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Dermatology Journal Club
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JAAD: A novel lotion formulation of 20% oxybutynin hydrochloride for the treatment of primary palmar hyperhidrosis: A randomized, placebo- controlled, double-blind, phase III study

- *What is the general condition, procedure or disease under study?*
    - Palmoplantar hyperhidrosis (PPH) is common in the general population. Topical aluminum chloride, a mainstay of therapy, can be extremely irritating to the skin, particularly at high concentrations. Other options include injection with neurotoxins (botox), iontophoresis, and systemic anticholinergics. This study aims to explore the role of topical anticholinergics in the treatment of PHH.

- *What were the research question(s)?*
    - Does 20% oxybutynin lotion applied daily to the palms for four weeks significantly decrease palmar sweating (by 50%) over the course of 4 weeks?

- *Was the question answered to your satisfaction - validity? Do you trust the conclusions and recommendations?*
    - Prospective, randomized, double- blind, placebo-controlled multi- center study conducted at 21 Japanese outpatient dermatology from October 19, 2020 to February 13, 2021.
    - Patients had to be over the age of 12, could not have any other skin disease of the palms, be on any other medications for PPH, and have greater mean sweat volumes (over a 3 day period during baseline measurement prior to randomization) than 0.5 mg/cm2/min.
    - A ventilated capsule perspiration meter was used to measure sweat volume. This was repeated in a similar fashion described above after the 4 weeks of treatment.
        - A cup-form capsule was placed on the base of the and fed with ambient air, and sweat volume is calculated by determining the difference in humidity of the air before and after it has passed through the capsule. The outside temperature was standardized to 23-26 degrees C and 40% relative humidity
    - Patients applied 500 uL of 20% OL to the entire surface of both palms once daily before going to sleep.
    - The two arms were compared with a fisher's exact T test. Roughly 140 patients in each arm.
    - <u>After 4 weeks, the treatment arm demonstrated significant difference in response rate (> 50% drop in sweat volume) compared to the placebo arm (52.8% vs 28.3%, p<0.001, respectively). However, there is not seem to be a</u>

difference between groups for change in hyperhidrosis disease severity scale (HDSS) or dermatology life quality index score (DLQI) after 4 weeks of treatment.
    - This is a very well designed study with good objective and subjective measures. Based on the response rates from the HDSS, I wonder if the statistical significance of reduced volume sweat actually translates to clinical significance in patient satisfaction.
    - Only 5% of patients in the treatment arm experienced "thirst" although this was not severe enough to discontinue therapy. This makes topical oxybutynin an attractive option in comparison to systemic anticholinergics.

- *Does this study prompt or inspire a different and better study?*
    - Sweating can either be an autonomic response or related to emotion (anxiety) and it is difficult to control for the ladder.
    - Population being studied limited to Japanese – further studies needed to see if generalizable across ethnic groups.
    - A study that directly compares topical aluminum chloride to oxybutynin that measures sweat response and quality of life measures is needed to extrapolate how to implement this therapy into our drug algorithm for PPH.

JAMA DERM: Risk of Venous Thromboembolism Among Adults With Atopic Dermatitis

- *What is the general condition, procedure or disease under study?*
    - Recently, the literature has suggested that atopic dermatitis (AD) can be associated with an increased risk for cardiovascular diseases. Furthermore, adults with AD have been found to have elevated levels of inflammatory markers and prothrombotic markers. This study aims to better decipher the relationship between AD and venous thromboembolism (VTE) in adulthood.

- *What were the research question(s)?*
    - Do adult patients with AD have an increased risk for VTE?

- *Was the question answered to your satisfaction - validity? Do you trust the conclusions and recommendations?*
    - Retrospective cohort study that collected data from Taiwan's National Health Insurance Research Database (NHIRD).
    - Patients in the AD group were over the age of 20, had a new diagnosis of AD from 2003-207 validated across three office visits (dermatologists or rheumatologists) according to criteria from ICD. The non-AD cohort was matched by gender and age among other systemic comorbidities.
    - VTE was analyzed via ICD codes generated for DVT and PE after the third confirmatory visit for AD.
    - The AD group was subdivided between mild and severe (patients prescribed systemic agents), age (under and over 45 years)
    - Cox proportional hazard models were used to estimate hazard ratios.

    - Incident rates of VTE were 1.05 and 0.82 per 1000 person-years for AD vs non-AD, respectively.
    - Adults with AD were at an increased risk of incident VTE (HR, 1.28; 95% CI, 1.17-1.40) compared with adults without AD and this was true of both DVT and PE (even when stratified among mild and severe AD). This relationship remained statistically significant with patients > 45 years old, but not in the younger cohort.
        - I am doubtful of the conclusions for this study. The incidence of VTE increased proportionally as a function of time for both AD and non-AD groups with the confidence interval for HR starting ~1.1 suggesting that the risk of VTE may be more directly related to age than systemic inflammation from AD.
- *Does this study prompt or inspire a different and better study?*
    - This study did not control for smoking history which is a known risk factor for thrombosis
    - This study did not stratify patients on systemic therapies by medication type (MTX, AZA, phototherapy) or how long they were on these medications for.
    - This research inspires a study that compares long term data for VTE among patients taking JAK-I vs other conventional systemic therapies

CYCLING BACK TO DOXYCYCLINE'S ROOTS AS THERAPY FOR BULLOUS PEMPHIGOID

By Warren R. Heymann, MD, FAAD
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Patients with moderate to severe bullous pemphigoid are usually treated with systemic corticosteroids. Four patients were treated with tetracycline hydrochloride and niacinamide because of the steroid-sparing anti-inflammatory properties of these agents. An excellent clinical response free of side effects was observed in all patients. The lesions recurred whenever treatment was discontinued. It is believed that these drugs suppress the complement-mediated inflammatory response at the basement membrane zone by suppressing neutrophil chemotaxis and mediators of the inflammatory response in this bullous disease.

This 1986 abstract from the seminal article by Berk and Lorincz crystallized the use of tetracyclines as anti-inflammatory agents, rather than antimicrobial drugs, as steroid-sparing agents for treating bullous pemphigoid (BP) in concert with niacinamide. (1) The concept of antibiotics (usually doxycycline or minocycline) as anti-inflammatory agents was novel in the 1980s and has become a standard first-line treatment for BP, aside from corticosteroids (ultrapotent topical or systemic). Treating BP requires a thorough medical knowledge of the patient and their comorbidities — tailoring therapy to include second-line agents (azathioprine, mycophenolate mofetil, dapsone, or methotrexate) or

third-line therapies (IVIG, rituximab, omalizumab, dupilumab, and others) must be individualized to the patient's overall health. (2)

This commentary will focus on the use of doxycycline for BP. Can its efficacy be solely due to its anti-inflammatory effect?

Doxycycline was FDA-approved as an antibiotic in 1967. It is a broad-spectrum bacteriostatic agent that inhibits bacterial protein synthesis by targeting the 30S ribosomal subunit of gram-positive and gram-negative bacteria. The anti-inflammatory effects of doxycycline have been reviewed by Henehan et al and include inhibition of multiple matrix metalloproteinases, diminishing protease-activated receptor 2 (PAR2), reducing both random migration and guided chemotaxis of neutrophils, decreasing pathogenic nitrous oxide synthase levels, reducing IgE production, scavenging radicals thereby reducing oxidative stress, hindering granuloma formation, and inducing apoptosis via caspase pathways. (3)

Eosinophils are potent pro-inflammatory cells; the tetracyclines (tetracycline, doxycycline, minocycline) have been used to advantage in disorders such as asthma or BP where eosinophils play a pathogenic role. Gehring et al have demonstrated that the tetracyclines significantly induce eosinophil apoptosis and strongly overcome the strong survival-enhancing effects of pro-eosinophilic cytokines and *Staphylococcus aureus*(SA) enterotoxins. (4)

(Niacinamide, also known as nicotinamide, was initially observed to be beneficial for dermatitis herpetiformis, hence its use in BP. Niacinamide is the pyridine-3-carboxamide form of niacin, a component of the vitamin B complex. It is the precursor for nicotinamide adenine dinucleotide and acts as an inhibitor of poly- [adenosine diphosphate–ribose] polymerase, which plays an essential role in the expression of cytokines, chemokines, and adhesion molecules via enhanced transcription of nuclear factor kB. It also blocks IgE-induced histamine release.) (1,5)

The anti-inflammatory effects of doxycycline, which seemed revolutionary decades ago, are now accepted as routine. For years, I have been telling patients that we are administering the drug as an anti-inflammatory agent, not for its role as an antibiotic. That statement is correct when using doxycycline in subantimicrobial doses — in typical doses, however, perhaps doxycycline is exerting its antibiotic effect.

Any seasoned dermatologist will be on the prowl for secondary infection in patients with BP. In a retrospective review of 110 hospitalized patients with BP, infections were present in 40% (44/110) of the patients. *Staphylococcus aureus* (72.7%, 32/44) was the most common bacterium, and it was highly resistant to penicillin (81.3%, 26/32), erythromycin (62.5%, 20/32), and clindamycin (56.3%, 18/32), but 100.0% sensitive to vancomycin and tigecycline. (6) BP may be complicated by methicillin-resistant SA (MRSA) and sepsis. (7)

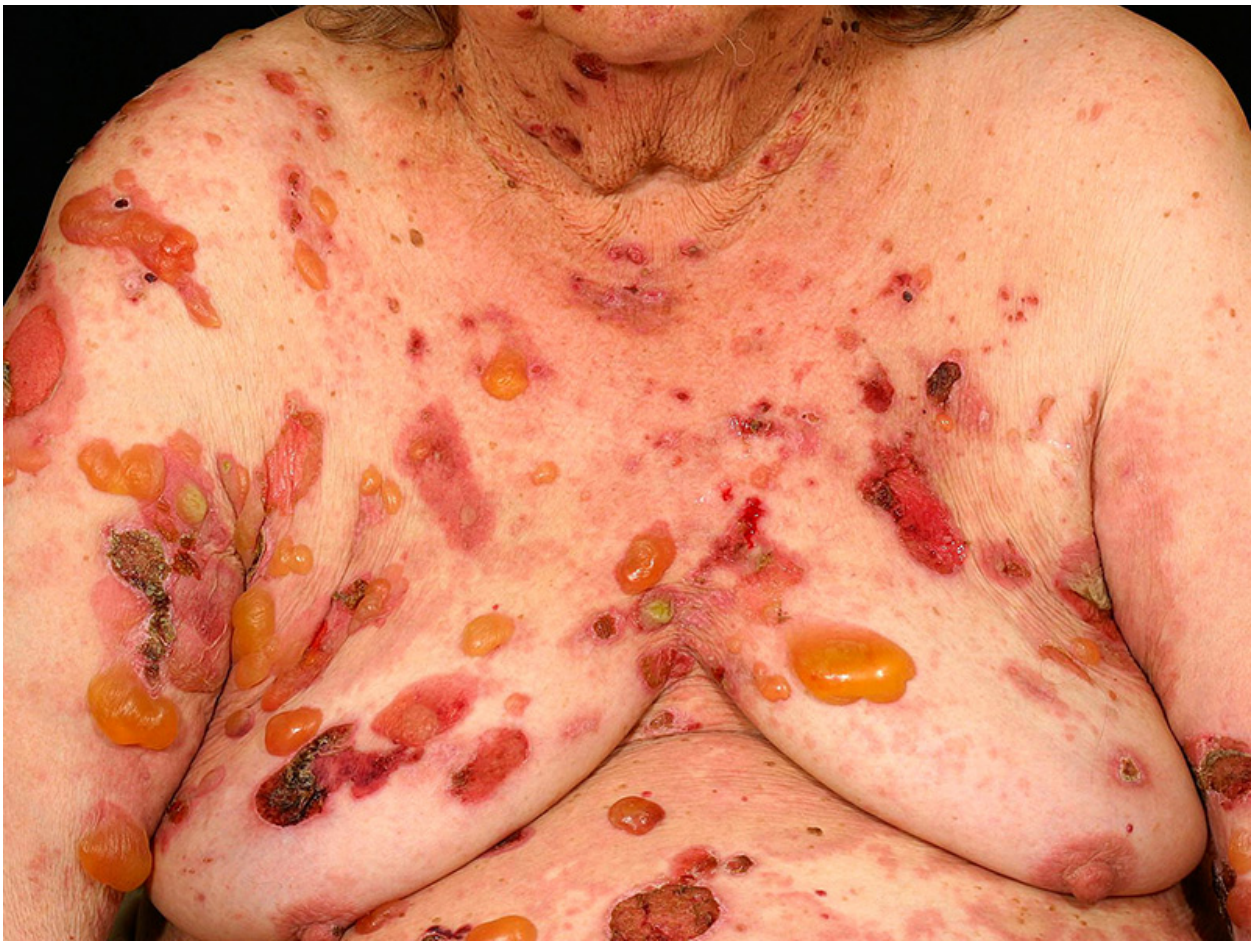

Image from DermNetNZ.

The complex interplay of SA with skin disease is well-known in atopic dermatitis when SA is isolated from patients during flares; as the normal microbiota is reduced, many species that produce inhibitors of SA are also decreased. (8) Scaglione et al studied microbiota of patients with pemphigus vulgaris (PV) and BP using high-throughput sequencing of the V1-V3 hyper-variable regions of 16S rRNA to compare the bacterial community composition of stool, skin, and oral mucosae swabs in a cohort of PV and BP patients. They determined that the Firmicutes phylum and *Staphylococcus* genus were the most represented bacteria in oral cavity and cutaneous swabs of PV and BP microbial populations. (9)

Last week, we discussed the “intimate dance” of SA and cutaneous T-cell lymphoma. Could SA be a trigger of BP aside from being a potential infectious complication? Is doxycycline working as an antibiotic AND an anti-inflammatory agent?

Messingham et al propose that the antimicrobial effects of tetracyclines play an important therapeutic role in BP by the clearance of SA. Their abstract follows: “A potential role of *S. aureus* in bullous pemphigoid was explored by examining the colonization rate in patients with new-onset disease compared with that in age- and sex-matched controls. *S. aureus* colonization was observed in 85% of bullous pemphigoid

lesions, 3-6-fold higher than the nares or unaffected skin from the same patients ($P \leq 0.003$) and 6-fold higher than the nares or skin of controls ($P \leq 0.0015$). Furthermore, 96% of the lesional isolates produced the toxic shock syndrome toxin-1 superantigen, and most of these additionally exhibited homogeneous expression of the enterotoxin gene cluster toxins. Toxic shock syndrome toxin-1–neutralizing antibodies were not protective against colonization. However, *S. aureus* colonization was not observed in patients who had recently received antibiotics, and the addition of antibiotics with staphylococcal coverage eliminated *S. aureus* and resulted in clinical improvement. This study shows that toxic shock syndrome toxin-1–positive *S. aureus* is prevalent in bullous pemphigoid lesions and suggests that early implementation of antibiotics may be of benefit. Furthermore, our results suggest that *S. aureus* colonization could provide a source of infection in patients with bullous pemphigoid, particularly in the setting of high-dose immunosuppression." (10)

I reread Berk and Lorincz's article. (1) None of the four cases had any wound cultures performed.

The latest data about doxycycline's anti-inflammatory capabilities, especially in eosinophil-rich disorders, and the purported role SA plays in triggering (or complicating) them, solidifies its position as a first-line therapeutic agent for BP. Despite its potential benefit, clinicians must use antibiotics judiciously in this age of increasing antimicrobial resistance to SA and other bacteria. (11)

Point to Remember: **Staphylococcus aureus** ***has the potential to trigger or complicate bullous pemphigoid by infection. Tetracyclines may exert their efficacy via their anti-inflammatory and antimicrobial properties.***

Our expert's viewpoint

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Tetracycline antibiotics have been used in bullous pemphigoid (BP) for almost 30 years. Multiple mechanisms have been proposed for their beneficial effects in BP, including antioxidant effects, inhibition of matrix metalloproteinases, and through their antimicrobial activity (12,13,14). These possibilities are not exclusive, and it is likely the beneficial effect of tetracyclines in BP is multifactorial.

BP patients are typically elderly with multiple co-morbidities, and most will receive therapeutic immunosuppression. In addition, BP patients suffer increased hospitalizations and mortality within the first year of diagnosis, with the most common causes being infectious complications, including sepsis and pneumonia (15, 16). Thus, clinicians should be aware of the widespread *S. aureus* colonization of BP lesions (10) and consider that early implementation of antimicrobial therapy may be of benefit, particularly in patients receiving immunosuppressants.

In practice, doxycycline is usually included in the initial therapy for our BP patients. Based on our detection of *S. aureus* toxins in BP blister fluid, we have used short-term clindamycin in patients with severe disease since it inhibits toxin production in a manner independent of its antimicrobial activity (17). Rapid elimination of *S. aureus* toxins may be important in BP patients due to the direct effect of these toxins on immune cell dysregulation, keratinocyte inflammatory responses, and upregulation of damaging matrix metalloproteinases, all of which are of concern for potential worsening of BP (18, 19, 20).

Our understanding of role of *S. aureus* in BP is evolving but this topic story is of interest to those of us who treat this disease. Stay tuned.

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