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Journal Watch

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Mortality of bullous pemphigoid in Singapore: risk factors and causes of death in 359 patients seen at the National Skin Centre

Cai SC, Allen JC, Lim YL, Chua SH, Tang MB.
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Bullous pemphigoid (BP) is an immunobullous disease commonly seen in elderly that may increase mortality compared with the general population in Western studies. This is a retrospective cohort study to investigate the mortality rate within three years of all newly diagnosed BP. The inclusion criteria of BP should base on having at least three of the following: (1) clinical findings consistent with BP; (2) histopathological findings of a subepidermal blister; (3) direct immunofluorescence findings of linear deposition of IgG and / or complement along the dermoepidermal junction; and (4) indirect immunofluorescence findings of either roof pattern or roof and floor pattern or positive anti-BP 180 NC169A IgG Ab measured by enzyme-linked immunosorbent assay.

There were 359 BP mortalities included. One hundred and eighty-seven (52.1%) were female and 172 (47.9%) were male. The mean age±SD was 75.7±2.6 years. The mean duration of follow-up was 2.1 years. Corticosteroids (88.0%) was the mainstay of treatment, followed by doxycycline (25.9%), dapsone (13.9%) and azathioprine (3.9%). For those treated by systemic steroids, the majority (65.2%) were treated by low-to-moderate dose at ≤0.5 mg/kg/day and the mean initial dose used was 0.49 mg/kg/day. The 1-year mortality was 26.7% (95% CI 22.2%-31.6%), 2-year mortality was 38.4% (95% CI 33.4%-43.7%) and 3-year mortality was 45.7% (95% CI 40.4%-51.0%). The standardised mortality ratio (SMR) was 2.74 (95% CI 2.34-3.19) for the whole study period that was significantly increased after adjusting for age and sex. Patients on wheelchair or who were bedbound had a significantly higher mortality than those who were ambulant [Hazard Ratio (HR) 1.67, 95% CI 1.08-2.56]. Patients continued to have active disease at the last follow-up also had significantly increased mortality than those in remission (HR 4.40, 95% CI 2.94-6.58). Concerning the medical conditions, infections such as pneumonia, urinary tract infection, soft tissue infection and septicaemia were the common causes of death in BP patients but they were not significant when the SMR was compared with the general population. Only patients with heart failure (HR 2.09, 95% CI 1.13-3.82), Parkinson's disease (HR 1.85, 95% CI 1.15-2.96) and chronic renal disease (HR 1.81, 95% CI 1.11-2.95) were significantly increased in mortality. Patients treated with low-to-moderate systemic steroids were associated with a significantly lower mortality (HR 0.47, 95% CI 0.26-0.86) than those who were prescribed doxycycline alone. Those who received combination therapy of low-to-moderate corticosteroids and doxycycline had a significantly reduced mortality (HR 0.27, 95% CI 0.14-0.52). Those who were started on a higher dose of steroids (>25 mg prednisolone daily) trended to correlate with a decreased, yet insignificant mortality in the univariate analysis (p=0.09).

In summary, the authors concluded that the BP patients have increased mortality rates compared with the general population and heart failure, chronic renal disease and Parkinson's disease were the risk factors. Those treated with systemic steroids and doxycycline were significantly associated with a lower mortality.

Clinical and immunological outcomes of high- and low-dose rituximab treatments in patients with pemphigus: a randomized, comparative, observer-blinded study

Kanwar AJ, Vinay K, Sawatkar GU, Dogra S, Minz RW, Shear NH, et al.
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Pemphigus is an autoimmune bullous dermatosis with a potentially fatal outcome and corticosteroids and immunosuppressants are the mainstays of treatment. Recently rituximab, which is a monoclonal antibody directly against CD20, is considered to be the treatment of choice for pemphigus. However, there is still a lack of consensus on treatment dosage. This study was a prospective, randomised, observer blinded pilot study to compare the use of rituximab 1000 mg x 2, 15 days apart (group A) and rituximab 500 mg x 2, 15 days apart (group B) in treating pemphigus. Patients who were aged between 16 and 70 years without active infections and cardiac problems like arrhythmia or <40% ejection fraction with pemphigus vulgaris (PV), pemphigus foliaceous (PF) and pemphigus erythematosus (PE) were included. Those who were previously treated with rituximab, pregnant, breastfeeding and who had a known hypersensitivity to murine protein were excluded. A total of 22 patients were randomised to group A or group B. Patients in both groups received oral corticosteroids and other adjuvant immunosuppressants like azathioprine or mycophenolate mofetil if they failed to achieved a complete remission with oral corticosteroids and rituximab. Fifteen (seven in group A and eight in group B) had PV and the remaining seven (four in group A and three in group B) had PF. Twelve patients (six in each group) were defined as resistant to treatment as multiple immunosuppressants had been used. Six (four in group A and two in group B) were defined by Ikeda Severity Score (ISS) or Sarawat's modified oral pemphigus score (SMOPS) as severe disease (score >7). Four (one in group A and three in group B) were mild-to-moderate in severity. The baseline demographic and disease characteristic between groups A and B were not significant. There was no significant difference in time to disease control, end of consolidation phase, mean time to partial remission and mean time to complete remission between the two groups. However, there was a significant decrease in ISS and SMOPS in both groups ($p<0.001$) and the fall in ISS was significantly greater in group A than in group B at week 40 ($p=0.049$). In group A, the decline in Dsg 1 index was significant at 16 and 24 weeks and the decline in Dsg3 index was significant in 8, 16, 24, 32, 40 and 48 weeks whereas there was no significant change in group B. In summary, the authors suggested that group A regime might significantly improve the outcomes but further long-term follow-up studies with a larger population are needed as the sample size of this study was too small.

Prevalence of *Trichomonas vaginalis*, *Mycoplasma genitalium* and *Ureaplasma urealyticum* in men with urethritis attending an urban sexual health clinic

Khatib N, Bradbury C, Chalker V, Koh G, Smit E, Wilson S, et al.
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Chlamydia trachomatis (CT) infection is one of the common causes of non-gonococcal urethritis (NGU) in men. Empirical treatment of NGU by azithromycin or doxycycline is a common practice in sexual health clinics. However, other pathogens especially *Trichomonas vaginalis* (TV), *Mycoplasma genitalium* (MG) and *Ureaplasma urealyticum* (UU) may also cause NGU. A knowledge of their prevalence can be useful for a more focused screening process and choice of treatment. The aim of this study was to determine the prevalence of TV, MG and UU in patients with urethritis.

Men over 18 years of age with urethritis (defined as a Gram-stained urethral smear having ≥5 polymorphonuclear leucocytes (PMNLs) per high-power (x1000) microscopic view that was averaged over five fields with the greatest concentration of PMNLs) were included whereas those with previous episodes of urethritis or who received doxycycline, metronidazole, macrolide or second/third generation quinolone in the previous three months were excluded. Their first-pass urine was collected for nucleic acid amplification test (NAAT) of *Neisseria gonorrhoeae* (GC), CT, TV, MG, and UU.

A total of 83 subjects were studied. There was no causal organism identified in 42.1% (35/83) of patients. The prevalence rate of CT was 28/83 (33.7%, 95% CI 24-44%), GC 14/83 (16.8%, 95% CI 10-26%), TV 3/83 (3.6%, 95% CI 1-10%), MG 10/83 (12.0%, 95% CI 6-19%) and UU 4/83 (4.8% 95% CI 2-12%). The co-infection rates were not low (9/83, 10.8%). Three patients were co-infected with CT and GC, one with CT and TV, one with CT and MG, one with CT, MG and UU, one with GC and TV, one with GC, MG and UU, one with GC and MG.

The authors concluded that given the prevalence of CT, GC, TV, MG and UU together with a high co-infection rate, there is a need for further large studies looking at the optimal treatment regimens and screening strategies in NGU.

Use of cerebrospinal fluid enzyme immunoassay for diagnosis of neurosyphilis

Chan Y, Yeung KH, Ho HF, Ho KM, Lam TK, Leung WL, et al.
Int J STD AIDS 2013;25:571-8.

Neurosyphilis (NS) is the complication of syphilis that affects the central nervous systems caused by *Treponemal pallidum*. There is no single effective method for reaching a diagnosis. Elevated CSF protein, CSF leucocytosis and CSF-VDRL are used commonly for the diagnosis of NS. However, it is not uncommon to have NS patients with non-reactive CSF-VDRL and equivocal CSF protein or white cell count. A more accurate laboratory test would be valuable in diagnosing NS. *Treponema pallidum* enzyme immunoassay (TP EIA) is used commonly as the screening test for syphilis in serum owing to its high sensitivity and specificity. It analyses three recombinant *T. palladium* antigens – *Treponema palladium* Nichols strain (TpN) 15, TpN17 and TpN47. However, its use in CSF for screening of NS is not well documented. The aim of this study was to examine the performance of the TP EIA test in CSF in the diagnosis of NS. The case definition of NS was defined according to the International Union Against Sexually Transmitted Infections (IUSTI) 2008 guidelines which defined NS as either positive CSF-FTA-abs or CSF-TPPA, together with CSF mononuclear cell $>5/mm^3$ or reactive CSF-VDRL.

Forty-five patients were analysed. More than half (26/45, 57.8%) were co-infected with HIV. Fourteen patients (31.1%) had CNS symptoms such as dementia, ophthalmic symptoms and signs and sensorineural hearing loss. The remaining five patients (11.1%) had persistently high VDRL after syphilis treatment. The results showed that CSF TP EIA test had a poor specificity of 46.4% (95% CI 31.8-61%) and positive predictive value (PPV) of 53.1% (95% CI 38.5-67.7%). If the significant blood contaminated CSF samples were excluded, the specificity could have improved to 80.8% (95% CI 68.4-93.2%). However, it provided 100% sensitivity and 100% negative predictive value (NPV) when compared to that of CSF-FTA-abs and CSF-TPPA.

The authors concluded that the CSF TP EIA may be a better laboratory tool to exclude neurosyphilis according to its high sensitivity and high negative predictive value.

The proactive wet-wrap method with diluted corticosteroids versus emollients in children with atopic dermatitis: a prosepective, randomized, double-blind, placebo-controlled trial

Janmohamed SR, Oranje AP, Devillers AC, Rizopoulos D, van Praag MC, Van Gysel D, et al.
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Wet-wrap treatment (WWT) often serves as a crisis intervention in patients with severe atopic dermatitis (AD). However, its efficacy as compared with conventional treatments has not been fully studied in severe AD patients. In this study, the authors aimed at evaluating the use of WWT with diluted corticosteroids in comparison with emollient with severe AD in a proactive manner.

Patients aged under 10 years with severe AD, which was defined as having scoring atopic dermatitis (SCORAD) greater than 40±5, were recruited. Those who had underlying severe illness, infected eczema or signs of systemic infection, abnormalities of hypothalamic-pituitary-adrenal axis, current systemic therapy and those showing severe growth retardation were excluded.

They were then randomised to receive either WWT with dilute corticosteroid (0.1% mometasone furoate ointment: 20% petrolatum cetomacrogol cream, body 1:3, face 1:19) or WWT with emollient (20% petrolatum cetomacrogol cream). In the treatment group, patients applied the diluted steroid cream to whole body once daily in week 1, and on 4 consecutive days per week over lesions only on the subsequent three weeks. Emollients were used in both groups on the remaining three days in weeks 2 to 4. The skin condition was checked on day 0, 1, 4, 7, 14 and 28. Outcome measures including SCORAD, patient-oriented eczema measure(POEM)/quality of life(QoL), and adverse events were recorded. Morning cortisol was also checked on day 0, 1, 7, 21 and 28.

A total of 39 patients were included, and their mean SCORAD at baseline was 44 in the treatment arm and 42 in the control, which was not statistically different. Both groups showed improvement in SCORAD over time, but significantly faster and more pronounced in the treatment group. The QoL score also showed similar result but not for POEM scoring. And this was more pronounced in the age group 6-9 years and 0-3 years. However, there was significantly more folliculitis in the treatment group. And at one measurement, three patients in the treatment group showed suppression of the hypothalamic-pituitary-axis.

The authors concluded that WWT with diluted conticosteroids acted faster and was more efficacious than WWT with emollients. However, this study was limited by the small sample size and a relatively short treatment period and follow-up.

Diet and psoriasis, part I: impact of weight loss interventions

Debbaneh M, Millsop JW, Bhatia BK, Koo J, Liao W.
J Am Acad Dermatol 2014;71:133-40.

Psoriasis is well known to be associated with obesity. However, the exact mechanism is not fully understood. It is postulated that adipoctyes produce various pro-inflammatory cytokines, which may potentially worsen the existing psoriasis or trigger the development of psoriasis. Yet, the effect of body weight interventions on psoriatic control is unclear.

In this study, the authors reviewed all English articles published between 1950 to 2013 in MEDLINE and examined the relationship between body mass index (BMI) and psoriasis incidence, severity and response to treatment. Also, they studied the efficacy of weight loss interventions, namely low-calorie diet and gastric bypass surgery, on the outcome of psoriatic treatment.

Several large scale cross-sectional, case-control and cohort studies (with subjects >200) were identified and all showed an increased risk of developing psoriasis and psoriatic arthropathy in obese patients. Moreover, the severity of psoriasis and risk of developing psoriasis were positively correlated with an increase in weight.

Concerning the effect of BMI on treatment efficacy, conflicting results were shown. But the existing evidence revealed that BMI greater than 30 kg/m^2 had a negative impact on patients' ability to achieve full therapeutic response to some therapeutic agents.

There were seven small-scale (n<100) prospective, controlled trials studying the impact of dietary interventions on psoriatic management. Most studies found that patients taking a low-calorie diet (800-1600 kcal/day) had a significant reduction in weight, an improvement in cholesterol level and improvement in psoriasis control. In one study, patients on a low-calorie diet have a tendency for a slower rebound after achieving remission with methotrexate. Finally, there were several retrospective case series and reports which showed that patients who had undergone gastric bypass surgery had an improvement in psoriatic control.

The authors concluded that an elevated BMI was associated with the onset and severity of psoriasis. Also, it may affect the therapeutic outcome. They postulated that it might be the consequence of decreased drug distribution due to the increase in body mass or an increase in pro-inflammatory cytokines due to the increase in adipocyte count. Existing evidence suggests that weight reduction may be a useful preventive and adjunctive

treatment for psoriasis and psoriatic arthropathy. However, larger studies are required to further delineate its efficacy.

Outcomes after diagnosis of mycosis fungoides and Sézary syndrome before 30 years of age: a population-based study

Ai WZ, Keegan TH, Press DJ, Yang J, Pincus LB, Kim YH, et al.
JAMA Dermatol 2014;150:709-15.

Mycosis fungoides (MF) and Sézary syndrome (SS) are uncommon in children and young adults. The incidence, overall survival and risk of second cancers in this patient population are not well studied. This is a retrospective population-based study to assess the outcomes of MF and SS in patients diagnosed before 30 years of age.

The data was obtained from two population-based cancer registries: California Cancer Registry (CCR) and National Cancer Institute's Surveillance, Epidemiology, and End Results programme of 9 population-based cancer registries (SEER 9). The incidence of MF or SS was rare before 30 years of age, with an incidence rate of 0.05 per 100,000 persons per year before age 20 and 0.12 per 100,000 persons per year between ages 20 and 29 in the CCR. It was noted that Asians or Pacific Islanders and blacks had the highest incidence rates, followed by non-Hispanic whites and Hispanics. It was found that patients in the CCR had a 5-year overall survival of 97.1% and a 10-year overall survival of 94.3% while patients in SEER 9 had a 5-year overall survival of 93.3% and a 10-year overall survival of 88.9%. The most common cause of death was non-Hodgkin's lymphoma, followed by infection, including human immunodeficiency virus infection. It was noted that patients in SEER 9 had a significant increased risk of developing secondary cancers, particularly lymphoma and melanoma.

In summary, it was found that the incidence rates of MF and SS were much lower in this young population than that in older patients, and demographic patterns differed between the two age groups. However, like older adults, young patients with MF or SS also carry an elevated risk of second cancers, in particular melanoma and lymphoma. Despite the favourable outcome of MF or SS in this young age group, continual monitoring is warranted to determine whether this excess risk persists throughout life and is due to the increased medical surveillance, long-term treatment, or underlying disease processes.

Characteristics and associations of high-mitotic-rate melanoma

Shen S, Wolfe R, McLean CA, Haskett M, Kelly JW.
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Mitotic rates of melanoma are closely correlated with melanoma survival and studies have demonstrated that it is an independent prognostic factor. However, its clinicopathologic associations have not been well studied. The objective of the current study was to delineate the clinical, phenotypic and histologic associations of high-mitotic-rate melanoma.

This was a cross-sectional retrospective study of patients seen at the Victorian Melanoma Service from January 2006 to December 2011. A total of 1,441 patients with 1,500 primary invasive melanomas were included in the study. The mitotic rate was determined histologically by first examining the entire tumour, looking for mitotic figures. The area with the greatest density of mitotic activity was used as the focus, and the number of mitoses in an area of 1 mm^2 was counted. Patient demographics, phenotypic markers, historical data, tumour presentation and histopathological features were recorded.

It was discovered that high-mitotic-rate melanomas were more likely to occur in men, in patients 70 years or older and in those with a history of solar keratosis. Moreover, these melanomas occurred more frequently on the head and neck and presented more often as amelanotic and rapidly growing lesions. Melanomas with very high mitotic activity ($\geq$10 mitoses/mm^2) were predominantly thick and ulcerated nodular tumour subtypes. Conversely, the superficial spreading melanoma subtype, features of regression and the presence of preexisting naevi were found to be the characteristics of lesions with sparse mitotic activity.

The use of transient elastography and FibroTest for monitoring hepatotoxicity in patients receiving methotrexate for psoriasis

Lynch M, Higgins E, McCormick PA, Kirby B, Nolan N, Rogers S, et al.
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Liver fibrosis is considered as the main disadvantage of methotrexate in the treatment of psoriasis. The 2009 American Academy of Dermatology guidelines suggested that liver biopsy should be considered in low risk patients who have persistent abnormal liver function test results during treatment or after a total cumulative methotrexate dose of 3.5 to 4.0 g. Liver biopsy is the standard for diagnosing liver fibrosis, but it may be associated with a significant morbidity and mortality. Serial monitoring of procollagen III peptide (PIIINP) has reduced the need for liver biopsy considerably. However, serum PIIINP levels may be a less reliable marker of liver fibrosis in patients with concomitant psoriatic arthritis since elevated levels may be related to active joint disease. Transient elastography (TE) using pulse-echo ultrasonography measures the propagation and velocity of sound wave in the liver in one dimension, correlating with tissue stiffness and serving as an indirect measurement of fibrosis. FibroTest is an artificial intelligence algorithm that has been validated as an indirect serum marker of fibrosis in patients with hepatitis C. It is a fibrosis index that uses input values of five serum markers (γ-glutamyltranspeptidase, bilirubin, haptoglobin, apolipoprotein A-I and α2-macroglobulin) and is corrected for age and sex, leading to a composite value to determine the presence of liver fibrosis. The objective of this study was to define the role of these tests in monitoring patients receiving methotrexate for the treatment of psoriasis.

Seventy-seven patients receiving methotrexate therapy for psoriasis between January 2008 and September 2009 were recruited from a dermatology outpatient department. Transient elastography and FibroTest were performed, and patients with abnormal results were considered for liver biopsy. Serial PIIINP results were also recorded. It was found that the body mass index and age were correlated with abnormal TE results. The duration of methotrexate treatment, cumulative methotrexate dose, alcohol consumption and sex showed no significant correlation with abnormal TE results. Age, cumulative methotrexate dose and methotrexate duration correlated with abnormal FibroTest results. There was no significant correlation between PIIINP results and TE results or between PIIINP and FibroTest results.

TE and FibroTest are screening tools to determine the presence of hepatic fibrosis. The authors suggested that abnormal results in at least two of the three tests (PIIINP, TE and FibroTest) were required before liver biopsy should be considered. This strategy should be evaluated in larger prospective studies.