

Journal Watch

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Milk consumption and acne in teenaged boys

Adebamowo CA, Spiegelman D, Berkey CS, et al. J Am Acad Dermatol 2008;58:787-93.

This prospective cohort study sought to examine the association between dietary dairy intake and acne among teenaged boys. The authors studied 4273 boys, members of a prospective cohort study of youths and of lifestyle factors, who reported dietary intake on up to 3 food frequency questionnaires from 1996 to 1998 and teenaged acne in 1999. They computed multivariate prevalence ratios and 95% confidence intervals for acne.

The results showed that after adjusting for age at baseline, height, and energy intake, the multivariate prevalence ratios (95% confidence interval; P value for test of trend) for acne comparing highest (>2 servings/d) with lowest (<1/wk) intake categories in 1996 were 1.16 (1.01, 1.34; 0.77) for total milk, 1.10 (0.94, 1.28; 0.83) for whole/2% milk, 1.17 (0.99, 1.39; 0.08) for low-fat (1%) milk, and 1.19 (1.01, 1.40; 0.02) for skim milk.

The authors concluded that a positive association between intake of skim milk and acne. The authors proposed that skim milk contained hormonal constituents, or factors that influenced endogenous hormones, in sufficient quantities to have biological effects in consumers. Nevertheless, the findings were subjected to a number of limitations. Firstly, not all members of the cohort responded to the questionnaire. Secondly, acne assessment was by self-report and boys whose symptoms might have been part of an underlying disorder were not excluded. Lastly the authors did not adjust for steroid use and other lifestyle factors that may affect occurrence of acne.

Intravenous immunoglobulin selectively decreases circulating autoantibodies in pemphigus

Czernik A, Beutner EH, Bystryń JC. J Am Acad Dermatol 2008;58:796-801.

Autoantibody-mediated diseases such as pemphigus are caused by a single or very limited number of pathogenic autoantibodies. A major problem with all current therapies for these diseases is that they target all antibodies rather than selectively targeting only pathogenic antibodies. The authors conducted the study to confirm observations made in a limited number of patients that suggest intravenous immunoglobulin (IVIg) may be able to selectively lower serum levels of pathogenic autoantibodies.

The study was conducted in 12 patients who received IVIg for the treatment of recalcitrant pemphigus. Serum levels of antibodies to desmoglein 1 (Dsg 1) and desmoglein 3 (Dsg 3) were measured by enzyme-linked immunosorbent assay immediately before IVIg treatment and after a median of 2 cycles (range, 1-3) of treatment. As control, serum levels of several non-pathogenic antibodies (against herpes simplex virus types 1 and 2, mumps, and varicella) were measured concurrently.

The results showed that within a median of 2 weeks following the last cycle of IVIg, serum anti-Dsg 3 declined in all patients who tested positive at baseline and in 8 of 10 (80%) patients testing positive for anti-Dsg 1. On average, anti-Dsg 3 decreased by 45% and anti-Dsg 1 by 32%. By contrast, serum levels of the 4 normal antibodies increased in almost all patients, by an average of 408% ($p < 0.001$).

The results indicated that IVIg could selectively and markedly decrease serum levels of abnormal antibodies in pemphigus without decreasing the levels of normal antibodies. It appears that IVIg is able to achieve the ideal goal of treatment in autoantibody-mediated diseases—by selectively removing only those antibodies that cause the diseases from the circulation. This study was limited by the lack of correlation of clinical response to treatment with IVIg and small sample size.

Fate of manuscripts declined by the Journal of the American Academy of Dermatology

Armstrong AW, Idriss SZ, Kimball AB, Bernhard JD.
J Am Acad Dermatol 2008;58:632-5.

Submissions to the Journal of the American Academy of Dermatology (JAAD) undergo a rigorous peer-review process. However, little is known regarding the fate of manuscripts declined by the JAAD. The authors sought to firstly determine the proportion of manuscripts declined by the JAAD that are subsequently published elsewhere; secondly, identify the journals in which they were published; and lastly study whether the authors of declined manuscripts adopted in their final publications the changes suggested by the JAAD reviewers.

The authors reviewed the outcomes of the 489 submissions declined by the JAAD during two 4-month periods: from March 1, 2004, to June 30, 2004, and from March 1, 2005, to June 30, 2005. Of the 981 manuscripts submitted to JAAD during the two 4-month periods, 489 manuscripts (50%) were declined. Among the declined manuscripts, 201 (41%) had been subsequently published in other medical journals as of March 1, 2007. Among the 55 journals that published manuscripts declined by JAAD, 23 (42%) were non-dermatology journals. The median impact factor for these 55 journals was 1.638, compared with the JAAD's impact factor of 2.402. Among the declined manuscripts, case reports comprised the largest proportion (n=149, 31%), followed

by Original Research Reports (n=90, 18%). Overall, 46 (51%) rejected Original Research Reports were subsequently published, compared with 145 (36%) rejected submissions in other categories that were later published (p<0.01). Among the 101 subsequently published manuscripts for which full texts were available, 82% of the authors incorporated at least one change suggested by the JAAD reviewers. The manuscripts that adopted JAAD-reviewer suggestions were published in journals with higher impact factors than those that did not incorporate any JAAD-reviewer suggestions (p=0.0305).

The authors concluded that approximately half of the manuscripts rejected by the JAAD were subsequently published in other journals within 28 months, among which, roughly 40% went to non-dermatology journals. The median impact factor of the journals that published JAAD-rejected manuscripts was lower than that of the JAAD. Rejected Original Research Reports have a significantly higher probability of being subsequently published than other category submissions. This may be a result of relative quality of Original Research Reports versus submissions for other sections of the journal (e.g., Case Reports). Manuscripts that adopted JAAD-reviewer suggestions were subsequently published in journals with higher impact factors than those that did not incorporate JAAD-reviewer suggestions. This indicates that peer-reviewer comments can be useful and important for improving the quality of scientific publications. The study was limited by the possibility that the average lag time of 28 months in this study is not sufficient for some rejected manuscripts to reach subsequent publication.

A cluster of chilblains in Hong Kong

Chan Y, Tang YM, Lam WY, et al.
Hong Kong Med J 2008;14:185-91.

Chilblain, also known as pernio, is an inflammatory skin condition due to prolonged exposure to cold environment. It often affects the extremities. The affected area is characterized by

erythematous, oedematous papules, and plaques. Blisters and ulceration may occur in severe cases. This article reported the clinicopathological features of a cluster of chilblains diagnosed in February 2008 at a regional hospital and a dermatology clinic (under Social Hygiene Service) in Western New Territories.

Of 11 patients identified with chilblains, 7 (64%) gave an antecedent history of prolonged cold exposure including contacting cold water, exposure in cold weather without protection and prolonged exposure in cold environment while playing TV game. Three patients (18%) had chronic illness including juvenile rheumatoid arthritis, Parkinson's disease and systemic lupus erythematosus (SLE). The diagnosis before skin consultation were vasculitis in four (36%), cellulitis in three (27%), dermatitis in one (9%) and no initial diagnosis in remaining three (27%). None of eleven patients reported Raynaud phenomenon. The main cutaneous features were painful, itchy and dusky erythematous purpura on the extremities. Five (45%) had digital swelling and two (18%) had erosion and ulceration. Skin biopsies were done in six (55%) patients. The histology was dermal perivascular lymphocytic infiltrates with additional features of fibrin thrombi, red cell extravasation, epidermal necrosis and re-epithelialization. Disregarding the patient with SLE and juvenile rheumatoid arthritis, two patients had ANA and rheumatoid factor positive and one patient had positive cold agglutinin. However, these three patients did not manifest systemic autoimmune disease. Topical steroid was prescribed to nine (82%) patients and three (27%) who initially diagnosed of cellulitis received antibiotics. Only the patient with juvenile rheumatoid arthritis received nifedipine because of severe painful lesion. All but one patient with SLE resolved after 6 weeks.

The clustering of chilblains in February 2008 was possibly related temporally to the prolonged cold weather at the end of January to mid-February, the longest cold spell in the past 40 years. Most of the patients developed chilblains as an isolated

condition and resolved spontaneously within a few weeks. General advice on keeping extremities warm by protective methods such as glove should be given.

The prevalence of dermatophyte infection in patients infected with human immunodeficiency virus

Rodwell EJG, Bayles LC, Towersey L, et al.
Int J Dermatol 2008;47:339-43.

Human immunodeficiency virus (HIV) infection is associated with an increased risk of certain fungal infections including candidiasis and systemic mycosis, but it is not known whether HIV infection is associated with an increased susceptibility to dermatophytes. This study sought to determine the prevalence of cutaneous fungal infection in a cohort of HIV-infected patients and HIV-negative controls, and to examine the factors associated with an increased risk of dermatophyte infection.

Participants were examined by the dermatologist for evidence of cutaneous fungal infection. Skin scrapings were taken from the right 4th and 5th toeweb space in all patients and also from any other sites where the sign was consistent with fungal infection. Dystrophy of nails was recorded and samples were taken from most affected nail. The presence of cutaneous fungal infection was defined by positive result from either KOH microscopic examination or culture whereas those having clinical signs but without positive KOH examination or culture were not considered to be positive fungal infection.

A total of 158 patients were examined. The most common fungus isolated by culture was *Trichophyton rubrum*, followed by *T. mentagrophytes*, *T. tonsurans*, *Candida albicans* and *Epidermophyton floccosum*. The prevalence of cutaneous fungal infection was 61% in HIV+ve men, 41% in HIV-ve men, 29% in HIV+ve women and 24% in HIV-ve women. Homosexual sex ($p=0.0008$) was the most significant predictor to cutaneous fungal infection. Duration of HIV infection over 11 years ($p=0.0315$), anti-retroviral use ($p=0.0479$), over two visits per week to gym

($p=0.0264$) were also significant predictors. However, there was no significant correlation between HIV infection or reduced CD4 count and the prevalence of dermatophyte infection. It was concluded that HIV infection was not independently associated with an increased risk of cutaneous fungal disease.

Association between beta-blocker, other antihypertensive drugs and psoriasis: population-based case-control study

Brauchli YB, Jick SS, Curtin F, et al.
Br J Dermatol 2008;158:1299-307.

Beta-blocker and angiotensin converting enzyme inhibitor (ACEI) are widely used antihypertensive drugs that had been reported to induce or exacerbate psoriasis in numerous case series. The authors aimed to study this association by conducting a case-control analysis on the UK-based General Practice Research Database (GPRD).

The study encompassed 36,702 cases with an incident psoriasis diagnosis between 1994 and 2005. The same number of control was identified randomly by matching the calendar time, age, sex, years of history in database. Previous exposure to antihypertensive drugs were stratified by exposure timing (current vs. past use) and exposure duration based on the number of prescriptions. Results showed that beta-blocker was not a substantial risk factor for psoriasis. Adjusted odds ratios (OR) for current use of 1-4, 5-19 or ≥ 20 prescriptions for b-blocker was 0.93 (95% CI 0.76-1.13), 1.10 (95% CI 0.97-1.24), and 1.10 (95% CI 1.01-1.20), respectively. There was no difference between cardioselective vs non-cardioselective β -blocker, nor between hydrophilic vs lipophilic agents. However, timolol prescription was found to have a substantially increased OR of 2.44 (95% CI 1.16-5.14), although the number of patients and control on timolol was small (25 cases vs 10 controls) and the difference could have been occurred by chance. The study also showed that the odds estimates for current use of other antihypertensive

agents including ACEI, calcium channel blocker (CCB), angiotensin II antagonist (AT II blocker), diuretics and clonidine were close to 1.0.

Thereby, this large population-based case-control study does not support the proposition that current use of β -blocker or other antihypertensive such as ACEI, CCB, AT II blocker, diuretics and clonidine is associated with an increased risk of psoriasis.

Blood exposure risk during procedural dermatology

Holzmann RD, Liang M, Nadiminti H, et al.
J Am Acad Dermatol 2008;58:817-25.

Dermatologists are at risk of body-fluid contamination during procedures. Guidelines to minimize this risk have been issued by several organisation including Centers of Disease Control. Even though the occupational hazards are well understood, compliance with these guidelines is variable. This study sought to determine the incidence of physician blood contamination during procedural dermatology. Furthermore, the authors conducted a survey to evaluate the physicians' strategies and attitudes toward exposure to bloodborne disease during procedures.

Five hundred consecutive excisions performed by 4 dermatologists were observed. Blood droplets on face shields and surgical gowns were counted postoperatively. A survey regarding universal precautions during procedures was also conducted with members of the American College of Mohs Surgery (ACMS).

Contamination from blood splashes during dermatologic procedures (Mohs micrographic surgery, excision and repair) occurred in 66.4%. Reconstruction type, anticoagulation use, wound location, and wound size correlated with a higher blood splash rate. The survey showed that face shields and goggles were used inconsistently.

Therefore the authors concluded that physician body-fluid contamination risk with procedural

dermatology is clinically significant. Not only the dermatologists, but their assistants should wear preventive barriers during procedures to minimize the risk of viral transmission. However, the result of this study may not be representative to all practicing dermatologists because only 4 dermatologists participated in the study.

Class-sparing regimens for initial treatment of HIV-1 infection

Riddler SA, Haubrich R, DiRienzo G, et al.
N Eng J Med 2008;299:1065-1074.

The use of either efavirenz (EFZ) or lopinavir-ritonavir (LPVr) plus two nucleoside reverse-transcriptase inhibitors (NRTIs) is recommended for initial therapy for patients with human immunodeficiency virus type 1 (HIV-1) infection, but which of the two regimens has greater efficacy is not known. Furthermore, the alternative regimen of LPVr plus EFZ may prevent toxic effects associated with NRTIs.

In this open-label study, the investigators compared three regimens for initial therapy. These regimens were: (1) EFZ plus two NRTIs (efavirenz group), (2) LPVr plus two NRTIs (Lopinavir-ritonavir group), and (3) LPVr plus EFZ (NRTI-sparing group). Seven hundred fifty-seven patients with a median CD4 count of 191 cells/mm³ and a median HIV-RNA level of 4.8 log copies/ml were randomised into the three treatment groups.

It was found that the time to virologic failure was longer in the EFZ group than in the LPVr group ($p=0.006$) at the median follow-up of 112 weeks. At week 96, the proportion of patients with plasma HIV-1 RNA <50 copies/ml was 89% in the EFZ group, 77% in the LPVr group, and 83% in the NRTI-sparing group ($p=0.003$ for the comparison between the EFZ group and the LPVr group). The groups did not differ significantly in the time to discontinuation because of adverse effects. At virologic failure, antiretroviral resistance mutations were more frequent in the NRTI-sparing group than in the other two groups.

The investigators concluded that virologic failure was less likely in the efavirenz group than in the lopinavir-ritonavir group. The virologic efficacy of the NRTI-sparing regimen was similar to that of the efavirenz regimen but was more likely to be associated with drug resistance.

Extended antiretroviral prophylaxis to reduce breast-milk HIV-1 transmission

Kumwenda NI, Hover DR, Mfenson LM, et al.
N Engl J Med 2008;359:119-29.

A major concern in developing countries is HIV-1 transmission through breast milk which is paradoxically critical for infant survival in the resource-limited settings. The aim of this trial was to determine whether extended prophylaxis of infants would decrease the rate of HIV-1 infection.

Women with HIV-1 infection who were breast-feeding infants were enrolled in a randomized, phase 3 trial in Blantyre, Malawi. At birth, the infants were randomly assigned to one of three regimens: single-dose nevirapine (NVP) plus 1 week of zidovudine (ZDV) (control regimen) or the control regimen plus daily extended prophylaxis either with NVP (extended NV) or with NVP plus ZDV (extended dual prophylaxis) until the age of 14 weeks. The control regimen was previously shown to be effective in a randomized trial in Malawi and is a recommended regimen in resource-limited settings. Using Kaplan-Meier analyses, the study assessed the risk of HIV-1 infection among infants who were HIV-negative on DNA polymerase-chain-reaction assay at birth.

Among 3016 infants in the study, the control group had consistently higher rates of HIV-infection from the age of 6 weeks through 18 months. At 9 months, the estimated rate of HIV-1 infection (the primary end point) was 10.6% in the control group, as compared with 5.2% in the extended-NVP group ($p<0.001$) and 6.4% in the extended-dual-prophylaxis group ($p=0.002$). There were no significant differences between the two extended-prophylaxis group ($p=0.002$). The frequency of breast-feeding did not differ

significantly among the study groups. Infants receiving extended dual prophylaxis had a significant increase in the number of adverse events (primarily neutropenia) that were likely to be possibly related to a study drug.

Therefore, the authors concluded that extended prophylaxis with NVP or with NVP and ZDV for the first 14 weeks of life significantly reduced postnatal HIV-1 infection in 9-month-old infants.

Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76 week results from a randomized double-blind, placebo controlled trial (PHOENIX 1)

Leonardi CL, Kimball AB, Papp KA, et al. *Lancet* 2008;371:1665-74.

Interleukins 12 and 23 were shown to have an important role in the pathophysiology of psoriasis. Genetic polymorphisms in the genes that encode the shared p40 subunit of these cytokines (interleukin 12B) and one of the interleukin 23 receptor subunits, have been linked to psoriasis. The p40 subunit of interleukin 12 and 23 is overexpressed in psoriasis plaques. Preclinical studies implicate p40-containing cytokines in the pathogenesis of psoriasis. Many current therapies in the treatment of psoriasis modulate level of interleukin 12 and 23. Ustekinumab, a newly developed human monoclonal antibody that binds to the shared p40 protein subunit of human interleukin 12 and 23 with high affinity and specificity, is developed for treatment of psoriasis.

This study investigated the safety and efficacy of ustekinumab in treatment of moderate to severe psoriasis by comparing with placebo for 76 weeks. The study was designed in three phases: placebo-controlled phase (week 0-12), placebo-crossover and active treatment phase (week 12-40) and randomized withdrawal phase (week 40-76). Patients had a baseline PASI of 12 or above and at least 10% body surface area involvement. They

were candidates for phototherapy or systemic therapy and had a diagnosis of plaque psoriasis for at least six months. Patients randomized in the treatment group were given ustekinumab by subcutaneous injections at dose of 45 or 90 mg at week 0 and 4, and every 12 weeks afterwards. Patients in the placebo group were given either 45 mg or 90 mg ustekinumab every 12 weeks after week 12. Patients initially randomized to treatment group with PASI 75 were re-randomized at week 40 to receive maintenance ustekinumab or placebo. Patients were retreated if they lost at least 50% of PASI improvement after a week 40 withdrawal.

About two-thirds of patients achieved PASI 75 in the treatment groups at week 12. The onset of response was rapid and some patients achieved PASI 50 at week 2 and PASI 75 at week 4. More than 70% of patients achieved PASI 75 at week 28. Half of patients in both treatment groups achieved at least PASI 90 at week 28. The response rate was maintained through week 40. Patients received maintenance therapy had a better maintenance of PASI 75 than those withdrawn from treatment and remain stable to at least week 76. Patients randomized to placebo in the beginning of study achieved similar response rate after crossover at week 12.

Adverse events were found to be mild, most commonly upper respiratory infection, nasopharyngitis, headache and arthralgia. Rates and types of adverse events, laboratory abnormalities were comparable between treatment and placebo group. Comparative rate did not suggest association of serious infection and malignancy with ustekinumab. Serious cardiovascular events were rare in this study. No mycobacterial or salmonella infections and no lymphoma or demyelinating diseases were reported.

In conclusion ustekinumab is a newly developed biologic which is efficacious for treating moderate to severe psoriasis. Maintenance therapy every 12 weeks maintain a satisfactory disease control for at least 1 year in most patients.

Confirmation of histological clearance of superficial basal cell carcinoma with multiple serial sectioning and Moh's micrographic surgery following treatment with imiquimod 5% cream

Ezughah FI, Affleck AG, Evans A, et al.
J Dermatol Treatment 2008;19:156-8.

There have been concerns about long-term outcome of superficial basal cell carcinoma (sBCC) treated by 5% imiquimod cream. The majority of efficacy data is based on clinical clearance and limited histological examination which may not identify tumour presence at the periphery. This study assessed the efficacy of topical 5% imiquimod cream for sBCC using detailed histological assessment 1 year after completion of treatment.

Nine Caucasian patients with biopsy proven sBCC treated with 5% imiquimod cream 1 year previously and who remained clinically clear were recruited. Eight of the nine sBCC were on the trunk, the remaining one was on the neck. Serial sectioning of the tissue from the center of the original target tumor site was histologically clear in all patients recruited. Moh's micrographic surgery of the surrounding skin revealed clear of tumor in eight of nine patients. The only positive specimen came from a small residual focus of sBCC on the chest at one lateral margin of Moh's specimen, i.e. a clearance rate of 89% at one year was achieved.

Although the study was limited by small sample size, the results showed good correlation between clinical and histological tumor clearance and supported the existing evidence of the efficacy of 5% imiquimod cream in treatment of sBCC.

Utility of lesion diameter in the clinical diagnosis of cutaneous melanoma

Abbasi NR, Yancovitz M, Gutkowitz-Krusin D, et al.
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The ABCDE acronym remains an important clinical recognition pattern to the public and clinicians in

the early diagnosis of melanoma. A challenge to this rule arises with the recognition of small melanoma of diameter less than 6 mm. Previous studies had shown that small melanomas composed 3-14% of all cutaneous melanoma but rarely resulted in recurrence, metastasis or death. This study sought to determine the utility of the current diameter criteria of larger than 6 mm for the early clinical diagnosis of cutaneous melanoma.

The in vivo lesion diameter was determined by the MelaFind computerized skin imaging system. Of 1657 biopsied lesions, 853 (51.5%) were 6 mm or smaller in diameter. Invasive melanomas were diagnosed in 13 of 853 lesions (1.5%) that were 6 mm or smaller in diameter and in 41 of 804 lesions (5.1%) that were larger than 6 mm in diameter. In situ melanomas were diagnosed in 22 of 853 lesions (2.6%) that were 6 mm or smaller in diameter and in 62 of 804 lesions (7.7%) that were larger than 6 mm in diameter.

This study is unique in using computer technology to measure the in vivo diameter of pigmented lesions. This will result in greater accuracy and less interobserver variation with rough human measurement. Previous studies used ex vivo specimen measurement which may result in underestimation of lesion diameter by as much as 20%. The proportion of small melanomas (diameter of 6 mm or less) found in this study is low even among the group of atypical melanocytic lesions removed by experienced dermatologists.

In conclusion the authors recommended that the diameter criterion remain at 6 mm for early detection of cutaneous melanoma with satisfactory sensitivity and specificity. Current theory proposes the increase in proportion of melanoma in lesions with diameter larger than 6 mm may have underlying abnormality in cellular mechanism but further research is needed. The combination of A,B,C,E criteria in addition to D criterion will increase specificity of detection but a decrease in sensitivity is resulted.