

Current Best Evidence

Current best evidence from dermatology literature

Zug KA, Rietschel RL, Warshaw EM, Belsito DV, Taylor JS, Maibach HI *et al*. The value of patch testing patients with a scattered generalized distribution of dermatitis: Retrospective cross-sectional analyses of North American Contact Dermatitis Group data, 2001 to 2004. *J Am Acad Dermatol* 2008; 59: 426-31.

Many patients presenting to the dermatologists have eczematous dermatitis in scattered generalized distribution (SGD) and such patients pose a difficult diagnostic and therapeutic challenge. "Scattered generalized" was defined as more than 3 body sites affected by the dermatitis, or 3 sites if the sites were trunk, arms, and legs. In this group of patients, patch testing is a strategy for evaluating allergic contact dermatitis as a relevant factor and thus avoidance of allergen resulting in resolution or substantial improvement in quality of life. A retrospective cross-sectional analysis of North American Contact Dermatitis Group 2001 to 2004 data was done and patch testing results of patients with SGD (1497 patients) were compared with those patients without SGD (8186 patients). Forty nine percent of SGD dermatitis patients had at least one positive patch test deemed of definite, probable, or possible current relevance. The two most common allergens identified in patients with SGD were nickel and *Myroxylon pereirae* (balsam of Peru). Preservatives, fragrances, propylene glycol, cocamidopropyl betaine, ethyleneurea melamine formaldehyde, tixocortol pivalate, and budesonide were the most frequently relevant positive allergens. Top allergen sources included cosmetics/beauty preparations/skin and health care products, clothing, and topical corticoids.

Comment: Many patients presenting in dermatology clinics have eczematous dermatitis affecting different body parts which does not qualify for the diagnosis of specific endogenous or exogenous eczema. In this group of patients, patch testing is a useful tool as shown in present study. In this study almost half (49%) of the patients with SGD had positive patch test results that were deemed at least possibly relevant to

their dermatitis. Allergens that were most commonly relevant were those that are often found in multiple different topical products such as preservatives, fragrances, propylene glycol etc. Additional allergens besides the standard series can be tested depending on the distribution of dermatitis and history of exposure to specific allergens. This study supports the role of patch testing in the evaluation of patients with SGD. More research is needed to understand the origin of SGD not caused by contact allergy, especially in the unclassified eczema category.

Brauchli YB, Jick SS, Meier CR. Psoriasis and the risk of incident diabetes mellitus: A population-based study. *Br J Dermatol* 2008; 159: 1331-7.

Several cross-sectional studies done mostly in hospitalized patients, report a possible positive association between psoriasis and diabetes mellitus (DM). However, information on the temporal relation is scarce, and incidence rates of new-onset DM in patients with psoriasis are not known. Authors have conducted a follow-up study with a nested case-control analysis within the U.K.-based General Practice Research Database to assess and compare incidence rates of new-onset DM between patients with psoriasis and a comparison group without psoriasis, and also explored the role of psoriasis severity and body mass index (BMI). The study population consisted of patients with a first-time diagnosis of psoriasis between 1994 and 2005 and a matched group of psoriasis-free patients. All patients with a prevalent diagnosis of DM were excluded from the study population. Within this study population of 65449 patients, they identified 1061 cases with an incident diagnosis of DM of whom 626 (59%) had a history of psoriasis and 435 (41%) did not. The crude incidence rate for DM was 4.06 per 1000 person-years in patients with psoriasis and 2.98 per 1000 person-years in the comparison group without psoriasis, yielding a crude incidence rate ratio of 1.36 patients with psoriasis compared with the comparison group.

The adjusted relative risk estimate for patients with

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>2 years disease duration and > 2 prescriptions per year for oral psoriasis treatment was 2.56 as compared with those without psoriasis. In an analysis restricted to patients with normal body mass index (BMI), to distinguish between the role of BMI and psoriasis on the risk of developing DM; the adjusted relative risk estimate was 2.02. In conclusion, this large observational study shows that the risk of incident DM was increased for patients with psoriasis as compared with a psoriasis-free comparison group and the risk increased with psoriasis duration and severity and was not driven by high BMI alone.

Comment: Metabolic syndrome and its components have been largely associated with psoriasis. The metabolic syndrome is a combination of diabetes mellitus type 2, hypertension, ischaemic heart disease, central obesity and combined hyperlipidemia. There are only a few studies on the association between psoriasis and diabetes and most are cross sectional studies. Present study is the first study which gives us the incidence rate of new onset DM (4.06 per 1000 person-years) in psoriasis patients which is more than the control group without psoriasis. BMI is a strong risk factor for type 2 DM, and patients with psoriasis have been shown to have higher BMI. Thus, BMI is likely to confound the association between psoriasis and the risk of DM. So the author has done separate analysis restricted to patients with normal body mass index (BMI) and the adjusted relative risk estimate was found to be 2.02 in psoriasis patients.

The herein reported association between the chronic inflammatory skin disease 'psoriasis' and DM may support the notion that insulin resistance, DM and the metabolic syndrome are triggered by chronic inflammation, i.e. that they are associated with a cytokine-mediated activation of innate immunity. The beneficial effect of thiazolidinediones in both DM and psoriasis additionally support the link via inflammation between the two diseases, as these substances are supposed to have anti-inflammatory properties. It is important that the dermatologist systematically seeks these components of metabolic syndrome among psoriatic patients and appropriate treatment of these concomitant pathologies may be an important part of the management of patients with psoriasis.

Murrell DF, Dick S, Ahmed AR, Amagai M, Barnadas MA, Borradori L *et al.* Consensus statement on definitions of disease, end points, and therapeutic response for pemphigus. *J Am Acad Dermatol* 2008; 58: 1043-6.

International Pemphigus Committee after 2 years of collaborative efforts attained mutually acceptable common definitions for pemphigus so that experts in the field can eventually accurately measure and assess disease extent, activity, severity, and therapeutic response at agreed-on time points, and thus facilitate and advance clinical trials.

"Baseline" is defined as the day on which therapy is started by a physician. Early end points define control of disease activity, the end of the consolidation phase, and remission. "Control of disease activity" is defined as the time at which new lesions cease to form and established lesions begin to heal. The "end of the consolidation phase" is defined as the time at which no new lesions have developed for a minimum of 2 weeks and the majority (approximately 80%) of established lesions have healed. A "complete remission off therapy" is defined as the absence of new and/or established lesions while the patient is off all systemic therapy for at least 2 months. A "complete remission on therapy" is defined as the absence of new or established lesions while the patient is receiving minimal therapy. A "partial remission off therapy" is defined as the presence of transient new lesions that heal within 1 week without treatment and while the patient is off all systemic therapy for at least 2 months. A "partial remission on minimal therapy" is defined as the presence of transient new lesions that heal within 1 week while the patient is receiving minimal therapy, including topical steroids. "minimal therapy" is defined as less than or equal to 10 mg/d of prednisone (or the equivalent) and/or minimal adjuvant therapy for at least 2 months. "minimal adjuvant therapy" is defined as half of the dose required to be defined as treatment failure.

A "relapse" and a "flare" of disease are considered as synonymous. They are defined by the appearance of 3 or more new lesions in a month that do not heal spontaneously within 1 week, or by the extension of established lesions, in a patient who has achieved disease control. "Failure of therapy" is defined as the failure to control disease activity (i.e., relapse/flare) with full therapeutic doses of systemic treatments. Hence, there is failure of therapy if there is continued development of new lesions, continued extension

of old lesions, or failure of established lesions to begin to heal despite 3 weeks of therapy on 1.5 mg/kg/d of prednisone equivalent with or without any of the following agents: cyclophosphamide 2 mg/kg/d for 12 weeks; azathioprine 2.5 mg/kg/d for 12 weeks (if thiopurine s-methyltransferase level is normal); methotrexate 20 mg/wk for 12 weeks; or mycophenolate mofetil 3 g/d for 12 weeks.

Comment: International Pemphigus Committee has done a commendable job by framing definitions for pemphigus to accurately measure and assess the disease extent, activity, severity, and response to therapy. This would help in better designing of the comparative drug trials. Definitions include the early observation end points, late observation end points and other definitions. The definition of “control of disease activity” is not very clear as no time frame has been given and also few established lesion might heal while others continue to extend in a given patient. The “end of the consolidation phase” has been defined as the time at which no new lesions have developed for a minimum of 2 weeks. In our opinion 2 weeks is a short span of time to declare the end of consolidation phase. Remission of disease has been categorized well and defined in detail. Separate definitions given for complete and partial remission and further detailed as ‘off therapy’ or while on ‘minimal therapy’. Minimal therapy and the minimal adjuvant therapy have been defined precisely. The definition of “failure of therapy” conveys precisely the doses of adjuvants and duration for which they should be given before considering a failure of therapy. These definitions would help in making good comparative drug trials and framing effective therapies for pemphigus patients.

Wollenberg A, Bieber T. Proactive therapy of atopic dermatitis: An emerging concept. *Allergy*. 2009;64(2):276-8

Atopic dermatitis (AD) is one of the most common skin disorder in developed countries and prevalence has increased two- to threefold during the past three decades. The common long-term treatment concept for AD is reactive treatment approach based on daily application of emollients accompanied with symptomatic anti-inflammatory therapy consisting of topical glucocorticosteroids (TCS) or topical calcineurin inhibitors (TCI) on an ‘as needed’ basis. Recently, an alternative treatment approach has been evaluated in clinical trials. This ‘proactive’ approach

starts with an intensive topical anti-inflammatory therapy until all lesions have mostly cleared, followed by long term, low-dose intermittent application of anti-inflammatory therapy to the previously affected skin together with daily application of emollients to unaffected areas. Several single and multi centre randomized long-term clinical trials comparing the proactive and reactive approach using topical steroids and tacrolimus in adults as well as the children show that the proactive therapy is an effective treatment which prevented, delayed and reduced the occurrence of AD exacerbations in most study patients. The author gives general evidence from basic science and immunobiology in support of long-term proactive treatment strategies. Defects of epidermal barrier function in AD lesions are mirrored by less pronounced, but clearly detectable similar defects in non-lesional AD skin. An analysis of the epidermal lipids essential for skin barrier function showed lower results for extractable long-chain fatty acids in both lesional (75%) and non-lesional (60%) AD skin. Loss of function mutations of the filaggrin gene recently detected in high association with AD will not revert even if the eczema is adequately treated. The histopathology of non-lesional AD skin revealed features of mild disease. So, there is overwhelming evidence that normal-looking, non-lesional AD skin is not ‘normal’ at all, but is characterized by a clinically meaningful barrier function defect and a sub-clinical eczematous skin reaction. Proactive regimen may paradoxically be steroid-sparing as it is an attempt to control residual disease in apparently normal looking skin with minimal use of anti-inflammatory drugs and thus preventing recurrences.

Comment: Atopic Dermatitis is one of the most common dermatological problems in the pediatric population in both developed as well as the developing countries. It takes a high toll on the quality of life of both the children and their family. Any treatment approach that would reduce the number of recurrences and their severity should be advocated. There are many studies in literature which support the proactive therapeutic approach. Topical steroids or TCIs are used by the patient intermittently while the disease is in remission. Authors have given evidences from basic science and immunobiology stating that normal looking skin of patients suffering from AD is not completely free of disease and therefore there is a need to apply medications intermittently while the disease seems apparently to be in remission. There

are apprehensions regarding the side effects of long term use of the steroids as well as the TCIs. Most of the studies of proactive approach report minimal side effects with the long term intermittent use of these drugs. Paradoxically the total amount of drug used over long period of time may rather be reduced as the number and severity of flares is reduced which demand higher doses of the drug. In daily practice, the pros and cons of both approaches should be explained and discussed with each patient individually in order

to reach a final decision together with the informed patient.

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