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Journal Watch

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Cephalosporin resistant Neisseria gonorrhoeae: time to consider gentamicin?

Ross JD, Lewis DA.
Sex Transm Infect 2012;88:6-8.

Antibiotic resistance is a depressing problem in Neisseria gonorrhoeae infection. For penicillin, the resistant process took a number of decades before the drug finally failed. With the subsequent use of tetracyclines, macrolides and fluoroquinolones, the resistant cycle has shortened. Now oral cephalosporins are threatened as the preferred treatment of gonorrhoea. Although there are still some debate on minimum inhibitory concentration (MIC) breakpoint for oral cephalosporins that can correlate with clinical failure, it may often occur at MIC of 0.125 mg/L or higher. Pharmacodynamic modelling suggested cephalosporins require a free drug level above MIC for 20-24 hours in order for reliable efficacy in treating gonorrhoea. These predicted that failures with standard doses of cefixime (400 mg) and ceftriaxone (250 mg) become likely around MICs of 0.125 mg/L and 0.25 mg/L respectively.

The mechanism of resistance to oral cephalosporins involves pen A encoded penicillin binding protein 2 and MtrC-MtrD-Mtr-E efflux pump. The extensively drug resistant N. gonorrhoeae strain (H041) has a ceftriaxone MIC of 2-4 mg/L and cefixime MIC of 8 mg/L which is 4-8 folds higher than previously reported. It is also resistant to β-lactams, tetracyclines, macrolides, fluoroquinolones, trimethoprim-suphamethoxazole and chloramphenical. However, this strain is sensitive to spectinomycin, rifampicin and gentamicin.

Gentamicin is an aminoglycoside with concentration-dependent bactericidal activity against Gram negative bacteria. The peak concentration of an IMI dose is at 30-90 minutes. The usual dose of gentamicin for gonorrhoea is 240 mg IMI once daily. Clinical and microbiological cure rates range from 89% to 100% and the MIC level is <4 mg/L. Therefore, the authors suggested gentamicin 240 mg once IMI may be the treatment option in gonorrhoea.

Surveillance of gonococcal antimicrobial susceptibility resulting in early detection of emerging resistance

Lo JY, Ho KM, Lo AC.
J Antimicrob Chemother 2012;67:1422-6.

Neisseria gonorrhoeae (GC) is a common cause of sexually transmitted disease (STD) but treatment failure and its resistance to extended spectrum cephalosporins is developing globally. The aim of this study is to undertake laboratory and clinical surveillance of gonococcal antimicrobial susceptibility to various therapeutic agents in Hong Kong during the period from 2005 to 2010 so as to monitor for emerging resistance and to decide an appropriate choice of empirical therapy.

The urethral swab or endocervical swab taken from male or female respectively were sent to Public Health Laboratory Centre (PHLC) for gonococcal culture by conventional methods. The PHLC is an active member of the WHO Western Pacific Region Gonococcal Antimicrobial Surveillance Programme and provides microbiological support to all government STD clinics. Concerning the ceftriaxone, around 70% to 82% strain of GC had the MIC ≤0.03 mg/L (susceptible) and around 18% to 30% had MIC of 0.06-0.125 mg/L (susceptible). None of the strain isolated was resistant to ceftriaxone during the

study period. Concerning spectinomycin, almost all strains (>98.5%) had MIC ≤16 mg/L (susceptible) while only <0.5% had intermediate MIC (64 mg/L) and none of strain was resistant to spectinomycin. For the susceptible surveillance of oral cephalosporin – ceftibuten, non-susceptibility was defined by (1) using the 30 ug disc diffusion test with the clear zone diameter <30 mm or (2) the cefixime MIC >0.064 mg/L. The mosaic penA gene which was the main reason causing ceftibuten resistance increased from ~1% (7/677) during April to December 2010 to 8.2% (71/861) during January to September 2011 (p<0.0001). In these 78 isolates, the disc diffusion test for ceftibuten yielded zone diameters of 20-31 mm and MIC ranged 0.125 to 0.5 mg/L. This signified that all isolates were resistant to ceftibuten but sensitive to ceftriaxone.

In conclusion, this study showed that ceftriaxone and spectinomycin remained effective against gonorrhoea in Hong Kong. There was an alarming increase in reduced susceptibility to ceftibuten.

Optimal tattoo removal in a single laser session based on the method of repeated exposures

Kossida T, Rigopoulos D, Katsambas A, Anderson RR.
J Am Acad Dermatol 2012;66:271-7.

Removal of unwanted tattoos is usually performed by Q-switched lasers. Many treatment sessions are often required for clearance. The time and financial cost for the patient is high.

The authors compared the results of tattoo removal using a single Q-switched Alexandrite laser treatment pass with 4 treatment passes separated by 20 minutes (R20 method). Twelve healthy white subjects with a total of 8 professional and 10 amateur tattoos were treated. Each tattoo was divided into two parts, and the parts were randomized to be treated with a single laser pass or by R20 method. All passes were made by the same investigator using a Q-switched alexandrite laser (5.5 J/cm^2, 755 nm, 100-nanosecond pulse duration, 3-mm spot size). Patients were followed for 6 months. At 3 months, results on a 5-point measure were significantly better on the R20 sides (p<0.01). In punch biopsy samples, more pigment had been removed from deeper areas with the new technique. Transient side effects included more epidermal injury and purpura on the R20-treated sides, but there was no scarring.

While this prospective study involved a small number of subjects and used only the Q-switched Alexandrite laser, if the results were reproducible by larger series and using other Q-switched lasers, this exciting finding will have an immediate effect on the standard of care. The mechanism of action is not known, but the authors hypothesize that immediate tattoo whitening after laser treatment is due to gas bubble formation that creates an optical blockage preventing the further penetration of light deep into the dermis, where the pigment particles are located; these gas bubbles appear to dissipate after a few minutes, allowing further, effective laser treatment to resume with subsequent passes. Unanswered practical questions include: how to arrange clinic time for treating these tattoo patients and how to price this service.

Eyelash growth in subjects treated with bimatoprost: a multicenter, randomized, double-masked, vehicle-controlled, parallel-group study

Smith S, Fagien S, Whitcup SM, Ledon F, Somogyi C, Weng E, et al.
J Am Acad Dermatol 2012;66:801-6.

Longer and fuller eyelashes are considered desirable physical features. Originally developed to treat glaucoma, bimatoprost 0.03% ophthalmic solution (a prostglandin structural analog) is now also FDA-approved for treating eyelashes hypotrichosis. In this study, the authors compared the safety and efficacy of once-daily bimatoprost 0.03% versus vehicle in increasing eyelash length, thickness, and darkness after topical administration to upper eyelid margins.

For five months, subjects were randomized to receive once-daily bimatoprost 0.03% (n=137) or vehicle (n=141). Eyelash prominence was assessed by the investigator global eyelash assessment scale and eyelash length, thickness, and darkness were measured by digital image analysis and patient-reported outcomes.

Bimatoprost 0.03% (78.1%) versus vehicle (18.4%) demonstrated at least a 1-grade increase in global eyelash assessment score at week 16 ($p<0.0001$). Subjects in the bimatoprost 0.03% group also had a statistically significantly greater increase in eyelash, thickness, length and darkness ($p<0.0001$) compared to those in the vehicle group. Conjunctival hyperaemia occurred at a statistically significant higher incidence rate in the bimatoprost 0.03% versus the vehicle group ($p=0.03$).

This study was limited by its short-term duration and its effects in other non-Caucasian races have yet to be established. The exact mechanism of action of bimatoprost is unclear but it probably works by increasing anagen phase duration, hence eyelash growth will revert to pre-treatment levels upon discontinuation of treatment.

A randomized double-blind placebo-controlled pilot study to assess the efficacy of a 24-week topical treatment by latanoprost 0.1% on hair growth and pigmentation in healthy volunteers with androgenetic alopecia

Blume-Peytavi U, Lonnfors S, Hillmann K, Garcia Bartels N.
J Am Acad Dermatol 2012;66:794-800.

Latanoprost is a prostaglandin analogue that is used to treat glaucoma. It may cause eyelash changes including pigmentation and hypertrichosis. Its effect on human scalp hair growth and pigmentation were assessed in this mono-center, double-blind, randomized pilot study.

Sixteen men with mild androgenetic alopecia (Hamilton II-III) were recruited. Latanoprost 0.1% and placebo were applied daily for 24 weeks on two mini-zones on the scalp. Measurements of hair density, hair growth, diameter, pigmentation, and anagen/telogen ratio were performed during the study. At 24 weeks, an increased hair density at the latanoprost-treated site was observed when compared to baseline ($n=16$, $p<0.001$) and the placebo-treated site ($p=0.0004$).

The authors concluded that latanoprost significantly increased hair density (terminal and vellus hairs) at 24 weeks when compared with baseline and the placebo-treated area. Therefore, latanoprost may be useful in stimulating hair follicle activity and in treating hair loss. The study was limited by its small sample size and only young men with mild androgenetic alopecia were included. The results may not be applicable to other patient groups. Further larger scale study is needed to pursue its use for treating androgenetic alopecia.

Association between atopic dermatitis and obesity in adulthood

Silverberg JI, Silverberg NB, Lee-Wong M.
Br J Dermatol 2012;166:498-504.

This retrospective cohort study was based on data from an allergy clinic in New York between 1994 and 2003 and the data were collected from 2003 for review. Patient aged over 18 years or with incomplete body mass index or questionnaire information were excluded. Atopic Dermatitis (AD) and non-atopic dermatitis were defined by self-report of eczema and positive skin-prick tests respectively. Multinomial logistic regression was used to determine the association between obesity and atopic disorders. A total of 2090 subjects were included in the study, 60.2% were normal weight and 277 (13.3%) were obese. Positive skin-prick test was found in 1688 subjects (80.8%). Obesity in adults was associated with increased AD with adjusted odds ratio (aOR) 1.43, but not with non-atopic dermatitis. This association remained significant after adjusted for history of asthma, rhinoconjunctivitis and food allergies (aOR 1.40, 95% CI 1.05-1.86, $p=0.02$). Obesity was also associated with an increased OR of atopic asthma with OR 2.05 and this association remained significant when controlling for sex, race, age (aOR 1.98, 95% CI 1.47-2.66, $p<0.0001$), but not with non-atopic asthma. The author thus concluded that obesity in adulthood is associated with AD but not with non-atopic dermatitis or atopy alone.

A European multicentre photopatch test study

The European Multicentre Photopatch Test Study (EMCPPTS) Taskforce.
Br J Dermatol 2012;166:1002-9.

This was a prospective multicenter study conducted in Europe between August 2008 and February 2011 to determine the frequency of photoallergic contact dermatitis (PACD) to common organic UV absorbers and topical NSAIDs using a standardized photopatch testing (PPT) technique. Patients aged above 18 years and those who had any exposed-site dermatitis, previous sunscreen reaction or topical NSAID skin reaction were included. The PPT series of 19 organic UV absorbers and five topical NSAIDs were applied to the skin and was then irradiated with UVA one to two days later. A total of 1031 subjects were recruited, there were 346 PACD reactions recorded in 200 subjects about 19.4% of subjects had PACD reaction. If NSAIDs were excluded, there were 148 PACD reactions to the UV absorbers in 95 subjects giving a lower PACD rate of 9.2%.

PACD was frequently caused by the NSAIDs: ketoprofen (128 subjects) and etofenamate (59 subjects). Topical UV absorbers, octocrylene (41 subjects), benzophenone-3 (37 subjects) and butyl methoxydibenzoylmethane (18 subjects) are commonly the culprits. There was an apparent relationship between the three agents, ketoprofen, benzophenone-3 and octocrylene in developing PACD, partly because of structural similarity. This study also showed that allergic contact dermatitis was less frequent with a total of 55 reactions recorded in 47 (4.6%) subjects. The author concluded that PPT series require periodic updating and this study may be of value on deciding which agents to be included in future European PPT series. This study had several limitations. The patients were not randomly selected and all are probably suspected to have PACD by physicians, which will lead to a higher prevalence. Small number of patients in some subgroup analysis and different study protocol for photopatch test (some applied the patches for 24 hours and other for 48 hours) were other pitfalls.

Efficacy and safety of topical WBI-1001 in patients with mild to severe atopic dermatitis: results from a 12-week, multicentre, randomized, placebo-controlled double-blind trial

Bissonnette R, Poulin Y, Zhou Y, Tan J, Hong HC, Webster J, et al.
Br J Dermatol 2012;166: 853-60.

This was a prospective multicenter study conducted in Canada between November 2009 and July 2010 to evaluate the safety and efficacy of topically applied WBI-1001[2-isopropyl-5-((E)-2-phenylethenyl) benzene-1,3-diol: IPBD] in atopic dermatitis (AD) patients. IPBD is a non-steroidal compound that had been showed to inhibit the proinflammatory cytokines and migration of T-cells in previous studies.

Patients with chronic AD with 3% to 20% of their total body surface area (BSA) affected and an Investigator's Global Assessment (IGA) of mild to severe (scale 2-4), aged between 18 and 65 years, were recruited. They were randomized (1:1:1) to receive WBI-1001 0.5%, 1.0% or the placebo. After 6 weeks, patients receiving WBI-1001 0.5% or 1.0% continued with the same treatment for an additional 6 weeks whereas the placebo group were randomized (1:1) to another 6-week treatment with WBI-1001 0.5% or 1.0%. A total of 148 patients were recruited and finally 124 completed the study. Folliculitis, contact dermatitis and headache were the common adverse events and were all well tolerated. There was a decrease of 1.3 (43%; $p<0.001$) and 1.8 (56.3%; $p<0.001$) in IGA at day 42 in the WBI-1001 0.5% and 1.0% groups respectively compared with a decrease of 0.5 (14.7%) in the placebo group. The proportion of patients achieving improvement in IGA, Eczema Area and Severity Index, SCORAD, BSA and pruritus severity score at day 42 were significantly higher for the treatment groups when compared with placebo group at day 42. The authors thus concluded that topical WBI-1001 at 0.5% and 1.0% is effective for the treatment of AD.

Prospective self-controlled trial of the efficacy and tolerability of a herbal syrup for the young children with eczema

Hon KL, Lo W, Cheng WK, Leung TF, Chow CM, Lau CB, et al.
J Dermatolog Treat 2012;23:116-21.

This is a prospective study to find out the tolerability and clinical usefulness of a traditional Chinese herbal medicine (TCM) formulary in syrup form in treating children with moderate to severe atopic dermatitis (AD). This is a open-labelled study and children with moderate to severe AD were recruited to a 12 weeks study. The disease status were assessed according to the SCORAD index (Scoring Atopic Dermatitis) and had a score of ≧15 at entry. The CDLQI (Children's Dermatology Life Quality Index) were also assessed. The SCORAD and CDLQI were evaluated at every visit and used as outcome measures.

In previous published studies, the authors demonstrated a five herbs formulary (*Flos Lonicerae, Herba Menthae, Cortex Moutan, Rizoma Atractylodis, Cortex Phellodendri (based on a widely used ancestral TCM concoction)*) was able to improve the quality of life and reduce topical corticosteroid use in children. However, previous studies employed a capsule form which is difficult to be swallowed by young children. This study improved by using a syrup form instead.

A total of 21 children were recruited, the mean age was 5.8 years and the mean SCORAD and CDLQI were 36.6 and 11.9 respectively at the start of study. There was a significant reduction of SCORAD (28, $p<0.05$) at the last visit (4 weeks after treatment finished). The pruritus score was also significantly lowered (5.8 to 4.0, $p=0.022$) at the last visit. A total of six adverse events were reported and 2 patients withdrew for the study due to skin rash. The other adverse events mostly resolved spontaneously. There was no increase in topical corticosteroid usage, the haematological and biochemical tests were within normal during the study period. There was no change in serum IgE level.

The authors concluded that a five herb syrup TCM is demonstrated to be tolerable and efficacious in treating children with moderate to severe AD. This study is significant in that it standardized the formulary of a TCM concoction in the treatment process. However, it is limited by the open-labelled nature and without a randomized placebo control group. The sample size is also too small to enable a robust conclusion to be drawn.

Evaluation of reliability, validity and responsiveness of the CADSI and the CAT-BM

Goreshi R, Okawa J, Rose M, Feng R, Lee LA, Hansen CB, et al.
J Invest Dermatol 2012;132:1117-24.

This study aimed at assessing the Cutaneous Disease and Activity Severity Index (CADSI) and the Cutaaneous Assessment Tool - Binary Method (CAT-BM) as the measurement of outcomes and severity of dermatomyositis (DM) when using the Physician Global Assessment (PGA) as the standard for comparison in clinical studies of DM. DM is an autoimmune disease that can have subtypes with minimal or no myopathy. However, although the skin disease in DM is well recognized by dermatologists, there are very limited systemic studies to determine the disease severity when comparing to other conditions such as psoriasis and eczema. It is important to create reliable measurement and assessment tools for cutaneous DM to determine the disease severity so that the outcome of treatment can be properly assessed.

The CADSI is a tool that had been revised and evaluated as more efficient and trustworthy when compared with other outcome measures such as the Dermatomyositis Skin Severity Index and Cutaneous Assessment Tool (CAT). The CAT-BM is a simplified and validated version of CAT and was showed to correlate well to the CAT.

CADSI is a one-page assessment to find out the disease severity of cutaneous DM, total scores range 0-132. The disease severity and damage is assessed by degree of erythema, scaling, any erosions or ulcerations, having poikiloderma or calcinosis in 15 different body areas. Nail fold lesions, hair loss and Gottron's papules were also recorded and scored. CAT-BM is also a one-page assessment with total scores range 0-28 (0-17 for disease activity and 0-11 for damage). Activity

of disease is based on presence or absence of erythema and other distinctive DM lesions in 7 body areas, but not scaling, erosions or ulcerations. Disease damage scoring is similar to CADSI except only assessed in 7 body areas.

A total of ten dermatologists were invited to the study and 14 patients with DM were also invited. The patients were all Caucasians, 3 men and 11 women. The total scores of CADSI and CAT-BM showed a normal distribution ranged from 1-72 and 1-20 respectively. The results showed that the CADSI had a good inter-observer reliability in disease activity and total scores, moderate inter-observer reliability in damage scores. When comparing with CAT-BM and PGA as gold standard, CADSI had the best inter-observer reliability with higher interclass correlation coefficient. The CADSI was also found to have the almost ideal intra-observer reliability in disease activity and total scores and good reliability in damage scores. The CADSI also showed a better intra-observer reliability than CAT-BM but post-hoc power calculation did not attain statistical significance.

In summary, CADSI is shown to be a more reliable assessment tool for DM outcome measures with better inter-observer reliability. This study is more like a pilot study and limited by small number of participants.

Ultraviolet A1 phototherapy: a British Photodermatology Group workshop report

Kerr AC, Ferguson J, Attili SK, Beattie PE, Coleman AJ, Dawe RS, et al.
Clin Exp Dermatol 2012;37:219-26.

Ultraviolet A1 (UVA1) phototherapy was first introduced in 1981, but currently used in limited centres in UK and Europe. The evidence and published guidelines on its use remained limited. A workshop by the British Photodermatology Group was held in May 2009 to provide an overview on its usage, safety and practicability, based on consensus expert opinion.

UVA1, with wavelength 340-400 nm, penetrates deeper into the dermis, with its cellular effects more in common with visible light. It exerts its direct effect through DNA and indirect effect through absorption by endogenous photodynamic photosensitizers including lipids and proteins. It generates free-radical damage to T lymphocytes in inflammatory dermatosis and malignant T-cells in mycosis fungoides, affects other immune cells like Langerhan cells and mast cells, and upregulates the activity of matrix metalloproteinases produced by fibroblasts.

The efficacy of UVA1 is best shown in morphea and atopic eczema. In morphea, UVA1 is definitely effective and valuable in inducing lengthy periods of remission, as shown in controlled studies. It can be used as low, medium to high doses with greater benefits of the latter. It is clearly beneficial in localized disease that poses restriction in joint or lung function, and in stopping or slowing widespread disease. A common side effect is local skin darkening, which may limit its use if the primary concern is cosmetic only. The workshop recommended the use of UVA1 therapy as second line for morphea, after failure of topical steroid.

For atopic eczema, at least medium to high doses of UVA1 is effective, but not superior to PUVA or narrow-band UVB, and it seems to be more effective in acute rather than chronic eczema. However, studies have involved UVA1 as monotherapy, rather than an adjunct to other standard therapies, which may undermine its efficacy. It is also useful and may be as effective as PUVA in dyshidrotic hand eczema. The workshop recommended the use of UVA1 for atopic eczema patients who failed other phototherapies.

Other conditions that are shown to be beneficial as third-line UVA1 treatment based on case reviews included sclerodermoid GVHD (first line therapy), scleroedema of Bushke (second line therapy), nephrogenic systemic fibrosis, lichen sclerosus, urticarial pigmentosa, chronic urticaria, granuloma annulare, cutaneous sarcoidosis, subacute prurigo, psoriasis, pityriasis rubra pilaris and pityriasis lichenoides.

UVA1 can be generated using fluorescent tubes or metal halide lamps. Low doses can be delivered through the former, while medium and high doses through the latter. There are no internationally agreed definitions of treatment doses, but the workshop considered <10 J/cm^2 "very low dose", 10-29 J/cm^2 "low dose", 30-59 J/cm^2 "medium dose" and >60 J/cm^2 "high dose". Regular dosimetry has to be performed. Recommended MED dose ranges are 7-56 J/cm^2 for skin phototype I, 7-80 J/cm^2 for skin phototype II and 10-112 J/cm^2 for phototypes III and IV. The maximum lifetime number of treatments for UVA1 is unclear, but the workshop considered those receiving more than 200 sessions of whole body treatment at increased risk of skin cancer.

UVA1 is generally well tolerated with few acute side effects, which include, delayed persistent tanning (most common), immediate erythema, polymorphic light eruption, reactivation of herpes simplex, cholinergic urticaria and transient change of mole appearance. Chronic side effects are limited so far. Three retrospective studies involving over 400 patients receiving 4 to 116 treatments in total, reported no chronic effects, but animal studies showed that UVA1 can induce squamous cell carcinomas and melanomas. The main limitations of UVA1 are the high cost and long treatment times (£40000 for acquiring and installing a high-output UVA1 device). Low-dose UVA1 using fluorescent sources is simpler to deliver and cheaper, but more studies are required to discover which patients can be effectively treated by it. Further studies on its efficacy compared to standard phototherapy and treatment regimen for individual disease are needed.

Sensitivity of Gram stain in the diagnosis of urethritis in men

Orellana MA, Gomez-Lus ML, Lora D.
Sex Transm Infect 2012:88:284-7.

Urethritis usually presents with mucopurulent urethral discharge, dysuria and sometimes itching over urethral meatus. It is the inflammatory condition of anterior urethra and often diagnoses by presence of polymorphonuclear leucocytes (PMNLs)/high-power field (HPF) (x1000 magnification). The aim of this study was to assess the sensitivity of Gram stain, compared with the organism isolated in urethral exudates and to assess the role of isolated organisms considered unlikely to be causal agents of urethritis.

This was a cross-sectional prospective study carried out in a primary care laboratory provided services to outpatients from the city of Madrid during 2006-2007. Gram stain with microscopy, culture, chlamydial PCR, *Ureaplasma urealyticum* and *Mycoplasma hominis* detection by Mycoplasma IST2 system and wet mount if the partner had history of *Trichomonas vaginalis* was performed on the urethral specimen. In general, if the positive case was classified as more than 2 PMNLs/HPF, the sensitivity for detecting pathogens was 38% (95% CI 30-46) and specificity was 79% (95% CI 75-84). If the positive case was classified as more than 5 PMNLs/HPF, the sensitivity was 25% (95% CI 18-33) and the specificity was 91% (95% CI 87-94). If taking >5 PMNLs/HPF as an indicator of urethritis, 76% of *Chlamydia trachomatis*, 20% of *Neisseria gonorrhoea* and 89% of *Ureaplasma urealyticum* would be missed by the Gram stain.

The authors concluded that the sensitivity of Gram stain was very low in the diagnosis of urethritis in men. The bacteriological analysis of urethritis should be performed in patients even when the leucocytes were not observed and the absence of leucocytes in the Gram stain did not exclude the diagnosis of urethritis.