

Journal Watch

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Skin colonization by Staphylococcus aureus in patients with eczema and atopic dermatitis and relevant combined topical therapy: a double-blind multicentre randomized controlled trial

Gong JQ, Lin L, Lin T, Hao F, Zeng FQ, Bi ZG, et al. Br J Dermatol 2006;155:680-7.

The study was a multicentre, double-blinded randomized controlled trial, aiming at investigating the colonization of Staphylococcus aureus (*S. aureus*) in lesional and nonlesional skin of patients with eczema and atopic dermatitis (AD) and to compare the therapeutic effect of mupirocin plus hydrocortisone butyrate with placebo plus hydrocortisone butyrate given for 28 days. Three hundred and twenty-seven patients were enrolled (208 eczema, 119 atopic dermatitis). Eczema Area and Severity Index (EASI) and skin swabs from the most severe lesions were taken at baseline and on day 7, 14 and 28 after treatment. Skin swabs for bacteria were also taken from nonlesional skin at baseline.

Colonization rate of bacteria was higher in lesional skin than in nonlesional skin in both eczema (70.2% versus 32.7%, $p < 0.01$) and AD (74.8% versus 34.5%, $p < 0.01$). The colonization density of *S. aureus* was also higher on lesional skin than on nonlesional skin in eczema and AD and was positively correlated with lesion severity. When evaluated at day 28, the effective therapeutic rate (defined as $>50\%$ improvement in EASI score) was similar between experimental group (on mupirocin plus hydrocortisone butyrate) and placebo group

(on placebo plus hydrocortisone butyrate) for both eczema and AD. However on subgroup analysis, for eczema patients with clinical score of >8 and AD patients with clinical score of >7 , the therapeutic effect was higher in the experimental group than the placebo group on day 7. But there were no difference in therapeutic efficacy on day 14 and 28. The clinical improvement on day 7 is parallel by a decrease in positive rates of all bacteria and *S. aureus*.

The authors concluded that in eczema and AD, colonization by *S. aureus* occurred more frequently on lesional skin and the colonization density correlated with disease severity. Topical corticosteroid alone and corticosteroid-antibiotic combination both had similar efficacy for eczema or AD but combined therapy might be more useful for patients with moderate to severe disease.

Assessment of epidermal sub-populations and proliferation in healthy skin, symptomless and lesional skin of spreading psoriasis

Korver JEM, van Duijnhoven MWFM, Pasch MC, van Erp PEJ, van de Kerkhof PCM. Br J Dermatol 2006;155:688-94.

The study was aimed at detecting the proliferation and differentiation characteristics of epidermal cells in psoriasis and comparing the transition between symptomless and lesional skin. Skin biopsies were taken from centre, inner margin (clinically involved skin at the margin of lesion),

outer margin (clinically uninvolved skin immediately adjacent to a plaque) and distant uninvolved skin of spreading psoriatic plaques from seven patients. As a control, skin biopsies were taken from seven healthy subjects. Expression of Ki-67, β 1 integrin, keratin 6, 10 and 15 were detected by immunofluorescence. Digital images were taken and their expression was calculated as percentage of total epidermal surface.

In the distant uninvolved skin, there was a relative decrease of β 1 integrin, expressed as percentage of total epidermal surface, when compared with normal controls (β 1 integrin was a marker of germinative cells). Moreover, keratin 15 expression was lost. Between the distinct uninvolved skin and the outer margin, although there was no significant difference in the number of Ki-67 positive cells, Ki-67 positive cells were observed in the suprabasal layers only in the outer margin. Between the outer and inner margins, several epidermal changes were seen: absolute increase in β 1 integrin positive cells (but when expressed as percentage of total epidermal surface, there was a relative decrease because of the acanthotic epidermis), increased in number of Ki-67 positive cells, decreased in number of keratin 10 positive cells and suprabasal expression of keratin 6. From the inner margin to the centre of lesion, patchy keratin 6 expression changed into a homogeneous pattern. In the central area, most keratinocytes coexpressed both keratin 6 and 10.

This study demonstrated that even in distinct uninvolved skin, there were subtle changes in keratinocytes. In transit from symptomless to lesional skin, there were abnormal inflammation, together with recruitment of proliferative keratinocytes and expression of proliferation-associated keratins.

Evaluation of methotrexate and corticosteroids for the treatment of localized scleroderma (morphea) in children

Weibel L, Sampaio MC, Visentin MT, Howell KJ, Woo P, Harper JI.

Br J Dermatol 2006;155:1013-20.

Localized scleroderma (LS) is often considered to be a benign self limiting condition. But at times, severe deformities occur, resulting in functional or cosmetic disability. The study retrospectively reviewed children receiving systemic steroids and methotrexate for LS in a single centre between 1998 and 2005. Thirty-four patients (age range: 2.3 to 15.2 years) were included, 91% had linear LS or a combination with linear subtype, 59% presented with a variety of deformities and 56% had more than 5% of body surface area affected. Most patients (82%) received two weekly courses of intravenous methylprednisolone as induction, oral prednisolone and maintenance with methotrexate weekly for one to three years. Six patients (18%) with mild disease received oral steroid and methotrexate only.

The mean duration of follow up was 2.9 years. The disease stopped progressing in 94% of patients when treatment was given. At the last follow-up, 71% had completely inactive disease. Four patients had disease flare during maintenance and seven patients relapsed after discontinuing maintenance. In comparing patients who relapsed and those who did not relapse, no significant difference was found in the duration of maintenance treatment. All relapsed patients responded to steroid, either intravenous or oral, and methotrexate. Adverse events were all mild and transient. Treatment had to be stopped or reduced transiently because of side effects like deranged liver function or leucopenia, but no patients dropped out because of the side effects. Thermography had been used for follow up of 26 patients. In 13 patients who had "active" thermography, 10 (77%) had clinically inactive lesions. A high false positive result was thus observed for thermography.

The retrospective study suggested that in selected cases of childhood LS that might cause severe functional or cosmetic disability, systemic corticosteroid and methotrexate could be beneficial and were well tolerated. But the study was not double-blinded and placebo-controlled, rendering it impossible to draw definite conclusions.

Childhood stye and adult rosacea

Bamford JTM, Gessert CE, Renier CM, Jackson MM, Laabs SB, Dahl MV et al.
J Am Acad Dermatol 2006;55:951-5.

This is a retrospective, matched control, longitudinal database review examining the relationship between childhood stye and adult rosacea. It compared individuals who were diagnosed to have stye as children with a matched control sample of patients who received health care with diagnosis other than stye. An additional group of non-stye patient, who were given a diagnosis of inflammation of the eyelid other than stye during childhood, was compared with a separate matched control sample. Matching criteria included age, sex and location of institution. The diagnosis of adult rosacea (>40 years of age) among all the subjects were searched in the database.

The median age of all patients (in 2002) was 48.0 years (range: 40.0-81.0); with 52.8% of females. There were 201 individuals with stye in childhood and the members of this group were nearly four times more likely to have adult rosacea than their matched controls. The prevalence of adult rosacea in the pooled group with the diagnosis of stye and other inflammation of the eyelids was slightly higher than the control (3.3% versus 2.1%), but did not reach statistical significance.

This study suggested that there might be an association between childhood stye and adult rosacea. It also suggested that the pathophysiology

of stye might not be solely due to *Staphylococcus aureus* and other environmental and genetic factors needed to be considered. Further studies are necessary to evaluate the issue.

Perioral dermatitis in children and adolescents

Nguyen V, Eichenfield LF.
J Am Acad Dermatol 2006;55:781-5.

This was a retrospective chart review to evaluate the history, morphology and disease course of perioral / periorificial dermatitis in 79 children (46 girls and 31 boys) aged from six months to 18 years. Those with periorcular contact dermatitis, lip licker's dermatitis, perianal dermatitis, staphylococcus-infected diaper rash, and rosacea-like eruption were excluded.

The average duration of the facial rash at presentation was eight months, ranging from 2 weeks to 4 years. At the time of presentation, they had been treated with topical steroids (66%), topical antibiotics (43%), topical antifungals (20%), topical calcineurin inhibitors (16%) and oral antibiotics (16%). In total, 72% of the patients had steroid exposure (via topical, inhaled or systemic route) before their initial visits. Fourteen percents of the patients had concurrent atopic dermatitis, 14% had keratosis pilaris, and 14% had one of the common viral infections such as *verruca vulgaris* or herpes simplex. A family history of atopy was found in 55% of the patients and 3% had family history of rosacea. The lesions were found in the perioral (70%), perinasal (43%) and periorcular (25%) areas. Most of them had erythema, scaling, or both (86%) and 66% had papules and 11% had pustules. Treatment with topical metronidazole or oral erythromycin or both were associated with good results and resolution of primary lesions at follow-up visits. On the contrary, treatment with topical calcineurin inhibitors, hydrocortisone or antifungals were associated with persistence of rash and poor results at follow-up.

In summary, perioral dermatitis may be associated with topical corticosteroid use and may be responsive to topical metronidazole alone or in combination with oral erythromycin.

The use of methotrexate alone or in combination with low doses of oral corticosteroids in the treatment of alopecia totalis or universalis

Joly P.

J Am Acad Dermatol 2006;55:632-6.

The study retrospectively reviewed 22 patients (7 men and 15 women; mean age 37.6±13.4 years) with persistent alopecia totalis or universalis of more than one year despite previous conventional treatments including clobetasol propionate 0.05%, psoralen-UVA therapy, tacrolimus and oral or pulse IV corticosteroid.

Methotrexate 15 mg (n=3), 20 mg (n=9), or 25 mg (n=10) was given once weekly either orally or subcutaneously and was continued until 18 months after the beginning of hair regrowth. Fifteen of the patients were also given oral prednisolone 20 mg/day and one patient at 10 mg/day, the other six patients were not given prednisolone owing to previous treatment failure or apprehension of side effects. Of the 22 patients, 14 (64%) had total hair regrowth, six had patchy incomplete regrowth and two showed no response. Complete hair regrowth was seen in 11 of the 16 patients (68%) treated with both methotrexate and prednisolone; and in three of the six (50%) treated by methotrexate alone. Their mean duration of regrowth of terminal hair was 3.0 and 6.3 months respectively. None of the three patients treated with 15 mg/wk methotrexate had a complete regrowth, compared to 14 of 19 (74%) treated with 20 to 25 mg/wk methotrexate. Eight of the 14 patients with complete response developed relapse during decrease or cessation of methotrexate, but most were focal relapses that

were easily treated with more conventional treatments. Severe side effects were not observed, two patients experienced transient elevation of liver enzymes but one patient experienced persistent nausea that needed methotrexate withdrawal.

Although being an uncontrolled study, methotrexate alone or in combination with low dose oral corticosteroid may be a useful treatment in alopecia totalis or universalis. However, considering the potential side effects of long term methotrexate, one should consider the risk/benefit ratio before contemplating such treatment.

Metastatic Crohn's disease in a Chinese girl

Yu JHT, Chong LY, Lee KC.

Hong Kong Med J 2006;12:467-9.

This is a case report of a 15-year-old Chinese girl having metastatic Crohn's disease (MCD) presenting with granulomatous vulval papules and nodules. The girl had recurrent vulval infection and perianal abscesses two years before presentation to dermatology clinic. Skin biopsy from vulva showed acute on chronic inflammation with non-caseating granuloma and lymphangiectasis. Ziehl-Neelsen stain, fungal stain and polymerase chain reaction for *Mycobacterium tuberculosis* were negative. One year later she began to have abdominal pain and diarrhea. Colonoscopy and colon biopsy findings were compatible with Crohn's disease. Her vulval lesions and gastrointestinal symptoms improved with treatment consisting of elemental diet, oral metronidazole, sulphasalazine and topical mometasone furoate.

The estimated age-adjusted incidence of Crohn's disease in Hong Kong Chinese is 1.0 per 100,000. Cutaneous manifestations of Crohn's disease, which rarely occur before the onset of bowel symptoms, can be divided into

granulomatous, reactive and nutritional deficiency-related. MCD is a rare complication of Crohn's disease in which granulomatous skin lesions are separated from the gastrointestinal lesions by normal tissue. MCD may present as erythematous nodules, plaques or ulcers. The most effective treatment for cutaneous Crohn's disease is oral metronidazole. Other treatment employed includes steroid (systemic topical or intralesional), sulphasalazine, immunosuppressants and surgery.

had to be added in four cases. Disease was controlled with topical steroid alone in one case. Remissions were seen in five patients (71%) after a mean follow-up of 5.7 years (range: three to nine years). Two other patients had a relapsing course requiring treatment. The authors concluded that systematic epidemiological surveys provided information on the disease characteristics in a particular region and might streamline future research.

Linear IgA bullous disease of childhood: an experience from Kuwait

Nanda A, Dvorak R, Al-Sabah H, Alsaleh QA. *Paediatr Dermatol* 2006;23:443-7.

The prevalence, incidence, clinical features and epidemiology of linear IgA bullous disease (LABD) of childhood in Kuwait was studied, based on the data collected in an autoimmune bullous diseases clinic. Eight patients with childhood LABD were registered over a period of 12 years, constituting an age adjusted minimum estimated incidence of 2.3 patients /million /year. The male: female ratio was 1.7:1 and age at onset ranged from 10.5 months to 13 years (mean 6.8 ± 4.17 years, median 7.25 years). Patients were diagnosed between five days and 11 years (mean 2.1 years) after onset of disease. Pruritus was common and most cases (62.5%) were of moderate severity (body surface area affected: 20-40%). No mucosal involvement was seen in any of these cases. Crohn's disease, post streptococcal glomerulonephritis, hepatitis A, β -haemolytic streptococcal throat infection were reported in individual cases.

All cases showed positive direct immunofluorescence for linear IgA deposition at the basement membrane zone and indirect immunofluorescence was seen in five cases (62.5%). Follow up data were available in seven patients. Dapsone (1-2.5 mg/kg/day) was used in 86% cases. Systemic steroids (prednisolone 0.5-1 mg/kg/day)

Lymphoma risk in psoriasis: results of the PUVA follow-up study

Stern RS.

Arch Dermatol 2006;142:1132-5.

A prospective cohort study of patients with moderate to severe psoriasis who were treated with psoralen-UVA (PUVA) was performed to assess the risk of lymphoma. The study spanned a 30-year period. Patients were interviewed and the extent of treatment with UVB, PUVA or methotrexate was determined.

Originally, 1380 patients were recruited in 1975-1976. At the final assessment period (2003-2005), there were 636 patients alive and still participating in the study, of which 526 (83%) were interviewed. There were 16 cases of lymphoma (non-Hodgkin's lymphoma: 14 cases; Hodgkin's disease: 2 cases). The incidence of lymphoma was significantly higher during the period 1997-2005 compared to 1975-1996 (incidence rate ratio (IRR): 4.38; 95% confidence interval (95% CI): 1.60-12.06). In patients who had been on methotrexate for 36 months or more, the incidence of lymphoma was also significantly increased (IRR: 4.39; 95% CI: 1.59-12.06). There was apparent interaction between follow-up year and exposure to methotrexate. Beginning in 1997, cases who had been treated with methotrexate for 36 months or more had a 7-fold increased risk of lymphoma compared to cohort members earlier in the study and with less exposure to methotrexate (IRR: 7.77; 95% CI: 2.83-21.39).

High-dose UVB exposure (at least 300 treatments), exposure to PUVA or ionizing radiation were not significantly associated with the development of lymphoma. After adjustment for methotrexate exposure, patient receiving high-dose UVB exposure had no increased risk of lymphoma (IRR: 1.02; 95% CI: 0.21-5.04). The risk of lymphoma for patients who had more than 400 PUVA treatments was similar to that in patients receiving less than 200 treatments (IRR: 1.12; 95% CI: 0.23-5.38).

It was therefore concluded that the risk of lymphoma in psoriasis patients of PUVA follow-up study was similar to that of the general population, unless exposed to high level of methotrexate.

A population-based analysis of laboratory abnormalities during isotretinoin therapy for acne vulgaris

Zane LT, Leyden WA, AL Marqueling AL, Manos MM.

Arch Dermatol 2006;142:1016-22.

The incidence of laboratory abnormalities in a retrospective cohort of patients treated with isotretinoin for acne vulgaris was determined in this study.

The number of patients studied was 13772 (median age 19 years, 51% male). The median duration of treatment with isotretinoin was 21 weeks (median cumulative dose 9 gm). The incidence of abnormal serum triglycerides raised from baseline to treatment period (14% versus 50%, $P < 0.001$), compared to total cholesterol level (15% versus 41%; $P < 0.001$) and transaminase (5% versus 13%; $P < 0.001$). Abnormalities of triglycerides were more severe compared to total cholesterol and transaminases. Most triglyceride abnormalities were of mild elevations although over 7% cases had a moderate to severe increase. A similar increase in the number of cases with moderate to

severe increase in total cholesterol (baseline 0.2% vs treatment 1.4%) and transaminase levels (baseline 0.4% versus treatment 1.5%) was seen. The majority of laboratory abnormalities were reversible on drug cessation. Abnormalities in triglycerides, transaminases and total cholesterol during treatment also occurred in cases with normal baseline parameters. The cumulative incidence of new abnormal triglyceride levels, total cholesterol levels and transaminases were 44%, 31% and 11% respectively.

Haematological abnormalities were mild and uncommon during isotretinoin therapy. In those with normal baseline haematological parameters, new haematological abnormalities were uncommon.

The authors concluded that elevation in lipid level was the most common abnormality seen during isotretinoin therapy, while increase in transaminases was generally mild. Both were usually reversible on drug cessation, although their clinical significance remains unclear.

Azithromycin versus tetracycline in the treatment of acne vulgaris

Rafiei R, Yaghoobi R.

J Dermatol Treatment 2006;17:217-21.

This is a prospective, randomized, investigator-blind study to determine the efficacy and safety of azithromycin versus tetracycline in the management of acne vulgaris. It was conducted at an outpatient clinic over three months, recruiting patients with moderate to severe acne who had first attack or relapsing acne and had no systemic diseases. Exclusion criteria were: drug-induced acne, hormonal disorders, pregnant or breast-feeding, those received systemic acne therapy in the last three months, and having a history of side effects with the two drugs.

Two hundred and ninety patients (228 female, 62 male), aged 11-28 years, were included and were

randomized into two groups. The azithromycin group (n=148) received azithromycin pulse (500 mg/day for 3 consecutive days a week for 4 weeks) and then 250 mg every other day for 2 months. The tetracycline group (n=142) were treated with tetracycline 1 gm/day for the first 4 weeks and 500 mg/day for 2 months. No other systemic drugs and/or topical therapy were allowed for the first month. Topical treatment including topical tretinoin 0.05% nightly was introduced for the last 2 months. The patients were assessed at baseline, 1 month and 3 month. The response was rated as no improvement, partial improvement and complete improvement. Because some patients defaulted follow-up, 118 patients of each group completed the study.

In azithromycin group, 84.7% achieved partial or complete improvement. In tetracycline group, 79.7% showed partial or complete improvement. There was no significant difference in clinical response rate between the two groups after 3 months (χ^2 test, $p > 0.05$). Gastrointestinal side effects were observed in 10.9% and 11% of azithromycin group and tetracycline group respectively.

The authors concluded that both azithromycin and tetracycline were effective acne therapeutic agents. Azithromycin, however, was more expensive than tetracycline and should be reserved in cases who were intolerant to tetracycline, having poor compliance or poor treatment results with tetracycline.

Is it necessary to have routine blood tests in patients treated with isotretinoin?

Ertam I, Alper S, Unal I.

J Dermatol Treatment 2006;17:214-6.

The authors studied the relationship between the side effects of isotretinoin on skin and mucosal surface and blood test changes with the total dose of isotretinoin taken. The study recruited 91

patients (34 male, 57 female) aged 17-28 years (mean 21 ± 2.19) with acne of 1 to 14 years of duration (mean 5.09 ± 2.65). Isotretinoin 0.5 mg/kg/day was given. Blood tests for complete blood counts, liver/renal function tests, cholesterol including HDL- and LDL-cholesterol, triglyceride, glucose level and urine analysis were monitored monthly. The initial and fifth month results were compared to see if there was any significant difference.

Eighty-nine patients completed the study. Two quitted at the second month due to impaired liver function and epistaxis. Total isotretinoin doses prescribed was 4800 to 7500 mg (mean 6283 ± 892). The most commonly seen side effects were xerosis (61.5%), cheilitis (51.6%), retinoid dermatitis (23.1%) and epistaxis (23.1%). There was no significant relationship between these side effects and total isotretinoin dose ($p > 0.05$). There was statistically significant increase in the cholesterol ($p < 0.01$), triglyceride ($p < 0.01$) and LDL-cholesterol ($p = 0.001$) observed in analyzing the initial and post-treatment blood levels. No significant changes were detected in HDL-cholesterol, transaminases and renal function test.

The authors concluded that blood tests for cholesterol, LDL-cholesterol and triglyceride should be monitored monthly in those with initial levels at the upper limits. Bi-monthly or 3-monthly monitoring should be adequate for other patients.

Association between HSV-2 and HIV-1 viral load in semen, cervico-vaginal secretions and genital ulcers of Thai men and women

Chu K, Jiamton S, Pepin J, Cowan F, Mahakkanukrauh B, Suttent R, et al.

Int J STD & AIDS 2006;17:681-6.

The authors aimed to study the association between HSV-2 and HIV-1 viral load in plasma, semen, cervico-vaginal secretions and genital ulcers in HIV-infected Thai men and women with

HSV-2 antibody, asymptomatic HSV-2 genital shedding and HSV-2 genital ulcer.

The recruited subjects were HIV-1 infected, over 18 years old and not on anti-retroviral drugs. In men, semen as well as swab samples were taken from penile shaft, urethra and anus. In women, swab samples were taken from cervix, vaginal wall, external genitalia and anus. Ulcer swabs were taken in those with genital ulcers and were tested by polymerase chain reaction (PCR) for HSV-DNA *Haemophilus ducreyi* and *Treponema pallidum*. Urethral and cervico-vaginal swabs were tested for *Chlamydia trachomatis*, *Neisseria gonorrhoeae* and *Trichomonas vaginalis* by PCR. HSV-1 and 2 serology were measured by ELISA based on glycoprotein G. Syphilis serology was measured using RPR and confirmed with TPHA. HIV-1 RNA in serum, cervico-vaginal, and seminal plasma were also measured.

One hundred and forty subjects were recruited (69 men; 71 women). HSV-2 antibody was positive in 68% of men and 80% of female. Genital shedding of HSV-2 was detected by PCR in 12 out of 68 men (26%) and 5 out of 66 women (8%). In those with HSV-2 antibody, HSV-2 genital shedding was significantly more common in female than male ($p=0.02$). HSV-2 antibody and HSV-2 genital shedding were not significantly associated with either CD4 count or HIV-1 viral load in serum, semen or cervico-vaginal secretions. Twenty-six subjects (11 men; 15

women) had HSV-2 genital ulcers. HIV-1 viral load in ulcers was associated significantly with the reported duration of ulcers. No association was found between HIV-1 viral load in the ulcer and that in plasma and semen in men or that in plasma and cervico-vaginal secretion in women. The mean genital tract HIV-1 viral load did not differ significantly between those with genital ulcer and those without in either sex.

Ten men and nine women with genital ulcers were followed up for a mean of 6 to 7.2 days respectively. The mean log plasma HIV-1 load was higher at the final visit than at the first visit only in men. The mean log ulcer HIV-1 viral load did not differ between the first and final visits for either sex. In women, the mean log HIV-1 viral load in the cervico-vaginal secretions showed no difference between first and final visits. In men, the mean log seminal HIV-1 viral load was significantly higher in men at the final visit in univariate analysis but not after adjusted for plasma viral load.

The authors concluded that HSV-2 serology or HSV-2 genital shedding were not associated with HIV-1 viral load in plasma, semen or cervico-vaginal secretions. The result did not support the hypothesis that HSV-2 increases the HIV-1 viral shedding in genital secretions or in genital ulcers. Further studies were required to confirm the findings. (This study was funded by Glaxo-SmithKline and the Nestle Foundation.)