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Journal Watch

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Repeat infection with *Neisseria gonorrhoeae* among active duty U.S. Army personnel: a population-based case-series study

Bautista CT, Wurapa EK, Sateren WB, Morris SM, Hollingsworth BP, Sanchez JL.
Int J STD AIDS;2017;28:962-8.

Repeated sexually transmitted infections (STI) are a burden and may represent a sustained reservoir in the community. The aim of this study was to determine the rate and determinants of repeat gonorrhoea infections among male and female US Army personnel.

This was a case-series study and the data was from the Defense Medical Surveillance System (DMSS) that is the central repository of medical surveillance data for the US Armed Forces containing personal demographics, reportable diseases, in-patient and outpatient medical encounters of US Armed Forces active personnel throughout their services. The definition of repeat infection was the diagnosis occurred at least 30 days from previous diagnosis and it was based on nuclei acid amplification tests (NAAT) which could detect non-viable bacteria for up to three weeks after treatment.

During the 6-year study period, 4987 women were found to have first gonorrhoea infection and 627 (12.6%) had one repeat infection of which 75 (1.5%) and 18 (0.4%) had two and three repeat infections respectively. The median time from first to the second infection was 3.0 months. The rate of repeat infection was 44.5 (95% CI: 14.8-47.9) per 1000 person-years. Young women aged 17-19 years and 20-24 years old had 1.51 and 1.40 times higher risk of repeat infection compared to women aged ≥25 years.

Overall, 12,615 men were found to have first gonorrhoea infection and 1401 (11.1%) had one repeat infection and 239 (1.9%) and 89 (0.7%) had two and three repeat infections respectively. The median time from first to the second infection was 5.5 months. The rate of repeat infection was 48.9 (95% CI: 46.9-51.0) per 1000 person-years. Young men aged 17-19 years and 20-24 years old also had 1.71 and 1.40 times higher risk of repeat infection compared to men aged >25 years.

The authors concluded that although no specific behavioural factor may predict re-infection for STIs, younger people tend to engage in more high risk sexual behaviour and are therefore more prone to repeat STI infection. Targeted prevention initiatives should therefore be implemented.

Effectiveness of a group B outer membrane vesicle meningococcal vaccine against gonorrhea in New Zealand: a retrospective case-control study

Patousis-Harris H, Paynter J, Morgan J, Saxton P, McArdle B, Goodyear-Smith F, et al.
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Gonorrhoea is a common sexually transmitted infection (STI). Despite continued efforts for over a century, an effective vaccine has not been successfully developed. Despite the differences in disease manifestation, there is 80-90% genetic homology in primary sequences between *Neisseria gonorrhoeae* and *Neisseria meningitides* that provides a biologically plausible basis for cross-protection after outer membrane vesicle (OMV) meningococcal vaccine against gonorrhea. This was a retrospective case-control study aimed at assessing the effectiveness of meningococcal vaccine against gonorrhoea.

The National Health Index numbers associated with all chlamydia and gonorrhea infections diagnosed between 1st January 2004 and 1st December 2016 for linkage to National Health Index and National Immunization Register databases were provided by sexual health clinics in New Zealand. This linkage was able to match the history of meningococcal vaccination and gonorrhoea infection.

Positive-vaccinated cases were defined as those who had completed three doses of meningococcal vaccines at least six months before laboratory confirmation of gonorrhoea whereas the controls were those who were unvaccinated.

Overall 14730 cases and control were analysed. There were 1241 incidences, 12487 incidences and 1002 incidences of gonorrhoea only, chlamydia only and co-infection of gonorrhoea and chlamydia respectively. Vaccinated cases were significantly less likely to have gonorrhoea than unvaccinated controls (511 (41%) vs 6424 (51%) adjusted OR=0.69[95%CI 0.61-0.79]). After the adjustment of sex, ethnicity, deprivation, age and geographical area, the estimated vaccine effectiveness was 31% (95% CI 21-39; $p<0.0001$).

The authors concluded that exposure to group B OMV meningococcal vaccine was associated with a reduced risk of gonorrhea. This cross-protection may provide substantial benefits in public health control of gonorrhoea and additionally for gonococcal vaccine development.

Effectiveness of omalizumab in a case of urticarial vasculitis

Fueyo-Casado A, Campos-Muñoz L, González-Guerra E, Pedraz-Muñoz J, Cortés-Toro JA, López-Bran E.
Clin Exp Dermatol 2017;42:403-5.

Treatment of urticarial vasculitis is clinically challenging. Corticosteroids are the mainstay of treatment but fraught with adverse effects. Other treatments including anti-histamines, dapsone, colchicine, antimalarials, cyclosporine and leukotriene antagonists have not proven efficacious. Omalizumab, an anti-IgE antibody is efficacious in patients with chronic spontaneous urticaria. This article adds to the currently available existing seven case reports of its use in urticarial vasculitis refractory to conventional treatments.

The report describes a 71-year-old woman who had a 10-year history of urticarial vasculitis refractory to the maximum dose of anti-histamines, montelukast and dapsone. Oral prednisone and cyclosporine had achieved remission but she relapsed early after treatment was ceased. Long-term maintenance on these treatments were deemed not acceptable.

She received subcutaneous omalizumab 300 mg every four weeks, which resulted in clinical improvement within the first month and remission was achieved in the fifth month. Both quality of life and sleep showed improvement, as measured

by the Chronic Urticaria Quality of Life Questionnaire. The investigators continued with omalizumab 300 mg monthly until 12 months when the dose was lowered to 150 mg monthly. Occasional wheals and pruritus were observed necessitating the use of anti-histamines as needed. At week 78, the dosing frequency was further reduced to 150 mg every 6 weeks. The patient remained stable at 23 months.

Omalizumab is an anti-IgE humanised recombinant monoclonal antibody that mediates its action through binding the IgE C3 domain. It produces immunomodulatory effects beyond IgE binding, namely reduction in IgE cell receptors in mast cells and basophils, reduction in B-cell activation and homing, induction of eosinophil apoptosis, increases in IL-2, IL-3, tumour necrosis factor-alpha and interferon-gamma, and reductions in IL-4. Adverse effects were not observed in this case. It remains unclear how the dosage should be tapered or maintenance therapy is needed, a question that beckons to be addressed in a larger scaled study.

Role of nail bed methotrexate injections in isolated nail psoriasis: conventional drug via an unconventional route

Daulatabad D, Grover C, Singal A.
Clin Exp Dermatol 2017;42:420-3.

The use of systemic therapies for patients with isolated nail psoriasis may not be justifiable because of potential toxicities. Yet, nail psoriasis can be a distressing condition to patients. This report investigated the role of nail bed methotrexate injections on four patients with 30 involved nails between them. An insulin syringe with a 30G needle was introduced into the proximal nail fold and advanced to the nail bed. Then, 0.1 mL of a methotrexate 25 mg/mL solution of was infiltrated until the end point of blanching of the nail bed occurred. Patients were offered pain control either in the form of digital anaesthesia or ibuprofen. Five treatments were given, with an interval of three weeks between them. The Mean baseline Nail Psoriasis Severity Index at baseline was 4.77 (range 2-8) and 2.43 (range 0-4) at 15 weeks. The index demonstrated successive reductions at each visit and the decline was statistically significant.

Adverse effects were pain during injection, although none of the patients required digital anaesthesia or ibuprofen afterwards. Functional handicap was never reported. Injection site hyperpigmentation was reported in two patients. In 8% of occasions, pin-point nail bed haemorrhage was recorded. The hyperpigmentation and haemorrhages were both entirely reversible, resolving within four to six weeks. No cases showed abnormalities in blood parameters.

Intralesional therapy appears efficacious possibly because it delivers a higher concentration of the drug at the site of action. The possibility of the response being effected by systemic absorption of the drug cannot be ruled out. One previous study used a much higher dose of methotrexate of 5 mg/week for six weeks. This study has shown that a lower dose may be enough to produce a clinical effect. The study is however limited by the small sample size, lack of controls and lack of independent observer.

The effectiveness for treatments of androgenetic alopecia: a systematic review and meta-analysis

Adil A, Godwin M.
J Am Acad Dermatol 2017;77:136-41.

Androgenetic alopecia is a hair loss disorder mediated by dihydrotestosterone and leading to significant psychological impact in both men and women. Currently, minoxidil , finasteride and low-level laser light therapy (LLLLT) are the only treatment options approved by FDA. In this systematic review and meta-analysis, the authors assessed the efficacy of these treatment options

in terms of improving hair density, thickness, growth or subjective global assessments done by patients and investigators.

Only randomised controlled trials studying non-surgical treatment for androgenetic alopecia, with placebo arm, and in double-blinded manner were included. A total of 19 studies were included for the meta-analysis and they were grouped under five main treatment strategies, namely laser treatment in men, 5% minoxidil in men, 2% minoxidil in men, 1 mg finasteride in men, and 2% minoxidil in women. All interventions showed to be significantly superior to placebo ($p<0.00001$). Moreover, the mean increase in hair counts in men were shown to be highest in 1mg finasteride daily group (18.37 hairs/cm^2), followed by LLLLT (17.66 hairs/cm^2), 5% minoxidil twice daily (14.94 hairs/cm^2), and 2 % minoxidil twice daily (8.11 hairs/cm^2). A mean increase of 12.41 hair/cm^2 counts was also found in women receiving 2% minoxidil twice daily. All treatment options were generally well-tolerated and only a few participants reported decrease libido with finasteride.

In conclusion, finasteride, minoxidil solution and LLLLT were effective treatments for androgenetic alopecia. However, this analysis was limited by the high heterogenecity in most studies and possibility of publication bias.

Evidence-based recommendations for the management of acne fulminans and its variants

Greywal T, Zaenglein AL, Baldwin HE, Bhatia N, Chernoff KA, Del Rosso JQ, et al.
J Am Acad Dermatol 2017;77:109-17.

Acne fulminans (AF) is an uncommon form of acne. It is characterised by the sudden development of painful nodules with ulceration, haemorrhagic crusts and disfiguring scars. However, there are no well-conducted studies or guidelines on the management of this condition. In this study, a group of experts in severe acne was convened and developed a consensus recommendation on the classification and treatment for acne fulminans.

The panel recommended classifying AF based on its association with systemic symptoms, like fever, malaise, bone pain, arthralgia, elevated inflammatory markers and radiological changes, and its relation with isotretinoin or other drugs. Namely, acne fulminans with systemic symptoms (AF-SS), acne fulminans without systemic symptoms (AF-WOSS), isotretinoin-induced acne fulminans with systemic symptoms (IIAF-SS) and isotretinoin-induced acne fulminans without systemic symptoms (IIAF-WOSS). AF usually occurred in young adolescent men aged 13-22 and usually with a mean duration of acne of two years. *De novo* AF has become less common with earlier recognition and treatment of acne, but the use of isotretinoin or anabolic steroids has increased the risk of AF.

Although there is lack of large-scale randomised-control studies on treatment of AF, various case reports and series support the use of isotretinoin and systemic corticosteroids in managing AF. The panel recommended the use of steroid of 0.5-1 mg/kg/day as monotherapy at the onset of AF for least 4 weeks for those with systemic symptoms and 2 weeks for those without and continued until crusted lesions healed. Low dose isotretinoin (0.1 mg/kg/day) then initiated and should overlap with steroid for at least 4 weeks. Steroid could then be slowly tailed down over a period over 4-8 weeks, halving the dose every week till a physiological dose has been reached and then reduced to every other day, while isotretinoin is slowly increased as tolerated. In case there is a flare during escalation of isotretinoin, prolonged course of systemic steroids or temporary withdrawal of isotretinoin may be required. An accumulated dose of isotretinoin of 120-150 mg/kg was recommended and a prolonged course may be required for recalcitrant cases.

Tetracycline alone was not recommended as a first-line treatment as clinical series showed that AF responded poorly to antibiotics alone and its efficacy with systemic steroid was also not clear. Moreover, the practice of pretreatment of patients with tetracycline before isotretinoin was not recommended as there were case reports of development of pseudotumor cerebri syndrome, although still controversial. Other treatment options included dapsone, cyclosporine, biologics, levamisole and pulse-dyed laser were shown to be effective in a few case reports and can be considered for those intolerant to isotretinoin.

Purpuric drug eruptions caused by epidermal growth factor receptor inhibitors for non-small cell lung cancer. A clinicopathologic study of 32 cases

Cho YT, Chen KL, Sheen YS, Yang CW, Liau JY, Cheng YP, et al.
JAMA Dermatol 2017;153:906-10.

The aim of this prospective study is to characterise purpuric skin eruptions caused by epidermal growth factor receptor (EGRF) tyrosine kinase inbibitors (TKI). Thirty-two patients, who presented with purpuric drug eruptions (PDE) after using EGRF-TKIs for non-small cell lung cancer, were enrolled during the three-year study period. Of these, 14 had PDEs without pustules (mean [SD] age, 60[11] years; 12 females and two males) and 18 with PDEs with pustules (mean[SD]age, 64[11] years; 12 female and six male). The median duration from the first intake of the EGFR-TKI to the development of PDEs was 3.5 months. Thirteen patients had marked xerotic changes that mimicked eczema *craquelé*. *Staphylococcus aureus* were identified in all PDE with pustules whereas *S. aureus* was only found in two patients without pustules. Systemic first-generation cephalosporin antibiotics were administrated to all patients for at least one week. The dosage of the EGFR TKIs was adjusted in 14 patients of which the dosage was reduced in three cases and EGFR TKIs were stopped in 11 patients and then resumed after improvement of their cutaneous lesions.

Histopathological features included epidermal dysmaturation, neutrophil aggregation, red blood cell extravasation, and endothelium plumping. Epidermal filaggrin and human β-defensin 2 expression in the lesional skin of these patients was markedly reduced.

This study reported an uncommon cutaneous adverse reaction caused by EGFR-TKIs. Purpuric drug eruptions have characteristic clinical and histopathological features. Treatment with systemic antibiotics resulted in improvement in most cases. With the increasing use of EGFR-TKIs in treating cancers, these will become increasingly important for the clinician.

Risk factors for melanoma in renal transplant recipients

Ascha M, Ascha MS, Tanenbaum J, Bordeaux JS
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The aim of this study was to determine the risk factors and characteristics of renal transplant recipients who develop melanoma. A cohort of renal transplant recipients from the United States Renal Data System (USRDS) database from the years 2004 through 2012 was studied. The authors examined the differences in baseline characteristics between those who did and did not develop melanoma and performed a survival analysis.

There was a record of melanoma after transplantation in 488 (0.46%) of 105,174 first-time kidney transplantat recipients between the years 2004 and 2012. Among those with melanoma, 349 (71.5%) were male. Risk factors for developing melanoma were older age among

recipients (mean [SD] age, 60.5 [10.2] vs 49.7 [15.3] years; P<0.001) and older age among donors (mean [SD] age, 42.6 [15.0] vs 39.2 [15.1] years; P<0.001). 96.1% of patients with melanoma were white. The group of patients who developed melanoma had a greater proportion of living donors than those who did not develop melanoma (44.7% vs 33.7%; P<0.001). In addition, patients with melanoma were significantly more likely to be taking cyclosporine (4.9% vs 3.2%; P=0.04) or sirolimus (22.3% vs 13.2%; P<0.001) than those without melanoma.

Regarding the risk factors significant on survival analysis, each extra year of age was associated with 1.06 times the hazard (95% CI, 1.05-1.06; P<0.001). Others include recipient male sex (HR, 1.53; 95% CI, 1.25-1.88; P<0.001), recipient white race, and living donors. Cyclosporine and sirolimus use for long-term immunosuppression were associated with hazard ratios of 1.93 (95% CI, 1.24-2.99; P=0.004) and 1.54 (95% CI, 1.22-1.94; P<0.001) respectively. A Kaplan-Meier estimate of the median time to development of melanoma among those patients who did develop melanoma was 1.45 years (95%CI, 1.31-1.70 years).

Renal transplant recipients are at greater risk of developing melanoma than the general population. This study analysed risk factors for developing melanoma in renal transplant recipients. It helps guide clinicians in patients' care and patient counselling regarding melanoma risk.

Randomized controlled trial comparing 35% trichloroacetic acid peel and 5-aminolaevulinic acid photodynamic therapy for treating multiple actinic keratosis

Holzer G, Pinkowicz A, Radakovic S, Schmidt JB, Tanew A.
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Actinic keratosis is common and various treatment modalities have been used to prevent its progress to squamous cell carcinoma. Photodynamic therapy with 20% 5-aminolaevulinic acid (ALA PDT) illuminated with red light is an established effective treatment of multiple actinic keratosis with involvement of large area. Malignant cells take up the ALA and will have higher intracellular protoporphyrin IX (PPIX) than normal cells. Red light-activated PPIX produce reactive oxygen species and kill malignant cells. Trichloroacetic acid (TCA) 35% as chemical peel has also been used by some dermatologists for multiple actinic keratosis and works by non-specific chemical ablation of skin layers.

This study was a randomised, observer-blinded study which compared the efficacy and safety of these two treatments for multiple actinic keratoses over 12 months. Twenty eight patients with multiple actinic keratosis in face and scalp with comparable anatomical area were enrolled. For ALA PDT group, ALA 20% was applied to the actinic keratoses and occluded with transparent film dressing for four hours. Lesions were then illuminated using a filtered metal-halide lamp (Waldmann PDT 1200, 600-740 nm; Waldmann Medizin Technik, Villingen-Schwenningen, Germany) using a dose of 75 J cm^2 at an irradiance of 75 mW cm^2. For the TCA group, EMLA cream was applied onto the patient (lidocaine 5% and prilocaine 5%) for 30 minutes as topical anaesthesia before application with TCA. Patients were followed up at 1, 3, 6 and 12 months for progress with secondary interventions to lesions that persisted.

The lesion count was reduced more effectively in ALA PDT group (58%) than TCA group (31%) at 12 months. Mean complete clearance rate of pre-existing actinic keratosis was also higher in ALA PDT group (74%) than TCA group (49%) at 12 months. Erythema and scaling were found in all patients and usually resolved within one week. Treatment-related pain was higher in ALA PDT group (visual analogue scale 7.5) than TCA group (visual analogue scale 5.1) but scarring was only seen in the TCA group (21%). The overall cosmetic outcome was graded as excellent or good in most patients. In conclusion, ALA PDT was more effective than TCA in treatment of multiple actinic keratoses over one year.

Efficacy of oxymatrine for treatment and relapse suppression of severe plaque psoriasis: results from a single-blinded randomized controlled clinical trial

Zhou H, Shi HJ, Yang J, Chen WG, Xia L, Song HB, et al.
Br J Dermatol 2017;176:1446-55.

Systemic treatments currently used for treatment of psoriasis are associated with liver toxicity (e.g. methotrexate, acitretin) or renal toxicity (ciclosporin). Oxymatrine is an alkaloid extract of the herb, *Sophora alopecuroides*, which has been widely used in China for the treatment of cancer and chronic hepatitis B. It is less hepatotoxic than acitretin and has immunoregulatory, anti-inflammatory, anti-viral, antiproliferative, antioxidant effects. It can lower pro-inflammatory cytokines and increase the level of interleukin 10.

This study explored the efficacy and safety for use of oxymatrine in the treatment of severe chronic plaque psoriasis. Inclusion criteria include severe plaque psoriasis, Psoriasis Area and Severity Index (PASI) score ≥12, disease last more than six months. Seventy three patients were enrolled and allocated to oxymatrine injection group (0.6 g per 100 mL intravenously daily for 8 weeks) or acitretin group (0.75 mg per kg daily from week 0 to week 2, then reduced to 20-30 mg daily from week 3 to week 8 as maintenance dose). Patients were followed up for 24 weeks after treatment.

Both groups had significantly decreased PASI score (6.6±6.0 in oxymatrine group, 7.5±4.7 in acitretin group), skin classification grade (1.4±0.7 in oxymatrine group, 1.5±0.7 in acitretin group), Dermatology Quality of Life Index (DLQI) score (5±1.5 in oxymatrine group, 5.2±2.7 in acitretin group) after eight weeks of treatment. No significant differences was found between two groups with respect to patients achieving ≥50% reduction in PASI (85% in oxymatrine group, 82% in acitretin group). The relapse rate in oxymatrine group (~5%) was significantly lower than acitretin group (~70%) at week 32. Number of patients with dyslipidaemia was increased in the acitretin group but significant reduced in oxymatrine group. Twenty-eight patients in acitretin group developed an adverse reaction (dry mouth, chelitis, deranged liver function, dry eye, skin itching, palmoplantar desquamation, hair loss and arthralgia). Fifteen patients in oxymatrine group developed mild adverse reaction (loose stools, increased frequency of urination but no adverse reaction on liver function). Oxymatrine group had a lower rate of side effects than the acitretin group. In conclusion, oxymatrine treatment for severe plaque psoriasis was effective with only mild side effects.