the case of a 14-year-old female patient who presented with severe nodulocystic acne on the face that started 6 to 8 weeks into treatment with isotretinoin. The patient complained of intermittent arthralgias but denied other systemic symptoms. She was diagnosed with acne fulminans without systemic symptoms induced by isotretinoin. She discontinued this medication and began a prolonged prednisone taper. As this began to mitigate the acute inflammation, isotretinoin was re-initiated and gradually up-titrated to induce long-term control of her acne. Acne fulminans has multiple clinical manifestations, thus making it difficult to distinguish at times. Management of this condition can also be challenging and requires a personalized approach. Isotretinoin-induced acne fulminans is increasing in incidence due to more widespread treatment of acne vulgaris with this medication. The prompt recognition and management of this adverse effect of isotretinoin can prevent it from progressing into fulminant disease, and diminish the number of disfiguring scars.

KEYWORDS

Acne fulminans, isotretinoin-induced acne fulminans, pseudo-acne fulminans, acne fulminans sine fulminans

GRAND ROUNDS QUIZ

1. Which adverse effect may occur with concomitant treatment with isotretinoin and tetracycline antibiotics?

a. Osteolytic bone lesions
b. Pseudotumor cerebri
c. Gastric ulcers
d. Leukocytopenia

2. What medication is the mainstay for quick resolution of inflammation in acne fulminans?

a. Oral corticosteroids
b. Topical corticosteroids
c. Oral antibiotics
d. Isotretinoin

3. At what point after starting isotretinoin does isotretinoin-induced acne fulminans generally present?

a. Immediately
b. Within the first 2 weeks
c. Between months one and two
d. Between months three and four

CLINICAL VIGNETTE

Initiating isotretinoin. A 14-year-old female patient presented to the dermatology clinic with a history of mild to moderate acne, which failed to adequately improve with use of dapsone gel, adapalene/benzoyl peroxide gel, 0.05% tretinoin cream, and one year of intermittent daily oral 55 mg extended-release minocycline. The acne consisted of comedones and small inflammatory papules predominantly on the forehead. The patient's brother and mother had both been treated with isotretinoin in the past with no adverse events, and her father had a history of severe cystic acne, not treated with isotretinoin. Due to the lack of improvement on traditional treatments and the patient's strong family history of acne, the decision was made to start the patient on isotretinoin.

At baseline, the patient had mild, intermittent headaches and a slightly elevated alanine aminotransferase (ALT), which returned to normal after two months on isotretinoin. She weighed 51 kg and was started on 0.7 mg/kg/day of isotretinoin. After the first month of treatment, her acne was stable, and her lab values were unremarkable, so she was increased to a dose of 1 mg/kg/day. Two months after starting isotretinoin, she complained of worsening acne that was now spreading to the lower face and back, as well as arthralgias. At this point, her dose was decreased to 0.8 mg/kg/day, and she was advised to take ibuprofen for the joint pain. She was reassured that it could take several months for the acne to improve while taking isotretinoin.

Concern for acne fulminans begins. After three months on isotretinoin, the patient presented with continued worsening of her acne. Her exam showed

multiple inflammatory papules and large nodules on the cheeks, with less involvement on the forehead. She had a few inflammatory papules on the upper back as well. The patient was still complaining of significant joint pain in her knees with exercise but denied any other systemic symptoms. It was decided to decrease her isotretinoin further (0.5 mg/kg/day) in addition to initiating a two-week prednisone taper (starting at 0.5 mg/kg/day).

Two weeks later, the patient's acne had not improved. Her exam showed clustering of inflammatory papules and large nodules, some of which were now eroded with hemorrhagic crusts, on the bilateral cheeks. Few inflammatory papules were noted on the forehead, chin, and upper back. The patient also described serous exudate coming from her acne lesions. Monthly lipid panels and liver function tests were unremarkable other than a mildly elevated triglyceride (108) and alkaline phosphatase level (173) after month 3 of treatment. The patient was diagnosed with isotretinoin-induced acne fulminans without systemic symptoms (IIAF-WOSS).

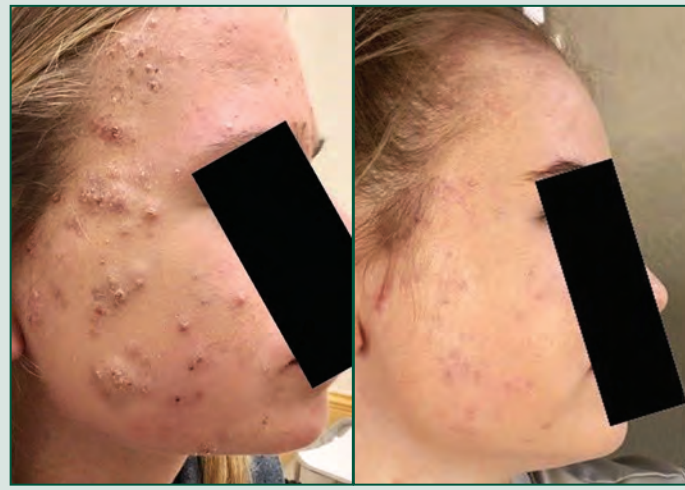

Figure 1. *Before and After. Patient's clinical appearance at onset of isotretinoin-induced acne fulminans and the significant improvement she demonstrated after oral corticosteroid taper and addition of isotretinoin.*

Prednisone (1 mg/kg/day) was immediately initiated, and isotretinoin was temporarily discontinued. Additionally, doxycycline 100 mg twice daily was started as an adjunct treatment and several inflammatory nodules were successfully treated with 2.5 mg/cc of intralesional Kenalog. Prednisone was subsequently tapered slowly over the next six weeks as the patient's inflammation decreased, hemorrhagic crusting diminished, and arthralgias resolved.

As the acne began to improve, re-starting low dose-isotretinoin was discussed with the patient and her mother several times. The patient's mother continually declined, for fear of this worsening the patient's acne again. The patient sought out a second opinion from a pediatric dermatologist at the Children's Hospital who also suggested re-starting low dose isotretinoin. She agreed to this plan.

Restarting isotretinoin. Six weeks after discontinuing isotretinoin and starting a slow prednisone taper, the patient was re-started on 0.4 mg/kg/day of isotretinoin in conjunction with increasing her prednisone back up to 0.4 mg/kg/day (she had been tapered down to 0.2 mg/kg/day). She also discontinued doxycycline 48 hours prior to initiating isotretinoin. The dose of isotretinoin was slowly increased as the oral prednisone was gradually tapered over a seven-week time period. She continued to improve slowly, a few persistent nodules resolved with intralesional Kenalog, and she showed no signs of relapse throughout treatment. She reached an isotretinoin dose of 0.7 mg/kg by month 6 and continued on the medication for a total of 12 months, at which point she reached a cumulative dose of 193 mg/kg and her acne had completely cleared. She was left with significant scarring on her forehead, bilateral cheeks, and upper back.

DISCUSSION

History of acne fulminans. The disease process consistent with acne fulminans (AF) was first described in 1959 under the name acne conglobata with septicemia; in 1975, it was re-named acne fulminans.[1] This new designation better describes the sudden onset of this severe condition and differentiates it from acne conglobata, which takes on a distinct disease course typified by polyporous comedones and noninflammatory cysts.[2]

AF is a rare disease, with around 200 cases published since first described in the literature.[3] It is most common in male adolescents and was originally thought to be a disease of teenage boys exclusively.[1,2] However, there have since been several cases reported in the literature of female patients with this condition.[4,5,6,7,8]

Clinical features and classifications. AF is the most severe variant of acne. It demonstrates abrupt onset of very inflammatory, tender, nodular, and ulcerative acne lesions involving the face, neck, and, most commonly, the upper trunk. Many patients who develop this condition have a history of only mild to moderate

Continued on page 22...

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...Continued from page 20

acne in the year preceding diagnosis.[1]

AF occurs on a spectrum of severity; in its most severe form, AF moves beyond the skin to include systemic symptoms (e.g., fever, malaise, arthralgias, and myalgias), laboratory abnormalities (e.g., leukocytosis, anemia, and increased sedimentation rate), and can even require hospitalization.[3,9,10] It has been proposed to call this AF with systemic symptoms (AF-SS).[3] When AF is limited to the skin with no systemic manifestations, it is called AF without systemic symptoms (AF-WOSS).[3] This has also previously been named "acne fulminans sine fulminans" [8,11] or "pseudo-acne fulminans."[11]

Isotretinoin is a known trigger of AF, and this phenomenon is increasing in incidence due to more widespread treatment of acne vulgaris with this medication.[3] It is generally thought that a higher isotretinoin initiation dose increases the risk of developing AF and flaring typically occurs 1 to 2 months after starting the medication.[3,4] AF induced by isotretinoin has been further designated into two categories. When the patient exhibits systemic involvement, the condition is called isotretinoin-induced acne fulminans with systemic symptoms (IIAF-SS).[3] When no systemic symptoms are involved, this condition is called isotretinoin-induced acne fulminans without systemic symptoms (IIAF-WOSS).[3]

AF, whether induced by isotretinoin or not, is generally easily identified because of its distinct skin and systemic features. Identification becomes more of a challenge when there are no systemic symptoms.

Pathogenesis. The pathogenesis of this disease is unclear. Proposed theories include infectious, hormonal, genetic, and immunologic causes. Infectious etiology is unlikely, due to the observation that bacterial cultures yield no pathological organisms and antibiotics have been ineffective as monotherapy.[2,4,5,6] An increased testosterone level was also initially thought to play a role in development of AF since this disease is most commonly seen in male adolescents.[9] However, subsequent cases of female patients with this condition, including those with normal blood testosterone levels, have been reported.[5] Genetics do appear to play a role in development of AF as demonstrated by reports of simultaneous development of AF in identical twins,[12] as well as siblings with identical human leukocyte antigen (HLA) phenotypes developing AF at the same age.[13]

Another theory states that AF occurs as a result of an immunologically mediated hypersensitivity reaction to *Cutibacterium acnes* (formerly P*ropionibacterium acnes*) antigens.[1] It has been postulated that isotretinoin leads to fragility of the pilosebaceous duct epithelium, thus leading to massive release of *C. acnes* antigens early in the treatment course; immune system contact with this organism may then cause a type III and/or type IV hypersensitivity reaction in those genetically susceptible.[9,14] It has also been proven that isotretinoin causes apoptosis of sebocytes in the skin.[15] Another theory states that large numbers of cytokines found in these sebocytes are subsequently released into the skin, causing exaggerated inflammation.[3,16]

Treatment options. Management of isotretinoin-induced acne fulminans can be difficult due to its poor response to traditional acne treatment.[7] Because of this, each patient requires a personalized treatment plan based on their particular circumstances and response to therapy. Oral corticosteroids plus isotretinoin are considered the mainstay of treatment for all forms of acne fulminans.[1,3,5,6,8,9] This regimen leads to long-term control of the acne.[1] Oral antibiotics have also been used with varying degrees of success.[3,4,6] In particularly resistant cases, there have been reports of treatment success with infliximab, cyclosporine, azathioprine, and dapsone.[7]

If isotretinoin-induced acne fulminans is suspected, discontinuing isotretinoin and initiating oral corticosteroids to gain quick control of inflammation is recommended; prednisone 0.5-1.0 mg/kg/day should be given for 2 to 4 weeks and then gradually tapered over weeks to months depending on the patient's response.[3] Once control of the acute flare has been achieved, low-dose isotretinoin should be re-initiated at a dose of 0.1-0.25 mg/kg/day, overlapping with corticosteroids for at least four weeks. The isotretinoin dose should then be gradually increased to 1.0 mg/kg/day and continued until a minimum cumulative dose of 120 mg/kg is reached and clinical clearance is observed.[3,8,9,10,17]

Oral antibiotics have proven to be unhelpful as monotherapy.[1,2,3,6] However, improvement has been demonstrated when oral corticosteroids are used in conjunction with antibiotics.[6,18] This may be valuable in cases where isotretinoin needs to be avoided for any reason. It is important to refrain from prescribing oral tetracycline antibiotics in conjunction with isotretinoin due to the possible additive risk of inducing pseudotumor cerebri.[11]

AF is slow to completely resolve, even with proper treatment, and often leaves disfiguring scars; therefore, prompt recognition is paramount to treatment success.

Prevention. It is recommended that patients who have severe inflammatory acne start oral corticosteroids prior to or in conjunction with isotretinoin to avoid triggering AF. The patient should be started on oral corticosteroids for 2-4 weeks before prescribing isotretinoin or concurrently with the start of isotretinoin (0.5-1.0 mg/kg/day).[3,19]

Prognosis. There is a good long-term prognosis in acne fulminans. Relapse is uncommon one year after treatment with isotretinoin.[4] However, significant scarring is likely to occur.

CONCLUSION

AF without systemic symptoms is not always easily recognizable, and cases induced by isotretinoin are increasing in incidence due to the widespread prescribing of isotretinoin for acne vulgaris.[3] This condition leads to disfiguring scars, as well as significant patient distress. Those practicing in dermatology should be able to distinguish these patients early to improve long-term outcomes and patient satisfaction.

JDPA Grand Rounds Quiz Answer Key:
1. B
2. A
3. C

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A Case Report of Successful Treatment of Acquired Reactive Perforating Collagenosis in a Patient with Skin of Color

By Jameka McElroy-Brooklyn, MSPAS, PA-C; Mahima Bhayana, MD, MBA; Ginette A. Okoye, MD , FAAD

ABSTRACT

Acquired reactive perforating collagenosis (ARPC) is a unique skin disorder that is a subtype of acquired perforating disorders (APD). ARPC is often associated with poorly controlled diabetes mellitus and chronic renal failure on dialysis. ARPC currently lacks standardized management. The current treatment modalities include phototherapy, topical corticosteroids, oral and topical retinoids, and antihistamines. These therapies have been implemented with varying degrees of success. It is classically described as skin-colored papules and nodules with a central keratotic plug commonly located on the upper and lower extremities. In this case report, we discuss a patient who presented with a two-month history of pruritic papules on the neck and trunk, ultimately diagnosed by skin punch biopsy as ARPC, and highlight the successful use of calcipotriene and tretinoin in treating this disorder.

KEYWORDS

Acquired reactive perforating collagenosis (ARPC), diabetes, calcipotriene, tretinoin

CONSENT

Informed consent was provided by the patient for use of associated images and publication of this case report.

CASE REPORT

A 42-year-old Black woman with a history of insulin-dependent diabetes mellitus, hypertension, and diabetic nephropathy, presented with a two-month history of a pruritic eruption on the neck, chest, and back. The lesions also occurred on areas of the skin that were induced by scratching.

On the physical exam, hyperpigmented papules, some with a central keratotic plug, were noted on the neck, chest, and back *(Figure 1A-D)*. Some lesions on the chest and back were distributed linearly (representing koebnerization). The Koebner phenomenon is the development of new skin lesions on previously healthy skin resultant from minor skin trauma or irritation.[1] The face, upper extremities, palms, soles, and mucous membranes were spared. The initial differential diagnosis included folliculitis, papular eczema, and arthropod bites. The patient completed multiple courses of mid-and high-potency topical corticosteroids and a one-month course of doxycycline 40mg daily, with no improvement.

A 4mm punch biopsy was then obtained from the left upper back and sent for hematoxylin and eosin (H&E) stain. The pathology report showed epidermal invagination with entrapped inflammatory debris and extruded collagen fibers traversing through the epidermis, consistent with a diagnosis of acquired reactive perforating collagenosis *(Figure 2)*. The patient improved after a one-month application of once-daily calcipotriene 0.005% and once nightly tretinoin 0.1% cream. During the one-month follow up, the patient reported a reduction of pruritus and lesions on the chest and back were notably thinner and less hyperpigmented. The patient was lost to follow-up and therefore total treatment duration and endpoint results were not obtained.

DISCUSSION

Acquired perforating dermatosis (APD) is a type of chronic skin condition with multiple subtypes including Kyrle disease, ARPC, and acquired elastosis perforans serpiginosa. They are commonly associated with diabetes mellitus, chronic renal failure, and in rare cases, human immunodeficiency virus (HIV), malignancy, liver disease, hypothyroidism, and medications such as biologics.[2] This group of skin conditions is characterized by perforation of the dermal connective tissue through the epidermis. In this case report, we will focus on the patient's specific subtype of ARPC.

ARPC is an uncommon skin condition that was first described by Mehregan et al in 1967.[3] There are two types of ARPC: the inherited type, which is more common in children, and the acquired type seen in adults.

Faver et al have proposed diagnostic criteria for the adult (acquired) form of reactive perforating collagenosis, as follows:[4]

- Elimination of necrotic basophilic collagen bundles into a cup-shaped epidermal depression as seen in biopsy specimens
- Umbilicated papules or nodules with a central, adherent keratotic plug
- Onset of lesions after age 18 years

Continued on page 27...

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* RAR-γ=retinoic acid receptor γ; AP-1=activator protein 1.
† Indicating a 2-week time frame until results on the face; a 4-week time frame until results on the trunk[6].
‡ IGA=Investigator's Global Assessment.

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- When you begin treatment with AKLIEF Cream, you should begin applying a moisturizer on your skin as often as needed.

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...Continued from page 24

The pathophysiologic mechanism contributing to ARPC is unknown but thought to be due to focal damage to dermal collagen and the resulting extrusion of collagen into the epidermis. ARPC can be distinguished from other perforating dermatoses by extrusion of collagen fibers from the dermis into the epidermal layer and pruritic keratotic papules on the trunk and extremities.

ARPC often occurs in association with chronic renal failure in patients with underlying diabetes, with a prevalence of 10 percent in dialysis patients in the United States.[5] This may be related to skin trauma secondary to uremic pruritus or xerosis. However, there have been reported cases in patients with hypothyroidism, liver disease, and lymphoma.

In the literature, ARPC has typically been described as skin-colored, umbilicated, dome-shaped papulonodules with keratinous plugging that sometimes occur at sites of trauma on extensor surfaces of the extremities.[3] Fewer reports describe lesions on the trunk and face. In this patient, the lesions were primarily on the trunk, sparing the extremities. Additionally, her lesions were hyperpigmented as could be expected in a patient with skin of color *(Fitzpatrick skin types IV-VI)*. The management of ARPC is challenging and often unsatisfactory as there is no standardized treatment algorithm. The literature documents cases of successful management of ARPC with oral and topical retinoids, calcipotriene, allopurinol, doxycycline, and ultraviolet B (UVB) and ultraviolet A (UVA) phototherapy.[6-8] In our patient, calcipotriene 0.005% cream in the morning and tretinoin 0.1% cream nightly proved to be an effective treatment for her ARPC after one month of starting treatment.

Calcipotriene, a vitamin D analog, has often been used to treat disorders of keratinization with considerable

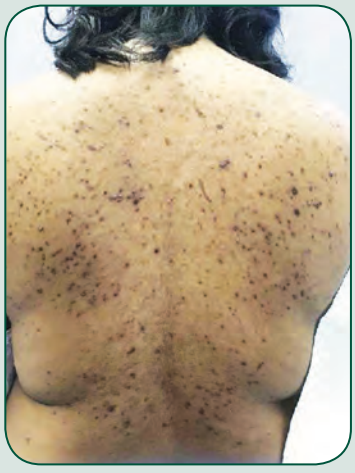

Figure 1A. *Back pre-treatment*

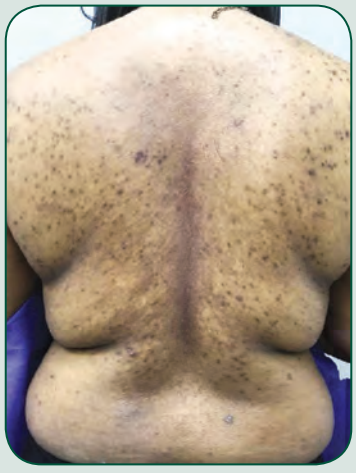

Figure 1B. *Back after 1 month use of Calcipotriene and Tretinoin cream.*

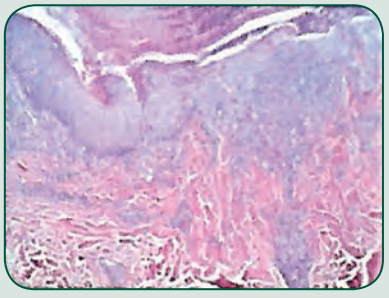

Figure 2. *Chest after 1 month use of Calcipotriene and Tretinoin cream.*

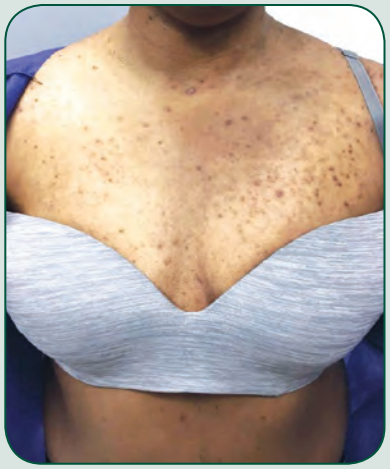

Figure 1C. *Chest pre-treatment*

Figure 1D. *Chest after 1 month use of Calcipotriene and Tretinoin cream.*

efficacy. The literature suggests that calcipotriene has a hypoproliferative effect on keratinocytes in the epidermis and demonstrates efficacy in inhibiting cell growth and development without direct harm to the cell.[9,10] Calcipotriene is FDA approved for the treatment of chronic plaque psoriasis, however, it may have potential benefits for conditions with a component of hyperkeratinization, such as ARPC. The mechanism of action of tretinoin is theorized to be drug binding with retinoic acid receptors to decrease matrix metalloproteinase activity and increase production of procollagen leading to the augmentation of collagen type I and III.[11,12] Although no current studies exist, tretinoin's effect on collagen homeostasis may contribute to its success in the treatment of ARPC. Tretinoin has also been proven to increase keratinocyte turnover which may improve the hyperkeratotic component of ARPC. Additionally, its ability to improve hyperpigmentation may be of further benefit to patients with skin of color who develop deeply hyperpigmented lesions and post-inflammatory hyperpigmentation.[13]

CONCLUSION

This case highlights the clinical presentation of ARPC in skin of color and the success of topical calcipotriene and tretinoin therapies. Some barriers to these treatment options could include issues with insurance coverage, the price associated with the number of tubes needed to treat larger body surface areas. Although these issues were not a factor in the case, we do acknowledge that these specific treatment options may not be readily available for every patient. ARPC has a strong association with diabetes and related nephropathy; chronic conditions that disproportionately affect The Black patient population.[14] This patient demographic is less likely to have access to a dermatology provider and other specialties including endocrinology and nephrology. Therefore, in the literature, there are few representative images and reports of this condition in patients with skin of color. Although ARPC is generally self-limiting, the resulting scarring and dyspigmentation can be striking, causing psychological distress and affecting the quality of life. For these reasons, timely diagnosis and treatment are paramount.

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Chronic Pruritus: Etiologies, Pathophysiology, and Therapeutic Options

By Cristina M. Foschi, BS, and Peter Lio, MD, FAAD

ABSTRACT

The purpose of this article is to discuss the pathogenesis of itch along with the four general categories of chronic pruritus in patients, how to clinically assess itch, and treatment options for each category of itch.

Histamine-driven and non-histamine-driven itch can be further subdivided into dermatologic, neuropathic, psychogenic, and systemic types of itch, each with evidence for certain therapies. There are several important categories of itch that can inform treatment approaches, some with significant evidence behind them, but gaps in both understanding and treatment remain.

KEYWORDS

Itch, pruritus, treatment, pathophysiology, management

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Learning Objectives:

1. *Describe the four general categories of itch.*
2. *Explore the key pathogenesis for itch.*
3. *Illustrate common assessments used for analyzing itch.*
4. *Discuss traditional and upcoming therapies for itch symptoms.*

INTRODUCTION

Itch, or pruritus, is a common presenting symptom seen with inflammatory skin diseases such as atopic dermatitis (AD), psoriasis, urticaria, neurodermatitis, prurigo, and cutaneous pruritus along with other dermatologic conditions such as seborrheic dermatitis or scabies. It is the most common symptom seen in dermatology with estimates showing that more than one-third of patients suffer from itch.[1] However, itch is also seen in patients with neuropathic, psychogenic and systemic conditions. There are two general types of itch which follow distinct pathways: acute itch, which often relies on the histaminergic pathway, and chronic itch, which generally is mediated via the non-histaminergic pathway.[2,3]

When the sensation of itch occurs for more than six weeks, it is defined as *chronic pruritus*, and this can have a significant effect on a patient's well-being by reducing sleep quality, affecting mood, and negatively impacting quality of life (QoL).[4,5] In addition, chronic itch has a prevalence of approximately 10 percent, is more prevalent in the elderly, and is difficult to treat, representing a significant social and economic burden to patients.[6] The cause of chronic itch has been historically divided into four categories: dermatologic (associated with primary skin diseases such as AD), neuropathic (associated with nerve fibers such as brachioradial pruritus and small-fiber polyneuropathy), psychogenic (associated with psychiatric conditions such as generalized anxiety disorder and delusions of parasitosis), or systemic (associated with hematologic diseases, end-stage renal disease [ESRD], and cholestasis).[3,4] It is important that clinicians identify the underlying condition producing itch in order to select the most appropriate therapy for relief. Here, we discuss the pathogenesis of itch, describe the four categories of chronic pruritus, outline tools for clinically assessing itch in patients, and list treatment options for each category of itch.

PATHOPHYSIOLOGY

Physiologic itch begins at the skin with a pruritogen that activates receptors on small itch-selective unmyelinated C fibers which are G protein-coupled

receptors (GPCRs).[4] In addition to this pathway, two subtypes of itch-sensitive neurons exist: histaminergic and non-histaminergic neurons.[4] These itch signals ascend through the spinal cord in separate tracts and have different patterns of brain activation.[6] The histaminergic pathway is involved in acute itch as histamine is released primarily by mast cells which bind to histaminergic neurons (afferent C-fibers) which then release neuropeptides such as calcitonin gene-related protein (CGRP) and substance P.[2] This causes local vasodilation, plasma extravasation and mast cell degranulation, which produces skin reactions such as urticaria and erythema.

In contrast, chronic itch is induced by the non-histaminergic pathway in which these neurons are elicited by pruritogens such as proteases, cytokines, or chemokines. In allergic and inflammatory conditions, there is an increased T helper type 2 (Th2) immune response and production of cytokines such as interleukin (IL)-31 that induce itch. This alternative pathway does not appear to promote the same intense inflammatory response compared to the histaminergic pathway.[3] Thymic stromal lymphopoietin (TSLP), which is secreted primarily by epidermal keratinocytes, is another key cytokine in promoting the Th2 immune response and induces itch by binding to neurons. Scratching the itch then induces epidermal keratinocytes to further express TSLP and this perpetuates a positive feedback loop of itching and scratching.[3] IL-4 and IL-13 are additional cytokines that are involved in Th2 immunity and induce chronic itch by activating sensory neurons through the IL-4 receptor subunit alpha, which is a shared subunit for both IL-4 and IL-13 along with Janus kinase (JAK).

After processing in the spinal cord, itch signals ascend through the spinothalamic tract to the thalamus and through the spinoparabrachial pathway to the parabrachial nucleus.[3] The signal is then projected to the primary and secondary somatosensory cortices. These areas contribute to the localization, intensity, and recognition of itch.

The mechanisms of neuropathic, psychogenic, and systemic itch are not well understood. Neuropathic itch occurs mainly due to damaged central or peripheral afferent nerves. It is a type of itch that is also accompanied by localized neuropathic symptoms such as pain and paresthesia likely due to damage of itch-inhibiting neurons.[3] Psychogenic itch is a diagnosis of exclusion where another reason for itch is not found, and mental health symptoms are present. Imbalances of serotonin, opioids, and dopamine may play a role in this pathway.[3] Finally, systemic itch is an itch that originates from organs other than the skin. Conditions that can cause this include hematologic disease, hepatobiliary disease, and ESRD.[5] Hematologic itch is usually aquatogenic, or occurs after a warm shower. While a confirmed mechanism is unknown, it is thought to be due to the up-regulation of serotonin receptors.[5] Other hematologic conditions that can induce pruritus include malignancy such as Hodgkin's lymphoma which is thought to be due to release of basophils, histamine, and leukopeptidase from white blood cells.[6] Interestingly, both iron deficiency and hemochromatosis where iron levels are elevated can cause itch.[6] Cholestatic pruritus is due to the accumulation of bile salts that then trigger histamine and lysophosphatidic acid release, which are powerful pruritogens. In addition, cholestatic patients have higher levels of endogenous opioids due to a diseased liver that can contribute to systemic itch. Itch seen in ESRD is very common and is thought to be due to increased levels of uremic toxins along with the up-regulation of endogenous opioids.[5]

DIAGNOSIS OF ITCH

Assessment of pruritus can be challenging as the sensation is subjective and there are many components that must be considered, such as other sensory symptoms, location, and duration. The International Forum for the Study of Itch (IFSI) established a classification system that divides chronic pruritus into three categories upon physical examination: 1) chronic pruritus on inflamed skin 2) chronic pruritus on normal skin, and 3) chronic pruritus with severe scratch lesions.[1]

Many scales have been developed to assess pruritus intensity. Mono-dimensional scales include the numerical rating scale (NRS) in which patients are asked to rate their itch from 0 (no itch) to 10 (worst imaginable itch) and the visual analogue scale (VAS) where patients indicate the intensity of their itch by marking on a 10cm-long, ruler-shaped scale using the same values as the NRS.[9] Scores below 3.0 on both of these scales are associated with mild itch while scores higher than 6.[9] are associated with severe itch.[9] However, these scales only provide the itch intensity at a specific point in time and thus are not as useful in understanding the larger outside-of-clinic picture.

Multidimensional scales, such as the 5-D itching scale (degree, duration, direction, disability, and distribution) evaluates many components of pruritus. The Itch-free Days (IFD) questionnaire, which was recently validated, contains questions that describe many parameters related to itch course and calculates a score to compare the results from different time points of assessment.[1] Another instrument is the pruritus-specific Patient Benefit Index (PBI-P), which has been developed to determine the benefits gained from treatment and

degree of global satisfaction. It assesses the relevance of 27 possible therapeutic benefits for patients before treatment and the extent to which they were met post-treatment. This has been validated for chronic pruritus patients and has a high correlation with scores from VAS.

In addition to using these questionnaire tools, management of pruritus includes first taking a thorough medical history and performing a physical examination. To rule out systemic causes of itch, the British Association of Dermatology recommends initial blood tests, including a full blood cell count, iron levels, thyroid function tests, urea and electrolyte levels, liver function tests, and an autoimmune screen to help diagnosis or exclude systemic causes.[3] In addition, a thorough history can provide information about the origin of pruritus such as trauma or comorbidities and a detailed skin examination is required to rule out primary dermatologic conditions that cause itch.[9]

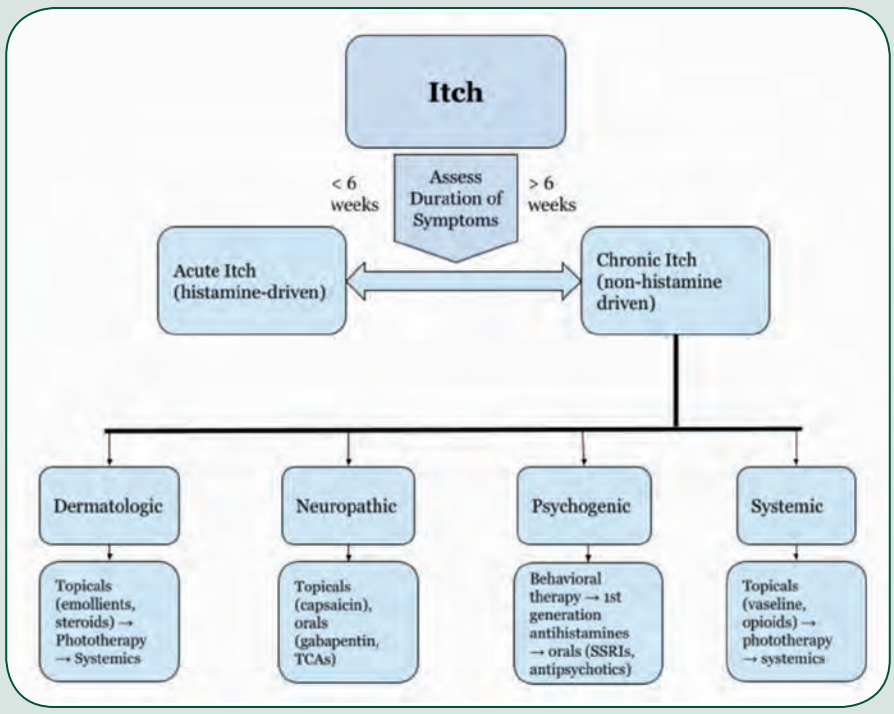
TYPES OF ITCH AND THERAPEUTIC OPTIONS

A general guideline of the categories of chronic pruritus along with initial steps in therapeutic management is outlined in *Figure 1*, with a more detailed description below.

DERMATOLOGIC ITCH

Inflammatory skin disorders causing dermatologic itch including AD are primarily driven by a type 2 immune axis response through cytokines IL-33, TSLP, IL-4, IL-5, IL-13, and IL-31.[10] Elevated levels of type 2 cytokines also promote production of immunoglobulin E (IgE), activation of mast cells, and release of histamine which can cause urticaria.[10] Reducing inflammatory mediators in the skin is crucial to reducing pruritus and achieving control in these conditions. Traditionally, psoriasis has been considered a non-pruritic dermatosis compared to AD, however, studies have demonstrated that itch is present in psoriasis and can have a debilitating impact on patient well-being.[11] Substances that have been associated with pruritus in psoriasis include nerve growth factor (NGF), substance P, CGRP, and neuropeptide Y (NPY). While the exact pathogenesis of psoriatic pruritus is not clear, extensive itching of the skin can cause the development of new psoriatic lesions in response to trauma, known as the Koebner phenomenon.[11] Additional causes of dermatologic itch include the severe, persistent itch that manifests with scabies. Many pathophysiologic mechanisms have been proposed for the severity of this itch which involve both type I (immediate) and type IV (delayed) hypersensitivity reactions.[12] In addition, the scabies mite produces proteins such as serine protease which digests skin proteins and contributes to the breakdown of the epidermal barrier, evoking itch.[12] While in children and adults AD is one of the most common causes of pruritus in this category, xerosis, or dry skin, is the most common cause of dermatologic-related itch in the elderly and has been reported in 69 percent of elderly chronic itch patients.[10] Xerosis should be considered in all elderly patients as many common drugs can cause pruritus in this population, such as calcium channel blockers and hydrochlorothiazide.[13] In addition, other skin conditions are more common in elderly patients which can cause pruritus including bullous pemphigoid and mycosis fungoides.[13] The therapeutic ladder in this type of itch generally follows topicals, then phototherapy, and, finally, systemics.

Figure I. Categorize Chronic Itch and Initial Therapeutic Options



Topical Treatments.

Chronic skin disorders are associated with an impaired skin barrier, which allows for moisture to leak out of the skin causing dry, itchy skin

characterized by redness, flakes, and a rough texture.[14] Topical therapy is the foundation of treatment for skin-barrier related pruritus and includes emollients, corticosteroids, and other immunomodulators.[14]

Effective emollients consist of water and lipids which act to rehydrate the skin and are first-line therapy for skin-barrier related itch.[14] Topical corticosteroids reduce pruritus in inflammatory skin conditions and are perhaps best utilized in more localized pruritic disease. These have been an essential method of therapy for acute inflammatory flares with multiple systematic reviews demonstrating that high-potency class I steroids significantly improve atopic itch within a few days of application.[15] Due to adverse effects from chronic use such as skin atrophy, telangiectasias, and changes in pigmentation, however, alternatives are preferred to minimize continuous use of topical steroids.[15] Calcineurin inhibitors, such as tacrolimus and pimecrolimus, are immunomodulators that have been shown to reduce AD-related pruritus in multiple studies.[2,15] This therapy offers an alternative targeted anti-inflammatory treatment without the side effects associated with corticosteroid use, and can thus be used more chronically. Crisaborole, a topical phosphodiesterase-4 (PDE4) inhibitor recently approved for use in AD, is another anti-inflammatory agent. PDE4 regulates multiple pro-inflammatory signals by degrading cyclic adenosine monophosphate in cells. This medication improved disease severity and pruritus with a favorable safety profile in those with mild to moderate AD.[17]

Phototherapy. Ultraviolet-A (UV-A), Narrow-Band Ultraviolet-B (nbUV-B), and psoralen and UVA (PUVA) improve pruritus by reducing nerve fiber density and semaphorin 3A levels in the epidermis.[4] This is an effective and safe treatment in dermatologic itch, such as psoriasis, as it reduces T cells and IgE-binding in the dermis.[2] Phototherapy also reduces the density of epidermal sensory nerves which can contribute to a direct antipruritic effect.[2] A systematic review demonstrated that UV phototherapy with UVB, combined UVA and UVB (UVAB), nbUVB, and high intensity UVA can be useful for management of AD.[15] However, not all studies demonstrate that UV therapy improves pruritus and multiple sessions per week are required for clearance, which can be time consuming and cumbersome to patients.

Antihistamines. The histamine-1 receptor (H_1R) and histamine-4 receptor (H_4R) antagonists have been implicated in the treatment of itch.[10] Although antihistamines have demonstrated efficacy in relieving acute itch, particularly H_1R antagonists for acute urticaria, they do not seem to be as beneficial in chronic itch conditions. In AD, histamine acts as a pruritogen through H_4-receptors and other cytokine mediators, and no high-quality randomized control trials of H1-antihistamines confirm their efficacy in these patients.[18] They are still sometimes used in chronic itch conditions mainly for their sedative effects. H_4R antagonists have particularly demonstrated both anti-inflammatory and antipruritic effects in chronic itch. Oral H_4R antagonists are currently being studied in the treatment of chronic itch in those with AD, although at this time antihistamines are not first-line in chronic pruritus patients.[19]

Cyclosporine. Cyclosporine binds to the intracellular receptor cyclophilin leading to decreased T-cell activation and transcription of IL-2, which is a mediator of pruritus.[2] A meta-analysis demonstrated reduction in itch severity in AD cases when cyclosporine was dosed at 3mg/kg to 5mg/kg for 6 to 8 weeks.[15] It is best used as a short-term solution to achieve rapid control of inflammation and itch in severe AD due to adverse effects such as renal dysfunction and hyperlipidemia.[15]

Purine Synthesis Inhibitors. Mycophenolate mofetil (MMF) inhibits inosine monophosphate dehydrogenase, preventing lymphocyte proliferation. This has proven to be a safe and effective option in dermatologic itch patients.[2] Azathioprine is a purine analog that inhibits normal purine synthesis and DNA production, limiting T-cell and B-cell proliferation. Several randomized control trials demonstrated improvement in atopic itch after treatment with azathioprine, although the potential for lymphopenia, nausea, or gastrointestinal upset must be monitored.[2] Methotrexate is an inhibitor of dihydrofolate reductase that indirectly inhibits purine synthesis and is used in those with inflammatory skin disease such as psoriasis or AD.[2]

IgE Antagonists. Omalizumab is a recombinant humanized anti-IgE antibody that blocks IgE binding to its receptor preventing activation of basophils and mast cells. In recent clinical trials in children with severe AD utilizing high doses of omalizumab, there was a reduction in the Eczema Area and Severity Index (EASI) compared to the control group.[10]

IL-4 and IL-13 Antagonists. Dupilumab is a fully human monoclonal antibody that targets the IL-4 receptor alpha, a shared receptor for IL-4 and IL-13. This drug demonstrated a remarkable reduction in pruritus severity, QoL, and AD disease severity after only two weeks of treatment compared to the placebo control group in trials and is the first targeted biologic agent approved for treatment of moderate-to-severe AD inadequately controlled with topical therapies.[19-21] Similarly, studies of anti-IL-13 monoclonal antibodies tralokinumab and

lebrikizumab have demonstrated promising results in those with AD. In particular, lebrikizumab reduced skin lesions and pruritus by Day 2 of treatment for adults with moderate-to-severe AD.[22]

IL-31 Antagonists. IL-31 was the first cytokine found to directly stimulate sensory nerves and mediate itch. The humanized anti-IL-31 receptor monoclonal antibody nemolizumab binds to the IL-31 receptor A on neurons and inhibits its signaling, alleviating pruritus directly with little to no effect on inflammation.[23] Promising trials demonstrate significant reduction in pruritus as early as day 2 of treatment in moderate to severe AD with monthly administration of 0.5mg/kg to 2.0mg/kg.[23]

Other Blockades. Epithelial cell-derived cytokines IL-33 and TSLP have been implicated in the pathogenesis of pruritic disorders by directly stimulating sensory neurons to mediate itch, which act upstream of IL-4, IL-13, and IL-31, and represent other potential targets for treatment of dermatologic pruritus.[10] Tezepelumab is an anti-TSLP monoclonal antibody that demonstrated a 50-percent reduction in EASI scores in combination with topical corticosteroids, however, this was not statistically significant.[10] On the other hand, an anti-IL 33 monoclonal antibody etokimab produced improvement in those with moderate-to-severe AD after a single dose.[10]

Janus Kinase Inhibitors. These agents provide anti-inflammatory effects through disruption of the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway used by many cytokine receptors with JAK1 expressed more in itch-specific effects.[22,24] A small case series of six patients reported efficacy of oral tofacitinib (JAK1/3 selective) and a recent phase 2 clinical trial with upadacitinib, which is a JAK-1 selective inhibitor, found improvement in itch as early as Week 1 of treatment.[22,24] In addition to oral JAK inhibitors, topicals such as tofacitinib and delgocitinib, also demonstrated a reduction in itch.

Neurokinin Receptor Antagonists. Substance P induces pruritus by stimulating the release of pruritogens from keratinocytes and other immune cells via the neurokinin-1 (NK-1) receptor, and both substance P and the NK-1 receptors are overexpressed in chronic pruritus.[25] Aprepitant, serlopitant, and tradipitant, which are NK-1 antagonists, have demonstrated significant reduction of pruritus. In particular, tradipitant exhibited a statistically significant decrease in itch in a randomized trial.[25]

Antimicrobial Agents. Staphylococcus-derived exotoxins and superantigens aggravate AD symptoms and are capable of directly triggering itch with the density of *Staphylococcus aureus* colonization correlating with disease severity.[26] The regular practice of dilute bleach baths with concomitant topical mupirocin can be helpful for improving AD-related itch, however, studies have demonstrated that this may not be more effective than water baths alone.[26] Since AD is associated with a higher prevalence of *S. aureus* colonization compared with healthy controls, anti-bacterial treatments have been considered to reduce bacterial colonization which may be inducing a flare.[26] For itch induced by scabies, topical permethrin 5% cream is widely used and is effective at killing both the mite and eggs with oral ivermectin usage indicated in cases of topical failure.[12] Topical hypochlorous acid (HOCl) found in bleach and a vital component of our innate immune system has demonstrated anti-microbial and anti-inflammatory properties to assist with pruritus as a topical regimen. This formulation has also been shown to decrease the activity of many cytokines that are upregulated in dermatologic itch and has demonstrated antimicrobial effects and therapeutic benefits in these conditions.[27] Finally, a topical 1% colloidal oat cream formulation has demonstrated effectiveness in reducing both the EASI and Atopic Dermatitis Severity Index by lowering the prevalence of Staphylococcus species and increasing microbiome diversity.[28] By serving as a probiotic and improving the diversity of the cutaneous microbiome, it can repair skin barrier defects that cause inflammatory flares.[28]

NEUROPATHIC ITCH

Neuropathic itch is one that arises because of disease located along the afferent neural pathway and accounts for 8 to 19 percent of patients affected by chronic pruritus.[9] Those with neuropathic pruritus tend to have very severe itch and, due to sensory nerve damage, this type of itch usually presents on normal appearing skin accompanied by burning and tingling.[9,29] A diagnosis of neuropathic itch is supported by an itch limited to a dermatomal distribution or an itch accompanied by other neurological signs of sensory nerve damage. Allokinesis, itch evoked by light touch, and other forms of hypersensitivity result from peripheral and central sensitization of neurons and can also be associated with neuropathic pruritus.[29] *Table 1* breaks down specific causes of neuropathic itch as categorized by originating in the central or peripheral nervous systems.[9]

Topical Neuromodulators. Topical capsaicin, a naturally occurring alkaloid derived from chilli peppers, has been used to relieve pruritus by activating transient receptor potential vanilloid 1 (TRPV1) ion channels on

Table 1. Etiologies of Neuropathic Itch

Peripheral Nervous System	Central Nervous System
Post-Herpetic Neuralgia	Multiple Sclerosis
Diabetic Neuropathy	Fibromyalgia
Brachioradial Pruritus	Syringomyelia
Notalgia Paresthetica	Transverse Myelitis
Suprascapular Entrapment Syndrome	Traumatic Brain Injury
Prurigo Nodularis	Brain/Spinal Cord Abscesses
Postburn Itch	Creutzfeldt-Jakob Disease

nociceptors which trigger the release and depletion of neuropeptides.[2] The long-lasting desensitization of local nerve fibers improves pruritic symptoms, although it can cause a hot or burning sensation after application. Patches of 8% capsaicin applied for 60 minutes have demonstrated a greater and longer lasting relief of neuropathic itch in patients.[9] In addition, topical cooling agents such as menthol and camphor exert their effects by activating thermosensitive channels expressed on keratinocytes and peripheral nociceptors, enhancing the sensation of cold and causing receptor desensitization which leads to analgesic and antipruritic effects.[9] For mild neuropathic pruritus, topical anesthetics such as lidocaine, prilocaine, and pramoxine have demonstrated some success in treatment at a lower cost for patients.[9] Additionally, there have been reports of patients with refractory brachioradial pruritus demonstrating efficacy from topical amitriptyline-ketamine in treatment of this itch. Topically, amitriptyline acts by blocking voltage-gated sodium channels and preventing the depolarization of axons, working similar to an anesthetic.[29] This combination has been studied in some clinical trials with mixed results and more studies are needed to understand its utilization and dosing.

Oral Medications. Gabapentin and pregabalin can reduce central neural hyper-sensitization and thus reduce pruritic conditions in neuropathic itch.[30] Gabapentin is a GABA analog that antagonizes the alpha-2-delta subunit of voltage-gated calcium channels. Gabapentin is started at low doses of 300-600mg nightly and gradually increased to achieve a total daily dose as high as 3600mg/d as tolerated.[9] Less commonly, oxcarbazepine and carbamazepine have demonstrated success in the treatment of neuropathic pruritus by antagonizing voltage-gated sodium channels.[9] Finally, tricyclic antidepressants, such as amitriptyline, have demonstrated improvement in neuropathic itch when dosed 5 to 10mg nightly and titrated upward.[9]

PSYCHOGENIC ITCH

Psychogenic pruritus is a functional itch disorder which is a compulsion to scratch otherwise normal skin due to irritating factors such as skin dryness along with psychiatric disease.[31] Psychiatric diseases associated with this itch include depression, obsessive-compulsive disorder (OCD), anxiety, psychosis, and substance abuse.[32] It is a diagnosis of exclusion, and it is important to first rule out dermatologic and systemic causes before undergoing medication and behavioral management, along with building a strong relationship with patients prior to navigating this conversation, as it can be challenging to explain.[32]

Behavioral Therapy. For those with an obsessive-compulsive component to their itch, cognitive behavior therapy (CBT) has shown to be the most effective.[32] Patients work on techniques to decrease the urge to pick by removing triggers and finding alternative coping mechanisms.[32]

Antihistamines. First-generation antihistamines, such as hydroxyzine and diphenhydramine, are used in the evening for their sedative effects in these patients. Doxepin is a TCA with strong antihistamine and sedative effects that can be useful and is usually started at 10mg nightly and then titrated up to 100mg as tolerated.[32]

Oral Medications. Generally, when selecting oral therapy, it is important to treat the underlying psychiatric condition in these patients. Selective serotonin reuptake inhibitors (SSRIs) such as paroxetine, sertraline, and fluvoxamine, can be effective in psychogenic pruritus.[4,32] In particular, low-dose oral mirtazapine (7.5-15mg) at night can decrease neural sensitization and reduce nocturnal pruritus.[4,32] For excoriation disorder in which individuals repeatedly pick at their skin, *N*-acetylcysteine has demonstrated effectiveness in reducing pruritic symptoms.[33] In one randomized trial, this amino acid dosed at 1200-3000mg/d for 12 weeks suggested that targeting the glutamate system may reduce compulsive picking behaviors.[33] In delusions of parasitosis, antipsychotics are the best choice. Aripiprazole has a lower side effect profile and is approved for both psychosis and depression, which can aid patients who also have depression in feeling less self-conscious about taking an antipsychotic for itch symptoms.[32] In many studies, pimozide has been shown to be first-line treatment for delusions of parasitosis with improvements in symptoms anywhere from 3 to 8 weeks of 1 to 6mg of medication per day.[32]

SYSTEMIC ITCH

Systemic itch is due to underlying conditions such as ESRD, biliary liver disease, hematologic disease, malignancy, and others as outlined in *Table 2*. It is important to obtain lab work in patients with chronic pruritus without obvious skin manifestations including a comprehensive metabolic panel (CMP), complete blood count (CBC) with differential, alkaline phosphatase, lactate dehydrogenase, and uric acid.[34] ESRD in particular is a growing problem in the elderly due to the increasing number of patients suffering from diabetes or hypertension, and chronic itch is a frequent symptom in these patients.[35] Chronic itch due to systemic conditions has a decreased QoL in these individuals and thus it is important to recognize conditions and treat itch appropriately.

Topicals. Emollients such as petroleum jelly are recommended in these patients to start at least 2 to 3 times per day.[35] In uremic pruritus, a randomized study found that topical glycerol 15% and paraffin 10% decreased pruritus in these patients. While moisturizers and topicals are beneficial for itch, it can be difficult for patients to apply these to a diffuse area and can often require caregiver assistance, which is not ideal.[35]

Phototherapy. Broadband UVB (BB-UVB) provides significant reduction in the skin content of phosphorus and reduction of pruritus scores in patients specifically with pruritus due to ESRD.[35] BB-UVB therapy significantly reduced chronic itch in hemodialysis (HD) patients and the antipruritic effect occurred earlier when the weekly frequency of treatments was increased.[36] BB-UVB can also be helpful in reducing itch within eight weeks of beginning treatment in patients with cholestatic liver or hematologic diseases.[37]

Table 2. Systemic Causes of Itch

RENAL
• End-Stage Renal Disease (ESRD)/Chronic Renal Failure
CHOLESTATIC
• Hepatitis B
• Obstructive biliary disease
• Cholestatic liver disease of pregnancy
HEMATOLOGIC
• Polycythemia vera
• Iron deficiency anemia
• Polycythemia rubra vera
• Hypereosinophilic syndrome
• Essential thrombocythemia
• Myelodysplastic syndrome
• Hemochromatosis
ENDOCRINE
• Hyperthyroidism or Hypothyroidism
• Diabetes Mellitus
• Hyperparathyroidism or Hypoparathyroidism
MALIGNANCY
• Hodgkin disease
• Non-Hodgkin lymphoma
• Leukemia
• Carcinoid syndrome
• Cutaneous T-cell lymphoma
• Multiple myeloma
• GI malignancies, CNS tumors, breast cancer, and lung cancer
INFECTIOUS
• HIV
• Hepatitis C
• Hepatitis B
• Trichinosis
• Parasitic infections including hookworms, pinworms, Ascaris species, or Onchocerca species
• Leptospirosis
OTHER
• Mastocytosis
• Sarcoidosis
• Dermatomyositis
• Scleroderma
• Systemic lupus erythematosus
• Sjogren syndrome
• Neurofibromatosis
• Primary cutaneous amyloidosis

Adapted from Legat FJ et al. Pruritus and dysesthesia. In: Bolognia JL, Schaffer JV, Cerroni L, eds. Dermatology. Vol. 1. 4th ed. Philadelphia, PA: Elsevier; 2018: 112-118.

Anticonvulsants. Anticonvulsant drugs, such as gabapentin, have been implicated in systemic itch. In those with uremic pruritus due to ESRD, gabapentin had improved pruritus scores in those on HD, although the optimal therapeutic dose has not been established.[38] Patients on HD need lower doses at less frequent intervals than patients with normal renal function, as gabapentin has a longer half-life in patients with chronic renal failure.[38] In order to avoid adverse effects, many studies suggest that gabapentin and pregabalin should be started at lower doses and progressively titrated with close observation.[30,38] Pregabalin has some advantages over gabapentin such as a higher potency and faster absorption, but there is limited evidence comparing the two.

Opioids. Opioid peptides can influence itch by binding to mu receptors, and thus excessive mu receptor stimulation from high levels of opioids can induce itch more, suggesting opioid antagonism as a potential therapeutic option.[39] Topical 1% naltrexone cream has demonstrated significant reduction in patients with various systemic chronic pruritic disorders and was felt within 15-30 minutes after application lasting for 2-6 hours.[40]

Aprepitant. A NK-1 receptor antagonist, aprepitant has been approved for the prevention of chemotherapy-induced nausea and vomiting. In many trials, patients with pruritus due to systemic

conditions such as cancers and ESRD have demonstrated symptom relief with short-term use of aprepitant for up to two weeks.[41] Few patients experienced adverse effects, however, and its high cost can be an economical burden to patients.[41]

Other Oral Medications. Peroxisome proliferator-activated receptors (PPARs) are nuclear transcription factors that regulate numerous genes and metabolism in the liver.[42] Fibrates are PPAR alpha agonists which have anti-cholestatic and anti-inflammatory effects, and bezafibrate has been shown to reduce pruritus in patients with cholestatic-induced itch by 75%.[42] Finally, ileal bile acid transporter (IBAT) inhibitors can be used to interrupt the enterohepatic circulation and help pruritus. Inhibition at the terminal ileum results in reduced uptake of bile salts and increased bile salt loss with the feces. Linerixibat at 90mg/day for 3 days followed by 180 mg/day for another 2 weeks demonstrated itch intensity dropping by 57 percent.[42]

LIMITATIONS

At this time, there are multiple studies being done for additional therapies in all four categories of chronic pruritus, with the most in dermatologic itch. Future studies targeted toward further understanding the mechanism of the less studied types of itch such as neurogenic, psychogenic, and systemic may lead to development of more therapeutic options for these patients down the line.

CONCLUSION

Chronic pruritus, or itch lasting more than 6 weeks, is a common presenting symptom seen in dermatology. While the pathogenesis of chronic itch due to dermatologic diseases is multifactorial and related to processes such as an over-activation of the Th2 immune response, the mechanism behind itch seen in neurologic, psychogenic, and systemic itch is less well-understood. Qualifying itch using tools such as NRS and VAS along with identifying the underlying trigger for itch are important for clinicians to pick an adequate therapy. Various topical therapies can be utilized as first-line treatments in dermatologic and neuropathic itch, while oral regimens are best for psychogenic and systemic itch. By correctly identifying the underlying cause of chronic itch, proper therapy can be selected to provide the most optimal relief for patients.

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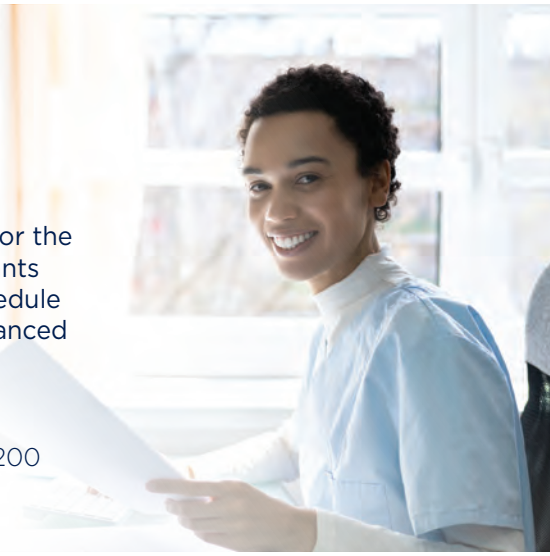

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FUNDAMENTALS OF DERMATOLOGY

Healthcare Documentation Review and Reminders

By Jaci J. Kipreos, CPC, CPMA, CDEO, CEMC, COC, CPCII

Introduction

Welcome to Compliance Corner, a department dedicated to providing information and tools to help keep your healthcare documentation for coding and billing compliant. This resource aims to help you navigate recent changes to Current Procedural Terminology® (CPT®) Evaluation and Management (E/M) guidelines for office visits, which became effective January 1, 2021. Written by the American Medical Association (AMA), these guidelines contain new methodology and new definitions, both of which affect the way you as providers document the account of the patient visit.

How are You Getting Along with the 2021 Documentation Guidelines?

Wow! It has already been a year since the AMA released the 2021 Documentation Guidelines. It would seem appropriate to check in with some reminders of what is important for the documentation of Medical Decision Making and time.

As I am sure you remember, medical decision making is comprised of three key areas, each with specific terminology and levels of complexity. Here are some questions you may want to ask yourself before completing your office note and submitting a claim.

The Three Parts of Medical Decision Making

The Complexity of the Problems Addressed

1. Does your documentation indicate if the condition is chronic or acute?
2. If this is a chronic condition, are the individual goals that were established as part of the treatment plan being met?
   a. Does your documentation indicate the goal and the status of the condition?
   b. Would an auditor know if the chronic condition was stable or not improving?
3. If this is an acute condition, does your documentation indicate if this is an uncomplicated or complicated acute condition?
   a. Does your documentation indicate if this acute condition will resolve on its own?
   b. Does your documentation provide information concerning any long term affects from this acute condition?
4. If multiple conditions are addressed, is there a status and plan for each condition?

The Complexity of Data Reviewed and Analyzed

Does your documentation accurately reflect any of these key points? Would someone reviewing your documentation be able to give you credit for any of the below data items?

1. If external data is reviewed that must be evident in the documentation. External refers to any source outside of the group or practice.
   a. External data could be notes from a referring provider or a provider from another specialty or group that is also participating in the care of the patient.
2. Labs, that are results only, that are performed in the office and are reported by the group may count as one point for either the order or the review.
   a. If labs are ordered and performed elsewhere, each will still be counted as one point for either the order or the review.
   b. The documentation should reflect the source of the lab data.
      i. If the lab was ordered by an external source, then the review of those labs will count toward the complexity of data.
   c. When labs are reviewed, the documentation should reflect how that value or information was used in the decision-making process.
3. Complexity of data also gives credit for conversations with external sources such as other providers who are external to the

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practice. The documentation should indicate which external provider will be contacted and the reason for the discussion.

a. The discussion must be verbal not written, such as email, and it must be between the two providers not any of their ancillary staff.

The Risk of Management Options—Reminders about your documentation

1. The AMA has indicated that this risk is based entirely on the risk to the patient based on treatment options that are considered and or suggested at that encounter. This treatment risk is not to be confused with risk associated with the condition.
2. If the risk of any treatment is discussed with the patient, that should be indicated in the documentation.
3. The AMA has stated that the term "risk" is used to indicated risk that is unique to that patient due to the treatment plan discussed.
4. If the condition poses a risk to the patient, that risk is considered under Problems Addressed.
5. The documentation should clearly indicate any risk to the patient
   a. Defining "risk"
      i. If the patient is obese or is a smoker and this will add risk to their recovery or ability to improve, this should be documented.
      ii. If the patient has co-morbid conditions that make it necessary to change a treatment plan, that should be documented.
6. If the treatment is over-the-counter medications, without any documentation of extenuating circumstances, then the overall risk will be considered low complexity risk.

Time-Based Documentation

The AMA updated the language for time-based coding and now allows for the total time on the date of service to be used when selecting the level of service. As with any CPT code reported, there must medical necessity to indicate what was performed during that time.

Examples of Typical Activities that Count Toward Time:

- ✔ Preparing to see the patient (e.g., review of tests)
- ✔ Obtaining and/or reviewing separately obtained history
- ✔ Performing a medically appropriate examination and/or evaluation
- ✔ Counseling and educating the patient/family/caregiver
- ✔ Ordering medications, tests, or procedures
- ✔ Referring and communicating with other healthcare professionals (when not separately reported)
- ✔ Documenting clinical information in the electronic or other health record
- ✔ Independently interpreting results (not separately reported) and communicating results to the patient/family/caregiver
- ✔ Care coordination (not separately reported)

The documentation should not be just a statement of total time. The activities that took place must be documented to support the time spent. Any activity performed from the list of examples given above should be documented.

Think about your documentation and what you are relating to someone who would be reviewing the medical record you created. Are you following the guidelines or are you following what your electronic health record is telling you the level of service should be? It will always be your documentation that will be needed to support the codes that are reported to the payer.

Congratulations to all for surviving the first year of significant changes to CPT E/M guidelines for office visits! Happy documenting through 2022!

If you have questions or suggestions for particular topics to cover in upcoming issues, please let us know at coding@dermpa.org.

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Listening To Patients
Expert Advice

By Alan Rockoff, MD

I once answered online skin questions. The most popular one was, *"Is my penis supposed to look like that?"*

Then the site was bought by an entrepreneur with a corporate sensibility. He opened two forums: for fifteen bucks, you could access the Medical Forum and ask a doctor. For ten, you could join the Community Forum and ask anybody with an opinion. One guess about which forum was more popular.

Years later, a colleague referred a fellow who had run a poison ivy website for a decade and wanted to interview a doctor. He had never spoken with one before, "because it never occurred to me." His site featured the usual folklore: that blister fluid spreads the poison, that you can catch it from your dog. His website had many pictures. Some were in focus, and a few actually showed poison ivy.

I checked a year later and found that he had never uploaded our interview to his website. When I emailed to ask how come, he said he'd been busy, and did I want him to? I told him I was OK.

What made me think of these old episodes was a phone chat I had the other day with an IT guy about my laptop.

After I told him my problem, he said, "Since you're a doctor, could I ask you a medical question?"

"Sure."

"Is the COVID vaccine safe?" he asked.

"I had two shots myself," I said, "and I'm planning a third. Does that tell you what I think about how safe it is?"

He didn't answer, and we got back to the laptop.

Five minutes later he said, "I just wonder whether we should mess with vaccines. Maybe we should let nature take its course."

"How about polio and diphtheria?" I asked. "Should we let nature take its course with them?"

He thought for a moment and said, "If you don't get vaccinated, can I get really sick, or is it just like the flu?"

"Yes, you can get really sick," I said, "even if you're not old or don't have a weak immune system."

Again, no response. We finished up with the laptop.

"Thanks for your medical advice," he said. "I get conflicting information from so many sources."

Yes, he does. He and everybody else always have. When the issues are poison ivy and genital blotchiness, the stakes are not high enough for anyone to talk about. To a large extent, people have always made their minds up about things based on what their friends think and tell them.

If your friends all wear masks, they will stare at you if you don't. If your friends don't wear masks, they will stare at you if you do. Or glare, or worse. Very few people like to be singled out and pointed at.

When an issue is public and the medical stakes high, as they are with masking and COVID vaccination, lay spokesmen and sage commentators give "reasons" for one opinion or another: social media disinformation, distrust of the establishment, personal freedom. When the stakes are low, no reasons are needed. Who cares why someone blames Fido for his poison ivy?

Addressing the reasons people give for their positions, or the reasons others assign to them, may sometimes help people reconsider. For all

those other times, the old adage applies: You cannot reason someone out of what he never reasoned himself into.

When it comes to contact dermatitis or penile blotches, you can try to straighten people out, but it doesn't matter much if you fail. When the people you are trying to convince are spreading disease, filling up ICUs, or dying, it matters a lot, which does not necessarily increase your odds of succeeding.

There have always been "Medical Forums"—where you ask a professional with official credentials—and "Community Forums"—where you ask Jerry next door or Hortense on Instagram. There always will be. Most of the time, this is a curiosity of little general interest. But not always.

Of course, I believe in expert advice. I spent my whole career dispensing it.

Still, modesty is proper. Knowledge may be evolving and tentative, and sensible advice often ignored.

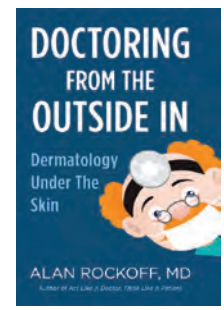
As Hippocrates said a long time ago: Life is short, and art long, opportunity fleeting, experimentation perilous, and judgment difficult.

They all still are.

Alan Rockoff, MD, *practices dermatology in Boston, Massachusetts. He graduated with his medical degree in 1972 from the Albert Einstein College of Medicine in Bronx, New York and then completed a pediatric internship and residency at Bronx Municipal Hospital Center in Bronx, New York. Continuing his education, Dr. Rockoff completed a dermatology residency program at the combined program at Boston University and Tufts University in Boston, Massachusetts.*

Dr. Rockoff is a Clinical Assistant Professor of Dermatology at Tufts University School of Medicine. He has taught senior medical students and other trainees for more than 35 years. Dr. Rockoff has been named one of Boston's Top Doctors by Boston Magazine for five years. Dr. Rockoff is board certified by the American Board of Pediatrics and the American Board of Dermatology. Dr. Rockoff is a Fellow of the American Academy of Dermatology and a member of the Massachusetts Medical Society and the Massachusetts Academy of Dermatology.

Dr. Rockoff's publications have appeared in numerous journals. He writes a monthly column for his dermatologic colleagues in Dermatology News as well as a blog for the magazine Psychology Today. His first book, "Under My Skin: A Dermatologist Looks at His Profession and His Patients" is available on Amazon and is his second book, "Act Like a Doctor, Think Like a Patient: Teaching Patient-focused Medicine" is available on Amazon and at Barnes and Noble. His third and most recent book, "Doctoring from the Outside in: Dermatology under the Skin" is available on Amazon in paperback and Kindle format.



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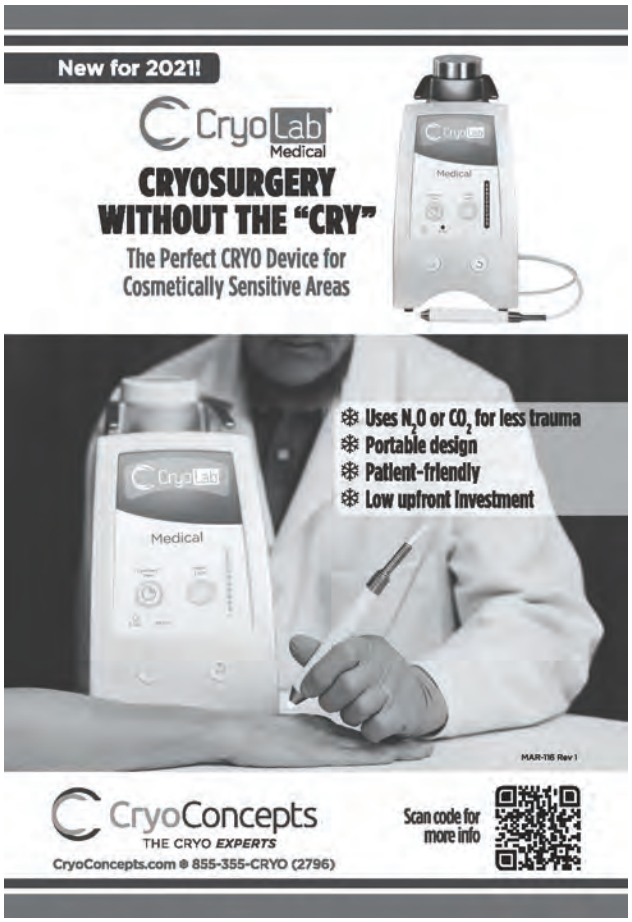

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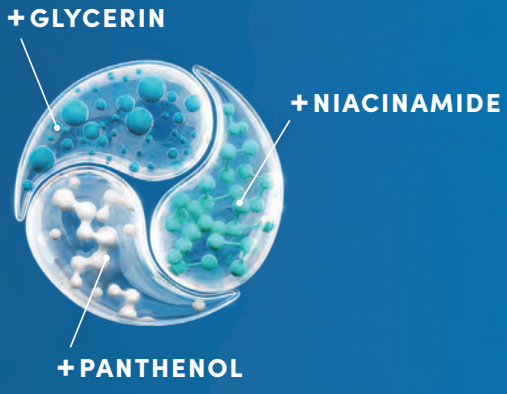

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