Atopic Dermatitis--Conclusions From Systematic Reviews

What's New in Atopic Eczema? An Analysis of Systematic Reviews Published in 2008 and 2009.

Batchelor JM, Grindlay DJ, Williams HC:

Clin Exp Dermatol 2010; 35 (December): 823-828

There is a strong association between development of atopic dermatitis and filaggrin gene mutations. The association is weaker for allergic rhinitis and weakest for asthma.

Objective: To review 9 systematic reviews regarding prevention, treatment, and etiology of atopic dermatitis. **Discussion:** 2 systematic reviews confirmed the consistent and strong association between filaggrin mutations and eczema, and filaggrin mutations and allergic rhinitis with and without eczema. A systematic review of 12 trials found only 3 trials correlating risk of atopic dermatitis with transforming growth factor-β (TGF-β) levels in breast milk. Two of the studies found no correlation while the other suggested that TGF-β levels were increased in breast milk of mothers taking probiotics and that the risk of atopic dermatitis in their children was reduced. A systematic review of 27 studies and >30,000 patients found no difference in the risk of developing atopic dermatitis after exclusive breastfeeding for at least 3 months. A meta-analysis of studies looking at the prevention and development of allergic diseases found a nonsignificant decreased risk of developing atopic dermatitis after omega-6 oil supplementation and a nonsignificant increased risk after omega-3 oil supplementation. A recent Cochrane review of dietary exclusions in 421 patients found no evidence to support diets in the treatment of atopic dermatitis. A meta-analysis of 5 trials on probiotics detected a nonsignificant reduction in the atopic scoring rates and nonsignificant difference in quality of life. A systematic review analyzed 10 randomized controlled trials (RCTs) on tacrolimus and 9 on pimecrolimus comprising >7000 patients with atopic dermatitis. Both agents were more effective than placebo.

Reviewer's Comments: I find it difficult to keep track of recent developments in atopic dermatitis. There is certainly an overload of papers dealing with all aspects of the disease and many times the studies have biased methodologies that complicate my interpretation of their results. I selected this paper because it summarizes findings from 9 recent systematic reviews. Systematic reviews are more useful than RCTs, as the latter are often contradicted by subsequent studies. In my opinion, the take-home messages from this paper are as follows: (1) There is a strong association between development of atopic dermatitis and filaggrin gene mutations. The association is weaker for allergic rhinitis and weakest for asthma; (2) Both tacrolimus and pimecrolimus are effective in atopic dermatitis. The recent systematic reviews did not add anything new to what we already knew about these agents; (3) The relationship between atopic dermatitis and TGF-B in breast milk is still unclear; (4) The current evidence does not support breast feeding as an effective way to prevent eczema; (5) It is premature to say whether fish oils are useful to prevent atopic dermatitis; (6) Significantly improved methodology is needed to test the usefulness of diets in the treatment of eczema; and (7) There is no evidence to support a beneficial effect of probiotics in atopic dermatitis. (Reviewer-Carlos Garcia, MD).

Keywords: Atopic Dermatitis, Eczema, Atopy, Asthma, Allergic Rhinitis, Systematic Reviews

Print Tag: Refer to original journal article

Evidence-Based Guidelines for Management of Lichen Sclerosus

British Association of Dermatologists' Guidelines for the Management of Lichen Sclerosus 2010.

Neill SM, Lewis FM, et al:

Br J Dermatol 2010; 163 (October): 672-682

Considerations when there is failure to respond to therapy for lichen sclerosus include: noncompliance; incorrect diagnosis; superimposed problems or diseases, such as contact dermatitis; secondary sensory problems such as vulvodynia; or mechanical problems such as scarring.

Background: Every so often it's nice for American dermatologists like me to take a good look at what's happening on the other side of the pond, and a good resource is the British Association of Dermatologists, also known by the acronym, BAD, which is not only incongruous but also inappropriate because they are in fact, a good if not great, resource. One of the things that make them great is publication of evidence-based guidance for investigation and treatment of dermatologic conditions, with identification of the strength of evidence available at the time of preparation of the guidelines, similar to those being generated by sister societies elsewhere, including the U.S. Recently, the Association published guidelines for the management of lichen sclerosus. **Discussion:** A highlight of some of the more salient recommendations follows. (1) A biopsy is not always essential when the clinical features are typical. However, histopathological examination is advisable if there are atypical features or diagnostic uncertainty and is mandatory if there is any suspicion of cancer or if there is failure to respond to therapy. (2) Cultures for herpes simplex or *Candida* should be performed in ulcerative disease and repeated in disease that flares or fails to respond to treatment. (3) An autoantibody screen to look for associated autoimmune disease should be performed if there are clinical features to suggest an autoimmune disorder. In particular, contemporaneous thyroid disease is common, especially in women. (4) An ultrapotent topical corticosteroid is the first-line treatment for lichen sclerosus in either sex or age group, at any site, but there are no randomized controlled trials comparing steroid potency, frequency of application, and duration of treatment. (5) Asymptomatic patients with evidence of clinically active disease should be treated. (6) Anogenital lichen sclerosus associated with squamous cell cancer (SCC) occurs, but fortunately, rarely. (7) Long-term dermatologic follow-up is unnecessary for uncomplicated disease that responds to <60 grams annually of an ultrahigh potency topical corticosteroid. Considerations when there is failure to respond include: noncompliance; incorrect diagnosis; superimposed problems or diseases, such as contact dermatitis; secondary sensory problems such as vulvodynia; or mechanical problems such as scarring. (8) Those patients with complicated lichen sclerosus that is unresponsive to treatment and those patients who have persistent disease with a history of a previous SCC should have long-term dermatologic follow up. (9) Surgical intervention is indicated for the complications of scarring, premalignant change, or an invasive SCC, or in males with severe irreversible phimosis. (10) Psychosexual issues should be sought and appropriate referrals made if necessary.

Reviewer's Comments: The article reviews clinical features and histopathology of the disease in adults and children. It also presents an excellent overview of the therapies reported with evidence-based weightings. (Reviewer-David L. Swanson, MD).

Keywords: Guidelines, Therapy, Lichen Sclerosus

Print Tag: Refer to original journal article

Gamma-Secretase Mutations Responsible for Familial HS

Gamma-Secretase Gene Mutations in Familial Acne Inversa.

Wang B, Yang W, et al:

Science 2010; 330 (November 19): 1065

Mutations in the γ-Secretase gene likely cause nonsense-mediated mRNA decay and result in complete loss of function of the γ-Secretase gene product.

Background: Hidradenitis suppurativa (HS) is a common disease with high morbidity. Some patients with this disease have been demonstrated to have an autosomal dominant inheritance pattern.

Objective: To investigate the genetic mechanisms underlying HS.

Participants/Methods: 6 Han Chinese families with features of hereditary HS were studied using a combined genome-wide linkage scan and haplotype analysis. Reverse transcription polymerase chain reaction analysis of peripheral lymphocytes was used to study mRNA expression of the mutant alleles.

Results: A linkage was suggested at chromosome 19q13. Mutations were identified in various subunits of the γ-Secretase gene. Affected individuals had marked decreases in transcript expression of the mutant allele.

Conclusions: The mutations likely cause nonsense-mediated mRNA decay and result in complete loss of function of the γ-Secretase gene product. This suggests a potential target for drug development.

Reviewer's Comments: This is a very important finding. For the first time, the gene that causes some forms of HS has been identified. Experiments with mice have already shown mutations in γ-Secretase-caused skin abnormalities that are similar to those observed in humans with HS. Interestingly, this gene has also been implicated as the cause of early onset familial Alzheimer disease, though none of the screened individuals were found to have both Alzheimer disease and HS. Hopefully, we will see the advent of novel therapeutic treatments as a result of this finding. It's important to keep in mind that most patients with HS do not have the familial form of this disease, but might still benefit from similar treatments. Genetic testing of potentially affected individuals is possible, but probably should not be done routinely, as the results are unlikely to change management of the disease. (Reviewer-Daniel Eisen, MD).

Keywords: Hidradenitis Suppurativa, Acne Inversa, Gamma-Secretase

Print Tag: Refer to original journal article

Is There a Link Between Alcohol Consumption and Incident Psoriasis?

Alcohol Intake and Risk of Incident Psoriasis in US Women: A Prospective Study.

Qureshi AA, Dominguez PL, et al:

Arch Dermatol 2010; 146 (December): 1364-1369

The only type of alcoholic beverage that appears to increase the risk for psoriasis in women is non-light beer.

Background: We have begun to recognize the interplay between genetics and environmental factors as they contribute to psoriasis development. An intriguing question is, "Can an environmental factor, such as alcohol consumption, predispose an individual to the development of psoriasis?"

Objective: To evaluate the independent association between alcohol consumption and risk of developing psoriasis and to determine if this risk is associated with different types of alcoholic beverages.

Design/Methods: The authors analyzed findings from the Nurses' Health Study II, a prospective study of 116,671 U.S. nurses aged 27 to 44 years in 1991. Specifically, authors evaluated a cohort of 82,869 women who were without a history of psoriasis prior to 1991 and who reported amount and type of alcohol intake on biennial questionnaires from 1991 to 2005.

Results: Compared with women who did not drink alcohol, the multivariate relative risk of psoriasis was 1.72 (95% confidence interval [CI], 1.15 to 2.57) for an alcohol consumption of 2.3 drinks per week or more. The authors further examined specific types of alcoholic beverages. They found that there was an association between psoriasis and non-light beer intake, with adjusted relative risk of 1.76 (95% CI, 1.15 to 2.69) for consumption of >5 drinks/week. Notably, light beer, red wine, white wine, and liquor were not significantly associated with psoriasis risk.

Conclusions: Non-light beer intake is associated with an increased risk of developing psoriasis among women.

Reviewer's Comments: This article will not only inform the readers about the relationship between psoriasis and alcohol consumption; it will also teach readers something about beer. I find it intriguing that the only alcoholic beverage that appears to increase the risk for psoriasis is non-light beer. The authors hypothesized that a nonalcoholic component of beer, possibly the starch source used in making the beer, may play a role in new-onset psoriasis. Apparently, beer is one of the few nondistilled alcoholic beverages that commonly use barley for fermentation. Barley contains gluten, which has been shown to exacerbate psoriasis in patients with gluten sensitivity. This study raises important questions regarding how we may consider counseling patients on the role of alcohol in the development of psoriasis. (Reviewer-April W. Armstrong, MD).

Keywords: Psoriasis, Alcohol Intake

Print Tag: Refer to original journal article

Extra-Office Visit Shows Greater Adherence, Improved Outcomes in Atopic Dermatitis

A Randomized Controlled Pilot Study of the Effects of an Extra Office Visit on Adherence and Outcomes in Atopic Dermatitis.

Sagransky MJ, Yentzer BA, et al:

Arch Dermatol 2010; 146 (December): 1428-1430

While this pilot study was not powered to detect small differences in adherence or outcomes, the extra-office visit group showed nonstatistically significant greater improvement in clinical outcomes compared to the control group.

Background: Medication adherence is an important dimension of clinical care. Patient adherence to topical medications for chronic conditions has been documented at around 25% to 35%. For one reason or another, many patients are simply not applying their topical medications as instructed.

Objective: To evaluate the effects of an extra office visit on adherence and outcomes in patients with atopic dermatitis.

Participants/Methods: The investigators enrolled 30 patients aged 2 to 15 years with atopic dermatitis in a randomized pilot study. All patients were asked to apply tacrolimus ointment to affected body areas twice daily for 4 weeks. After the initial visit, patients randomized to the control group were scheduled for a follow-up visit at week 4, whereas those randomized to the extra visit group had follow-up visits at weeks 1 and 4.

Results: During this 4-week study, patients randomized to the control group had mean adherence of 54%, whereas those in the extra-visit group had mean adherence of 69%. The difference in percentage adherence between the 2 groups was not significant. In terms of clinical outcomes, the extra-visit group showed greater improvement in outcomes, as assessed by the visual analog scale of itch intensity and Eczema Area and Severity Index. However, the difference in clinical outcomes between the 2 groups also did not reach statistical significance.

Conclusions: While this pilot study was not powered to detect small differences in adherence or outcomes, the extra-office visit group showed nonstatistically significant greater improvement in clinical outcomes compared to the control group.

Reviewer's Comments: There are many reasons why a patient may not be adherent to applying topical medications. While it may not always be possible to open our clinic schedules to accommodate a visit 1 week after the initial assessment, this study evaluates how such an intervention may be associated with improved clinical outcomes. Other ways by which clinicians encourage patient adherence include simplifying medication regimen, providing education on proper medication use, and leveraging technology to deliver automated, personalized reminders. Dermatologists need to address the issue of medication adherence explicitly with their patients because this is a worthwhile effort at the heart of effective therapeutics. (Reviewer-April W. Armstrong, MD).

Keywords: Patient Adherence, Medication Adherence, Medication Compliance, Atopic Dermatitis

Print Tag: Refer to original journal article

Mechanical Transport of Tissues--A Possible Explanation for Benign SLN Deposits

Solar Elastotic Material in Dermal Lymphatics and Lymph Nodes.

Pulitzer MP, Gerami P, Busam K:

Am J Surg Pathol 2010; 34 (October): 1492-1497

The finding of dermal solar elastotic fragments within the dermal lymphatic spaces and accompanying sentinel lymph node provides support for the concept of benign metastasis or passive mechanical transport of tissues to regional lymph nodes.

Background: The increasing use of sentinel lymph node (SLN) mapping has led to the occasional discovery of extrinsic cells that defy a clear histopathologic classification and etiologic explanation. While some of these tissues may represent heterotopic tissue, others have suggested the concept of benign mechanical transport to explain such deposits. However, convincing evidence for this latter concept is lacking.

Objective: To describe cases of dermal solar elastotic material within dermal lymphatics and regional lymph nodes.

Design: Retrospective study.

Participants: 9 patients with SLN performed for melanomas and Merkel cell carcinoma.

Methods: The skin excisions were compared to the SLN biopsies. Additional special stains for elastic tissue and lymphatic vessels (D2-40) were performed on selected cases.

Results: In both the lymph nodes and skin excisions, solar elastotic material was present. In the skin, solar elastotic material was present in the dermal lymphatics. In the SLN, the elastotic material was present within intracapsular lymphatic spaces and subcapsular sinuses. The deposits were present in both benign lymph nodes and in nodes that harbored metastatic melanoma or benign nodal nevi.

Conclusions: The finding of dermal solar elastotic fragments within the dermal lymphatic spaces and accompanying SLN provides support for the concept of benign metastasis or passive mechanical transport of heterotopic tissues to regional lymph nodes.

Reviewer's Comments: In this paper, the histopathological finding of solar elastotic material in lymph nodes provides support for the concept that mechanical transport of benign tissue may occur through dermal lymphatics and implant within the regional lymph nodes. As SLN mapping becomes more frequent and applied to more malignancies of the skin, it is important to recognize that benign heterotopic elements in a lymph node do not necessarily signify a metastatic malignancy. This is relevant with studies documenting benign nevus cells in SLNs harvested in cases of cutaneous malignant melanoma. The cytologic criteria of malignancy must be established in cellular deposits in lymph nodes before an unequivocal diagnosis of a metastatic malignancy is made. (Reviewer-Paul K. Shitabata, MD).

Keywords: Solar Elastosis, Nodal Nevus, Benign Mechanical Transport

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SMF May Be Misdiagnosed Clinically and By Histopathology

Syringotropic Mycosis Fungoides: A Rare Variant of the Disease With Peculiar Clinicopathologic Features.

Pileri A, Facchetti F, et al:

Am J Surg Pathol 2011; 35 (January): 100-109

In this study, syringometaplasia with lymphocytic epitheliotropism was present in all biopsies of syringotropic mycosis fungoides.

Background: The clinical and histopathologic spectrum of mycosis fungoides (MF) continues to evolve. Syringotropic MF (SMF) is a rare variant with a distinctive clinical and histopathological presentation.

Objective: To define the clinical and histopathology of SMF.

Design: Retrospective study.

Participants: 14 patients (male:female, 10:4) with a median age of 59 years.

Methods: H&E stained slides were reviewed and a standard panel of immunohistochemical stains was performed. Twenty biopsies were taken from the 14 patients. Polymerase chain reaction (PCR) for T-cell receptor (TCR) gene rearrangement was performed on 7 cases.

Results: The lesions were generalized in 8 of the patients and distributed over the trunk, thigh, arm, and eyebrow in the others. Alopecia was present in 7 patients. A prior history of MF was present in 4 patients. Syringometaplasia with lymphocytic epitheliotropism was present in all biopsies. Concomitant involvement of the epidermis was present in 13 biopsies and involvement of the hair follicles in 8 biopsies. Mucin in the hair follicles was present in 3 biopsies. Immunohistochemistry revealed a pan T-cell phenotype with no aberrant T-cell markers. PCR analysis showed a monoclonal arrangement of TCR genes in 6 of 8 cases. Follow-up showed 1 patient dying of disease progression but with only 1 of 20 biopsies showing SMF and another patient dying in tumor stage MF. Additional follow-up with 7 other patients showed persistent disease for a median follow-up of 19 months.

Conclusions: SMF is a rare but important variant of MF that may be misdiagnosed both clinically and by histopathology. Alopecia combined with the characteristic histopathology will assist practitioners to arrive at the correct diagnosis.

Reviewer's Comments: This paper sheds light on an important variant of MF. Since eccrine ducts and other adnexal structures may be involved in other variants of MF, notably follicular mucinosis, it was instructive to note that concomitant hair follicle involvement with mucinosis was present in only 3 cases, suggesting that SMF and follicular mucinosis are distinct. It was somewhat surprising to find that in the cases where immunohistochemistry was performed, there were pan T-cell markers with no aberrant staining. PCR analysis for TCR was helpful to establish monoclonality in selected cases. Ultimately, the diagnosis is a clinical-pathological correlation. It is important to utilize a punch rather than a shave biopsy since the lymphomatous involvement may vary from the level of eccrine glands to superficial eccrine secretory coils. (Reviewer-Paul K. Shitabata, MD).

Keywords: Mycosis Fungoides, Syringotropic, Alopecia

Print Tag: Refer to original journal article

Patients With Psoriasis Have a Higher Rate of Metabolic Syndrome

Prevalence of Metabolic Syndrome in Psoriasis. Results From the National Health and Nutrition Examination Survey, 2003-2006.

Love TJ, Qureshi AA, et al:

Arch Dermatol 2010; December 20 (): epub ahead of print

Patients with psoriasis had higher rates of blood pressure elevation, higher body mass index, and increased waist circumference compared with controls.

Background: Psoriasis has been linked with increased risks of obesity, cardiovascular disease, smoking, and dyslipidemia.

Objective: To utilize data from the National Health and Nutrition Examination Survey (NHANES), which is conducted every 2 years, and to compare the rates of metabolic syndrome between patients with self-reported psoriasis and those in the control group.

Methods: The authors evaluated patients from 2 cycles of the NHANES from 2003 to 2004 and 2005 to 2006, of which 6549 participants aged 20 to 59 years were asked if they were ever diagnosed with psoriasis. Of these participants, 2456 patients without a prior diagnosis of diabetes who had completed further medical evaluation and had the availability of information including sex, smoking status, waist circumference, body mass index (BMI), blood pressure metrics, fasting glucose, HDL, triglyceride, age, and psoriasis status were utilized in the analysis. Metabolic syndrome was identified based on the revised NCEP ATP III criteria (National Cholesterol Education Program Adult Treatment Panel III), which in summary identified a patient with metabolic syndrome as someone having ≥3 of the following criteria: elevated waist circumference, hypertriglyceridemia, low HDL, high blood pressure, and/or higher fasting glucose.

Results: From the 2456 patients, 71 patients had a current or history of psoriasis by self-report and 2385 patients had no history of psoriasis (controls). The prevalence of psoriasis was 4%. The mean age of the population was 39 years, with 50% male and 70% white. Mean BMI was 28. Mean age of patients with psoriasis was 42 years; 46% of them male, 83% white, and mean BMI was 30. It was found that patients with psoriasis had statistically significant higher rates of blood pressure elevation, higher BMI, and increased waist circumference compared with controls. Prevalence of metabolic syndrome was 40% in patients with psoriasis versus 23% of patients without, and the odds ratio for metabolic syndrome was 1.86 after adjustment for age, sex, race, smoking, and serum C-reactive protein levels in patients with psoriasis.

Conclusions: The increased rates of metabolic syndrome may partially explain the increased risks of cardiovascular morbidity and mortality in patients with psoriasis.

Reviewer's Comments: This is yet another study that demonstrated systemic implications of psoriasis, and the importance of treating our psoriasis patients beyond just looking at the skin. Multiple studies have found an association between obesity, cardiovascular risk factors, and smoking in psoriasis. The limitations of this study are its retrospective nature, the self diagnosis of psoriasis by the patient, and the small number of patients (71) that had a self-reported history of psoriasis in this cohort. (Reviewer-Amy Cheng, MD).

Keywords: Psoriasis, Metabolic Syndrome

Print Tag: Refer to original journal article

Pathologic Nodal Evaluation May Be Indicated for MCC

Pathologic Nodal Evaluation Improves Prognostic Accuracy in Merkel Cell Carcinoma: Analysis of 5823 Cases as the Basis of the First Consensus Staging System.

Lemos BD, Storer BE, et al:

J Am Acad Dermatol 2010; 63 (November): 751-761

A TNM staging system based on an analysis of 5823 cases was proposed in 2010 for Merkel cell carcinoma.

Background: Merkel cell carcinoma (MCC) is an aggressive neoplasm with metastatic potential. Prognostic data based on tumor size, nodal evaluation, and long-term survival data have been available through multiple smaller studies.

Objective: To utilize a larger dataset to determine the prognostic significance of tumor size and lymph node evaluation/status in order to derive a consensus staging/prognostic system for MCC based on the TNM system.

Design: The authors reviewed the National Cancer Data Base and identified 10,020 patients via histology codes for MCC between 1986 and 2004.

Results: Of all the reported cases, 61% were men; 94% were aged ≥50 years with a median age of 76 years. At presentation, 66% had local disease, 27% with nodal disease, and 7% had distant metastasis. In total, 5823 patients had 5-year follow-up data available (diagnosed prior to 2000); of these patients, 2856 cases had complete staging and follow-up, and 4707 cases had at least 1 TNM category staging available for analysis. Overall, 2282 patients were alive at the time of last contact. Median follow-up for this group was 64.1 months. The authors measured the extent of disease at presentation and survival and performed analysis on survival based on tumor size (T), nodal status (N), and metastatic status (M) when available. Using these data, the authors put together a TNM staging system similar to American Joint Committee on Cancer guidelines for other malignant tumors, including staging and prognostic information based on micro (N1a) or macrometastatic (N1b) or in transit (N2) disease. Survival curves were also delineated based on the data available. Patients with clinically positive lymph nodes were categorized as Stage IIIb and had a 26% survival at 5 years. Patients with Stage Ia disease had a 79% 5-year survival. There was a trend that patients with micrometastasis (not clinically detectable metastasis) had an improved survival of 42% at 5 years.

Conclusions: The authors presented a new consensus system and survival curves based on a cohort that is 10 times larger than used by any previous staging system.

Reviewer's Comments: One of the limitations of this paper is the incompleteness of the data available in terms of TNM staging from the data set. It also does not provide data on recurrence rates, especially in light of the high risks of recurrence with MCC. Patients with larger tumors >2 cm did not have substantially lower rates of survival compared with patients with small tumors, provided that the lymph node status was negative, and patients with positive lymph nodes have a much poorer prognosis. Treatment of positive lymph nodes with surgery or adjuvant radiation and their affects on survival will need to be further delineated in large studies. (Reviewer-Amy Cheng, MD).

Keywords: Merkel Cell Carcinoma, Staging

Print Tag: Refer to original journal article

Merkel Cell Cancers -- Consider Radiation

The Role of Radiotherapy Alone in Patients With Merkel Cell Carcinoma: Reporting the Australian Experience of 43 Patients.

Veness M, Foote M, et al:

Int J Radiat Oncol Biol Phys 2010; 78 (November 1): 703-709

The majority of patients with Merkel cell cancer will present with locoregional disease, and the addition of external radiation will likely benefit most patients.

Background: Merkel cell cancer is a dangerous but relatively rare skin cancer prone to both locoregional and distant recurrences. It occurs in the head and neck, in the upper extremities, and in older Caucasian patients who may be immunocompromised. Conventional treatment is surgical excision with adjuvant wide-field radiation. In this patient population, some people are not surgical candidates.

Objective: To review the experience with definitive radiation for Merkel cell cancer.

Design: Retrospective review from the Royal Brisbane and Westmead Hospital in Australia.

Participants: 33 of the 43 patients (77%) in this review had nodes that were clinically positive at presentation. Almost half (47%) of the patients had primaries in the head and neck. Many patients had biopsies that removed macroscopic disease. Seven patients had primary disease in the lower limb. There were occult primary tumors in 8 patients (cervical node in 6, the groin in 1, and the axilla in 1). Fifty-six percent of patients underwent radiation therapy at presentation; in 44%, failures were salvaged by radiation.

Methods: The median dose to the primary was 51 Gy, and the median dose to the nodes was 50 Gy. Six patients received large fractions (3 to 5 Gy) and the rest were treated using 2-Gy fractions. The patients treated with large fractions had their doses converted to 2-Gy equivalents. All but 3 patients had regional nodes radiated. Most treatments were done with single electron fields with bolus.

Results: With a median follow-up of 39 months, the in-field local control rate was 75%. The median time to first failure was 5 months. There were 11 local recurrences, with 8 of these being both an in-field and out-of-field recurrence. There were 20 distant failures, and 3 failures occurred in lymph nodes outside of the field irradiated. In 53% of patients, failure occurred outside of the irradiated field. Most out-of-field recurrences were in the visceral organs, with only 3 patients having out-of-field nodal recurrences. Multivariate analysis suggested that only nodal status (ie, nodes positive vs negative) was significantly related to relapse-free survival (P =0.005). In this study, no patient with primary macroscopic disease had an in-field recurrence if doses were >56 Gy. Nodal disease also showed some dose response.

Conclusions: The majority of patients will present with locoregional disease, and the addition of XRT will likely benefit most patients. For patients unable to undergo surgery, we recommend 50 to 55 Gy, with wide fields that encompass macroscopic disease, in-transit tissues, and regional nodes.

Reviewer's Comments: I was pleased with the local control but would suggest 56 Gy as the appropriate dose in head and neck cancers. Doses this high, using bolus and electrons, were apparently not well tolerated in the lower extremities. (Reviewer-Jonathan J. Beitler, MD, MBA).

Keywords: Merkel Cell, Radiation

Print Tag: Refer to original journal article

Isotretinoin Use Associated With Increased Risk of Ulcerative Colitis

Isotretinoin Use and the Risk of Inflammatory Bowel Disease: A Case-Control Study.

Crockett SD, Porter CQ, et al:

Am J Gastroenterol 2010; March 30 (): epub ahead of print

If absolute risk is very small, risk may be identified by individual temporally related case reports, but may be totally missed by case-control studies that are too small.

Background: Isotretinoin (Accutane®) is a vitamin A analog approved in 1982 for treatment of severe acne. Over the ensuing 27 years there were several case reports of patients developing inflammatory bowel disease (IBD) after exposure to isotretinoin, as well as 83 possible cases reported to the FDAs MedWatch program resulting in several multimillion dollar lawsuits. These cases and expert opinion are convincing; however, as late as last year, Bernstein et al (*Am J Gastroenterol* 2009;104:2774-2778), in a population-based case-control study concluded that isotretinoin is not associated with IBD. Now in the March 3, 2010 online issue of *Am J Gastroenterol*, Crockett et al, present convincing data that settle the issue.

Objective: To determine whether isotretinoin is a risk factor for IBD.

Design: Case-control study. **Patients:** 3664 Crohn disease (CD) patients, 4428 ulcerative colitis (UC) patients, and 97 indeterminate IBD patients were obtained from a database including 87 health plans from 33 states.

Methods: IBD cases were matched to 21,832 controls on the basis of age, gender, geographical region, and health plan. Isotretinoin exposure was assessed in a 12-month period before case ascertainment.

Results: 24 IBD cases and 36 controls were exposed to isotretinoin. UC patients were 4 times more likely than controls to have been exposed to isotretinoin (OR, 4.36). In contrast, there was no association between isotretinoin use and CD (OR, 0.68). The risk of development of UC increased with dose and duration of therapy. Compared with unexposed individuals, the OR for development of UC for those taking isotretinoin for <2 months was 2.5, while for exposure >2 months was 5.63.

Conclusions: Isotretinoin exposure is associated with an increased risk of UC, but not CD. This risk is related to the dose and duration of exposure.

Reviewer's Comments: This large case-control study (level 2 evidence) confirms the previous level 5 evidence (case reports and expert opinion), and should settle the issue that isotretinoin is a risk factor for the development of UC. Although the risk is increased, the absolute risk is small. For this reason, smaller case-control studies missed the association while expert opinion derived from case reports has been proven correct. (Reviewer-Allen L. Ginsberg, MD).

Keywords: Ulcerative Colitis, Isotretinoin

Print Tag: Refer to original journal article

Wanted -- 250,000 Nasal Reconstructions This Year

Nasal Reconstruction After Malignant Tumor Resection: An Algorithm for Treatment.

Moolenburgh SE, McLennan L, et al:

Plast Reconstr Surgery 2010; 126 (July): 97-105

Flaps are preferable to skin grafts for lining as their vascularity supports structural cartilage grafts.

Background: With 225,000 new cases of nasal skin malignancy each year, reconstruction of surgical defects of the nose is in great demand. Facility with the options and techniques is important to the majority of plastic surgeons.

Objective: To develop an algorithm for the reconstruction of nasal defects based upon detailed review of the extensive clinical experience of the authors.

Design/Participants: Literature review and retrospective clinical review of the records of clinical patients who underwent reconstructive surgery for defects resulting from the treatment of nasal skin malignancy. Patients were treated at the University of Toronto from 2001 through 2008. ***Guidelines Developed:*** (1) Adequate tumor resection, as histologically defined by Mohs' micrographic technique or hematoxylin and eosin stain is fundamental to any reconstruction. (2) Squamous cell carcinoma of the vestibular skin is best treated by interstitial radiation in preference to surgery. (3) Skin-only defects <1 cm in maximum dimension are usually suitable for primary closure or full-thickness skin grafts. (4) The forehead is an excellent donor site for full-thickness skin grafts for nasal reconstruction. (5) Miter and glabellar flaps are well suited to somewhat larger skin defects of the cephalic two-thirds of the nose. (6) Bilobed flaps are well suited to moderate skin defects of the tip. (7) Alar defects are best reconstructed with nasolabial flaps. (8) Skin defects >1.0 cm in dimension and/or involving multiple esthetic subunits are usually best reconstructed with a paramedian forehead flap. (9) Framework reconstruction requires a structure of greater strength than the native framework to effectively resist the forces of contraction. (10) Conchal, septal, and costal cartilages are the logical donor sites for framework grafts. (11) With some exceptions, turnover and septal hinge flaps are preferable to skin grafts for lining reconstruction because their vascularity supports the use of cartilage graft framework reconstruction. (12) For complex full-thickness defects, a 3-stage folded forehead flap is the most versatile and effective option.

Conclusions: The authors concluded that a systematic, algorithmic approach to nasal reconstruction, based on the recommendations outlined above, suited the needs of their reconstructive patients. They specifically emphasized the benefits of a detail-oriented, measured approach to these common defects.

Reviewer's Comments: This paper is a very worthwhile review of the issues, concepts, and techniques that are frequently relevant to the practice of reconstructive plastic surgery of the nose. In addition, it is well referenced for additional reading. Perhaps the only drawbacks of this paper are that it is based on a clinical experience that is predominantly limited to skin-only defects and it introduces no new concepts or techniques. (Reviewer-Norman V. Godfrey, MD).

Keywords: Nasal Reconstruction, Forehead Flap

Print Tag: Refer to original journal article

Tissue Expansion Offers Reliable Option for Nasal Reconstruction

Extended Forehead Skin Expansion and Single-Stage Nasal Subunit Plasty for Nasal Reconstruction.

Weng R, Li Q, et al:

Plast Reconstr Surg 2010; 125 (April): 1119-1128

Allow 2 to 4 weeks for tissue proliferation before transferring expanded forehead flaps.

Background: Forehead skin may be insufficient in quantity for total or subtotal nasal reconstruction. Many authors have suggested that tissue expansion is unnecessary and harmful to forehead flap nasal reconstruction. This paper offers a different perspective on forehead flap expansion.

Objective: The authors redefine the role of tissue expansion as a means of increasing the amount of forehead skin available for nasal reconstruction by offering their thoughts on the relevant biologic issues that make tissue expansion a helpful adjunct to nasal reconstruction.

Design/Methods: The paper is a topic review, description of personal surgical technique, and retrospective review of a clinical series. ***Details of Technique*:** Reconstruction involves 3 stages: (1) forehead skin expansion; (2) forehead flap transfer with any required framework reconstruction; and (3) pedicle division. Forehead flaps were designed with a 1.5- to 2.0-cm wide pedicle centered over a Doppler-located supratrochlear artery and angled obliquely toward the opposite side. Flaps were designed approximately 1 cm larger than the defect to compensate for elastic recoil. Tissue expanders were placed subgaleally via a scalp incision and initially inflated with sufficient saline to fill all corners of the expander. Biweekly injections of 10% of the expander volume were begun 2 weeks later. Expansion proceeded until the expanded dimensions equaled those of the planned flap width to permit donor site closure. Following this, the expander was maintained in place for an additional 2 to 4 weeks to permit adequate soft tissue proliferation. The distal flap was then raised in the subcutaneous plane to a point 2 cm cephalic to the orbital rim where the dissection was taken submuscular. The nasal framework was covered with the flap, and the donor site primarily closed. Three weeks later, the pedicle was divided.

Results: The authors reviewed 43 cases performed over a 9-year period. Nasal defects involved at least 2 nasal subunits. Causes included trauma, burns, and lesion ablation. The mean time of expansion was 78 days. Three-fourths of the patients rated their aesthetic and functional results as satisfactory or better. Most complications were related to framework failures. Flap-related problems were minor brow elevations or pigmentation changes. No late shrinkage was noted with a minimum of 12 months of follow-up.

Conclusions: The authors concluded that tissue expansion was a helpful, safe, and reliable means of increasing forehead skin availability for nasal reconstruction. With a proper time interval for skin proliferation, a subcutaneous flap, and an additional centimeter of flap dimension, late contracture deformity of the flap was not a problem.

Reviewer's Comments: The authors of this paper offer their ideas about the biologic processes and technical specifics that, if properly used, make tissue expansion of forehead flaps an appealing and reliable option. (Reviewer-Norman V. Godfrey, MD).

Keywords: Nasal Reconstruction, Tissue Expansion, Forehead Flap

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What Kinds of Medical Liabilities Can Arise From EMRs?

Medical Malpractice Liability in the Age of Electronic Health Records.

Mangalmurti SS, Murtagh L, Mello MM:

N Engl J Med 2010; 363 (November 18): 2060-2067

Providers have a legal duty to minimize risks during the transition period between the old medical record and implementation of the electronic medical record.

Discussion: Dermatology has been slow to adopt electronic medical record (EMR) systems. The main reasons that EMRs have been promoted is to reduce costs and medical errors. One area that has been neglected in the discussion is the malpractice implications of the EMR. One point of special liability occurs at the implementation of the EMR into the practice. Serious errors can result from individual mistakes such as incorrectly transferring information into the electronic record, EMR "crashes" or documentation gaps, or other problems that affect clinical care. Effective training and tailoring of new systems to existing technology are crucial, but these measures may not prevent errors entirely, and system failures may recur long after implementation, leaving clinicians to "practice blind," at least temporarily. At least 1 legal case suggests that providers have a duty to minimize such risks during the transition period, and that might include redundancies, such as combining old and new technologies in the transition period. After implementation, it has been presumed but is in fact unclear whether the use of EMRs is likely to increase or decrease malpractice liability. EMRs hold considerable promise for preventing harmful medical errors and associated malpractice claims and offer a safety net by reminding providers of clinical guidelines, but there is currently no evidence that the use of EMRs reduces diagnostic errors. And, the systems have potential new legal risks. There are data management pitfalls. Also, there are risks from linking physicians through electronic communications to unseen patients. Boilerplate emails and notes may provoke patient ire and dissatisfaction. In addition to affecting the risk of a lawsuit, EMRs increase the availability of documentation with which to defend or prove a malpractice claim including documentation of time stamps and orders that are discoverable an potential risk elements. Over the long run, the increase in volume of data may increase risk by forcing busy physicians to be responsible for an ever increasing database established over time. The excess of data exposes the practitioner to risk. With comprehensive EMRs, any deviation from standard of care becomes more problematic as documentation needs increase to explain the discrepancy from the EMR standard.

Reviewer's Comments: The bottom line is that, as use of EMRs grows, failure to adopt an EMR system may itself constitute a deviation from the standard of care, but physicians should consider practice liability implications of systems put into place. Whatever system is used should be one that not only reduces errors and streamlines documentation and billing, but also one that minimizes exposure due to unforeseen circumstances such as system failures or depersonalizing one's clinical practice. This article should be required reading if you are looking into establishing an EMR for your practice. (Reviewer-David L. Swanson, MD).

Keywords: Electronic Medical Record, Malpractice

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Improving the Results of Facial Rejuvenation

Molecular Effects of Fractional Carbon Dioxide Laser Resurfacing on Photodamaged Human Skin.

Reilly MJ, Cohen M, et al:

Arch Facial Plast Surg 2010; 12 (September/October): 321-325

Fractional CO_2 laser resurfacing appears to achieve its effect through upregulation of matrix-metalloproteinases.

Background: The aging skin process is defined histologically by mottled dermal and epidermal architecture, where the epidermis is thickened and the dermis appears hypercellular. The rate of collagen synthesis and dermal fibroblast lifespan are both reduced. CO_2 lasers have been shown to vaporize a surface layer of epidermal cells and cause coagulation necrosis of an underlying cell layer. The entire epidermis and varying thickness of the dermis are removed in the process.

Objective: To elucidate the molecular effects that produce the beneficial results seen with fractional CO_2 laser resurfacing.

Methods: 9 healthy facial rejuvenation patients underwent a 2-mm punch biopsy from the infra-auricular neck skin prior to CO_2 laser treatment. The patients then underwent fractional CO_2 laser resurfacing at a minimal dose (30 W for 0.1 second). On completion of treatment, another punch biopsy specimen was taken near the same site. Additional skin biopsy specimens were then taken from a similar area at day 7, day 14, or day 21. RNA was extracted from the specimen. Microarray protein analysis and reverse transcriptase-polymerase chain reaction were then performed on the specimen.

Results: There was evidence of statistically significant up-regulation of several matrix-metalloproteinases (MMPs), including MMPs 1, 3, 9, 10, 11, and 13. The MMPs break down and remove collagen, which allows for replacement with new, well-organized collagen bundles in the skin. Similar findings have been seen in a previous study using fully ablative CO_2 laser resurfacing.

Conclusions: Fractional CO_2 laser resurfacing works by upregulating the action of MMPs, which is similar to the mechanism of the traditional fully ablative CO_2 laser resurfacing.

Reviewer's Comments: Many modalities exist for facial rejuvenation, from minimally invasive to surgical. Fractional CO_2 laser resurfacing has gained significant popularity recently due to its effectiveness and decreased downtime relative to the traditional fully ablative lasers. It is thought that this is achieved through its spatially confined thermal damage, which allows re-epithelialization to complete usually within 24 to 48 hours. This study sheds some light on the possible molecular mechanisms responsible for the action of fractional CO_2 lasers. Treatments aimed at enhancing the expression of upregulated MMPs identified in this study may further improve the results of facial rejuvenation. (Reviewer-Tang Ho, MD).

Keywords: Fractional CO_2Laser Resurfacing, Matrix Metalloproteinase, Gene Expressions

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Large Outbreak of Chagas in Urban Center Due to Food Contamination

Large Urban Outbreak of Orally Acquired Acute Chagas Disease at a School in Caracas, Venezuela.

de Noya BA, Diáz-Bello Z, et al:

J Infect Dis 2010; 201 (May 1): 1308-1315

Contamination of food can be a cause of large outbreaks of Chagas disease in urban, affluent areas.

Background: In the past decade, there has been a campaign to eradicate the vector responsible for transmission of *Trypanosoma cruzi* in various American countries, with variable success. However, there are other reported modes of disease transmission: transfusion-related, transplant-related, congenital, and oral. In Venezuela, there have been some epidemiologic data that suggest an increase in Chagas disease. Recently, a large outbreak of orally acquired Chagas disease has been reported in Caracas, Venezuela.

Objective: To describe the epidemiology and clinical features of orally acquired Chagas disease. **Case Report:** A 9-year-old boy presented with fever of unknown origin (FUO) and was found to have acute Chagas disease. Multiple similar illnesses and high absenteeism were reported from the boy's school. This prompted researchers to conduct a nested, case-control study involving all school attendees and those related to them. The study involved collection of blood samples for smear evaluation, culture, and serologic studies. In addition, a questionnaire that collects clinical and epidemiologic variables was administered to the study population. A confirmed case was any suspected case patient or symptomatic person with the epidemiological link and blood parasites or specific anti–*T cruzi* antibodies by 2 different serological techniques. A suspected case was any person with an epidemiological link to the institution involved who developed FUO of 15 days' duration and other clinical manifestations.

Results: Of 1000 individuals tested, there were 103 cases of confirmed acute Chagas disease, including 1 death in a 5-year-old boy. There were 2 variables that were significantly associated with Chagas disease: attending school in the morning shift (vs afternoon shift) and consumption of guava juice. Guava juice was prepared in a poor neighborhood at the edge of the city. The woman in charge of preparing the juice was also infected. Fever, arthralgias, skin lesions (including erythema nodosum), and cardiac abnormalities were the most common findings. The majority of patients (75%) were symptomatic.

Conclusions: Oral acquisition of Chagas disease can cause large outbreaks in urban centers and may be underestimated as a route of transmission.

Reviewer's Comments: The authors describe the largest outbreak of Chagas disease secondary to food contamination. Contamination of food with the trypomastigotes is a frequently overlooked etiology of the disease but may be of rising importance. Also, the urban affluent location of the outbreak is unusual. However, given the increasing size of the poverty belts that are in proximity to forests on one end and the city on the other end, a shift in the epidemiology of the disease could be underway. Clinicians and public health authorities need to be aware of this evolving epidemiology. (Reviewer-Hana El Sahly, MD).

Keywords: Chagas Disease, Epidemiology

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