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ORIGINAL ARTICLE

A Randomised Study Comparing the Efficacy of Low-Dose Oral Azithromycin versus Doxycycline in Combination with Topical Benzoyl Peroxide in the Treatment of Moderate to Severe Acne Vulgaris

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Abstract
Background
Acne vulgaris is a common chronic inflammatory skin disease. Long term therapy involving antibiotics warrants for drug with a long half-life to increase compliance of patients.

Methods
A twelve-week prospective randomized study was performed on 40 subjects with moderate to severe facial acne to compare the efficacy of oral azithromycin with oral doxycycline. Thirty-six subjects completed the study. Subjects in azithromycin group received azithromycin 250mg three times a week plus topical benzoyl peroxide 5% (BPO), whereas subjects in doxycycline group received doxycycline 100mg daily plus topical BPO 5%. Efficacy evaluation included treatment success rate (Comprehensive Acne Severity Score /CASS of 0 or 1 or improvement of two grades from baseline) and lesion counts.

Results
Treatment was successful in 94.4% of subjects in azithromycin group, compared to 88.9% in doxycycline group (p=1.000) at week 12. However, percentage of clear or almost clear by CASS was higher in the doxycycline group (83.3% vs 66.7%; p=0.443). Percentage reduction of inflammatory lesion counts in azithromycin and doxycycline group following treatment for 12 weeks were 78.3% and 85.3% (p=0.133) respectively, whereas for non-inflammatory lesion counts were 77.7% and 78.8% (p=0.852) respectively. Nausea was reported in 77.8% at week 6 and 66.7% at week 12 in doxycycline group, but none in azithromycin group. There were no significant differences in incidence of diarrhoea and abdominal pain.

Conclusion
Azithromycin 250mg three times a week plus topical BPO 5% is as effective as doxycycline 100mg daily plus topical BPO 5%.

Key words: Acne vulgaris; Azithromycin; Doxycycline; Efficacy; Adverse effects

Introduction
Acne is an important disease worldwide and is the eighth most prevalent disease defined by the global burden of disease.1 Approximately 9.4% of the world’s population are affected, with over 90% of males and 80% of females in all ethnic group.1,2 The prevalence of acne varies among various countries.3 In Malaysia, the prevalence of acne is around 67.5% -68.1% among adolescents.
(13 - 18 years old), and among medical students from year 1 to 5, with males and females almost equally affected (1:1.1). Acne vulgaris affects both genders, but the severity may be greater in male patients. In the pathogenesis of acne, there is interplay between follicular epithelial hyperproliferation with resultant follicular plugging, excessive production of sebum, inflammation, and Propionibacterium acnes (P. acnes) activity. Face is the primary site of acne. It can also affect the back, chest and shoulders. At the trunk, lesions are usually concentrated near the midline.

Mild acne can be managed with topical treatments such as benzoyl peroxide, topical retinoids or topical combination therapy (e.g.: benzoyl peroxide + antibiotic or retinoid + benzoyl peroxide or retinoid + benzoyl peroxide + antibiotic). Systemic antibiotics have been widely used in the treatment of moderate to severe acne vulgaris. The anti-Propionibacterium acnes properties in antibiotics inhibit colonization of pilosebaceous glands by bacteria and prevent further inflammation. Doxycycline (tetracycline group) and erythromycin (macrolide group) are among the drugs commonly prescribed in these group of patients. Doxycycline use is contraindicated in certain populations, such as pregnant and lactating mothers, and children under 8 years of age. Oral erythromycin has been shown to be as effective as tetracycline with good tolerability. However, increasing evidence of the development of erythromycin resistant strains of P. acnes have prompted researchers to look for an alternative macrolide with a long half-life.

Thus, studies on azithromycin as an alternative treatment for acne vulgaris emerged. Successful usage of azithromycin in treating acne was first reported by Fernandez-Obregon AC in 1997. Azithromycin is a 9-methyl derivative of erythromycin. It has a long half-life of 2.3-3.2 days. Azithromycin is better absorbed and is more vastly distributed into tissues compared to erythromycin. It has the ability to achieve high concentrations within cells (including phagocytes) compared to serum. These properties improve the safety and efficacy of azithromycin, whereas the long half-life reduces the frequency of drug use. Besides that, metabolization of azithromycin via the hepatic pathways other than cytochrome P450 reduces the risk of drug interactions as well. There is also increasing evidence that azithromycin exert immunomodulatory effects by diminishing production of Interleukin-1alpha and Interleukin 8 cytokines (which are observed to be upregulated in acne patients).

Many studies have reported the efficacy and safety of azithromycin in comparison to other drugs with mixed results - either better than the other drug or no significant difference to the other drug. Additionally, studies also reported monthly pulse dosage of azithromycin, on 4 consecutive days a month to be as effective as daily dosage of doxycycline, which is an alternative option for subjects with poor compliance. In terms of safety, mild to moderate gastrointestinal discomforts were the most commonly reported side effects.

In the Malaysian setting, according to the Clinical Practice Guideline on Management of Acne, the recommended dose of azithromycin is 500mg three times per week. This is the most commonly used regime according to current available evidences. Two studies have shown that azithromycin 250mg three times per week can effectively treat acne. However, to the authors best knowledge at the time of this study, there has been no randomised study published to compare the efficacy of azithromycin 250mg three times per week with doxycycline 100mg daily for the treatment of moderate to severe acne vulgaris. Furthermore, there is no resistance of azithromycin towards P. acnes reported in Malaysia. On the other hand, erythromycin, which is a cheaper and commonly preferred macrolide in the current clinical setting till date, was already found to have a resistance rate of 7.5% towards P. acnes in 2010 and could be predicted to be higher at present time.

Therefore, the purpose of this study is to
determine whether azithromycin 250mg thrice weekly is as effective and tolerable in terms of its adverse effects as doxycycline 100mg daily in the treatment of moderate to severe acne vulgaris.

Materials and Methods

Study Drugs
In this study, oral antibiotics-doxycycline or azithromycin were combined with topical benzoyl peroxide 5% as recommended by acne guidelines to reduce antibiotic resistance.22

Disease Severity Assessment
Comprehensive Acne Severity Scale (CASS)
Evaluation included assessment of subjects using Comprehensive Acne Severity Scale (CASS),23 a validated tool for acne severity grading. It has reproducibility, inter-rater reliability and intra-rater reliability. All the inspection was done at a distance of 2.5 meters away for acne on face.

Acne lesion count
Other than CASS assessment, subjects’ acne lesions were also manually counted. The lesions were divided into non-inflammatory (open and closed comedones) and inflammatory (papule, pustule, nodule, cyst). Only lesions on the face were counted. The lesions were counted before the therapy (baseline), at 6-week and at 12-week of treatment by a single assessor. Photographs of the affected area were also taken from those who consented.

Finally, all subjects were evaluated for possible side effects by conducting an interview and then a complete physical examination. Subjects were also informed to contact the dermatology clinic / the principal investigator in the event they experienced undesirable side effects any time before their follow up assessment scheduled dates, once the treatment started.

All subjects were thoroughly briefed on the technique of benzoyl peroxide 5% (BPO 5%) gel application, i.e. to wash their face, pat dry and allow to dry thoroughly before application and to apply enough to cover the affected face area (avoiding the eye area) once a day at night.

Study Population
The study population were patients seen and diagnosed with moderate to severe acne vulgaris at the Dermatology Clinic of Hospital Tengku Ampuan Rahimah who fulfil the inclusion and exclusion criteria during the study period 1st October 2019 – 31st July 2020. Convenience sampling method was used and all subjects who met the eligibility criteria within the study period were randomized to receive either doxycycline or azithromycin.

The inclusion criteria were subjects aged 18 to 40, diagnosed with moderate to severe facial acne vulgaris as defined by Comprehensive Acne Severity Score (CASS: score of 3-4 on a scale from 0 -5), willing and able to comply with the requirements of study protocol. All subjects should be able to give written informed consent as well.

The exclusion criteria were subjects younger than 18 years and aged more than 40 years, subjects with acne conglobata, acne fulminans, drug induced acne, and nodulocystic acne that would require oral isotretinoin; subjects who were pregnant or breastfeeding mothers, subjects that received systemic antiacne antibiotics within 1 month, history of oral isotretinoin in the last 6 months, use of topical antiacne preparations, medicated shampoos or cleansers within 2 weeks, subjects with symptoms of hyperandrogenism, females with irregular menstruation, subjects who had chemical peels or physical therapies (e.g. laser) within 1 month, liver disease, history of arrhythmias, heart failure, history of hypersensitivity to doxycycline or azithromycin, subjects with concurrent use of oral contraceptive pills, concurrent dermatological problems that would interfere with the course of treatment or evaluation and finally patients who were treated with doxycycline for acne previously.

Subjects were also given the liberty to withdraw from the study at any time if the protocol was not followed or the investigator deems that it is detrimental or risky for the subject to continue.
However, all withdrawn/dropout subjects were not replaced.

**Randomization and Blinding**

Block randomization was carried out by an independent unit—the Hospital Tengku Ampuan Rahimah (HTAR) Clinical Research Centre to ensure the number of recipients of azithromycin therapy and doxycycline therapy were similar during all phases of the study. The sizes of the blocks were also randomized to reduce possibility of guessing the choice of treatment for the next patient. Randomization was done using the “RANDBETWEEN (0,1)” function in Microsoft Excel 2007, whereby “0” was assigned to azithromycin group; and “1” was assigned to doxycycline group. Concealment of allocation was done by placing the printed, folded allocation into sealed opaque envelopes. The sequence of the envelopes was then printed on a separate piece of paper and pasted on the front of the envelopes.

**Study Design**

This was an interventional, prospective, randomized, open label comparative study of azithromycin 250mg three times a week with BPO 5% and doxycycline 100mg daily with BPO 5% in moderate to severe acne vulgaris. The study was conducted at the Dermatology Clinic of Hospital Tengku Ampuan Rahimah over a 12 weeks period. After obtaining consent, subjects were screened and those who met the inclusion/exclusion criteria were randomized to either azithromycin group or doxycycline group during the baseline visit.

In azithromycin group, subjects received oral azithromycin 250mg three times per week for 12 weeks along with topical benzoyl peroxide gel 5%. In doxycycline group, subjects received oral doxycycline 100mg daily with topical benzoyl peroxide gel 5 % for 12 weeks. Each group consisted of 20 subjects. The subject and the investigator were aware of the type of medication allotted after baseline assessment was done by the investigator. Subjects were clinically assessed and evaluated at baseline, 6 weeks and 12 weeks by the principal investigator, who was the only assessor. Subjects were provided with a diary to record the medication taken, any missed pills, and adverse events. At each visit, pills were counted and topical BPO tubes were inspected.

**Efficacy Measures**

Primary efficacy outcome of the study was an improvement in CASS from baseline to week 12. This outcome was dichotomized to success or failure using one of the following two criteria to be selected:

a) Clear or almost clear (Grades 0 or 1) as success: Success is defined as “Clear” (Grade 0) or “Almost clear” (Grade 1) at week 12.

b) Two grades improvement as success: Success is defined as improvement of two grades from the baseline score.

Success rate was defined as the percentage of subjects with a CASS of 0 (clear) or 1 (almost clear) at each post baseline visit or improvement of 2 grades from baseline score to week 6 and 12.

Secondary efficacy outcome was the change in acne lesion count. Percentage change from baseline to week 6 and week 12 in acne lesion counts (inflammatory, non-inflammatory and total lesion counts) were determined.

**Safety Assessment**

Safety outcome was assessed by incidence of adverse effects self-reported by subjects, and by using a checklist for side effects attributable to either drug. Adverse events were managed accordingly depending on the type and severity.

**Ethical Approval**

This study was conducted in compliance with ethical principles outlined in the Declaration of Helsinki and Malaysian Good Clinical Practice Guideline. Ethical approval was obtained from the Medical Research and Ethics Committee with the research code of NMRR-19-2433-49831.
Statistical analysis
Normality of continuous data was assessed using Shapiro Wilk test. Natural log transformation was performed on acne counts (inflammatory lesion, non-inflammatory lesion and total lesion), and percentage of change in acne counts at 12 weeks prior to comparison analysis, as the data were found to have skewed distribution. Mean and standard deviation were used to describe normally distributed data, while median and interquartile range were used to describe skewed distributions. Frequencies and percentages were used to describe the categorical data. Independent t-test or Mann Whitney U Rank test was used to compare continuous data between the treatment groups. Paired t-test was used to compare continuous data within groups. Fisher's Exact test or Chi Square test was used to assess the association between categorical variables and study groups.

Statistical analyses were performed with IBM SPSS Statistics 25.0. All statistical significance was set at $p<0.05$.

Results
A total of 40 subjects were randomized to doxycycline and azithromycin group. Each group consisted of 20 subjects. Two subjects from each group were lost to follow up. Thirty-six subjects completed the study.

Demographic and Clinical Characteristics of the Study Population
Majority of the subjects were females (82.5%), and distribution of subjects according to gender and ethnicity were similar in both treatment groups ($p=1.000$ for age; $p=0.737$ for ethnicity). Median age of subjects were 21 years (IQR=4.0). Median duration of acne among subjects was 2.5 years (IQR=4.0). Median CASS score of the study population was 3.0 (IQR=0.0). Mean lesion counts for inflammatory lesions, non-inflammatory lesions and total lesions were 25.5 (SD=13.0), 41.0 (SD=22.1) and 66.5 (SD=40) respectively. There were no significant differences in demographics and baseline characteristics between the 2 treatment groups ($p>0.05$). (Table 1)

Efficacy
Comparison of treatment success at 6 and 12 weeks between azithromycin and doxycycline treatment groups are displayed in Table 2. Treatment was a success in 11.1% of subjects in azithromycin group, as opposed to 22.2% in doxycycline group at 6 weeks ($p=0.658$). However, at 12 weeks, 94.4% of subjects in azithromycin group achieved treatment success, as opposed to 88.9% in doxycycline group. The treatment success rates at week 12 were not statistically significant between the treatment groups ($p=1.000$).

Table 1. Demographic data and clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total (n=40)</th>
<th>Azithromycin plus topical BPO (n=20)</th>
<th>Doxycycline plus topical BPO (n=20)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>n (%)</td>
<td>7 (17.5)</td>
<td>4 (20.0)</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td>Female</td>
<td>n (%)</td>
<td>33 (82.5)</td>
<td>16 (80.0)</td>
<td>17 (85.0)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malay</td>
<td>n (%)</td>
<td>36 (90.0)</td>
<td>19 (95.0)</td>
<td>17 (85.0)</td>
</tr>
<tr>
<td>Chinese</td>
<td>n (%)</td>
<td>2 (5.0)</td>
<td>1 (5.0)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Others</td>
<td>n (%)</td>
<td>2 (5.0)</td>
<td>0 (0.0)</td>
<td>2 (10.0)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Median (IQR)</td>
<td>21.0 (4.0)</td>
<td>20.5 (4.0)</td>
<td>22.0 (5.0)</td>
</tr>
<tr>
<td>Acne duration (years)</td>
<td>Median (IQR)</td>
<td>2.5 (4.0)</td>
<td>3.0 (4.0)</td>
<td>2.0 (4.0)</td>
</tr>
<tr>
<td>CASS score</td>
<td>Median (IQR)</td>
<td>3.0 (0.0)</td>
<td>3.0 (1.0)</td>
<td>3.0 (0.0)</td>
</tr>
<tr>
<td>Inflammatory lesion count</td>
<td>Mean (SD)</td>
<td>25.5 (13.0)</td>
<td>21.7 (13.6)</td>
<td>22.9 (12.2)</td>
</tr>
<tr>
<td>Non-inflammatory lesion count</td>
<td>Mean (SD)</td>
<td>41.0 (22.1)</td>
<td>43.5 (25.2)</td>
<td>38.6 (17.5)</td>
</tr>
<tr>
<td>Total lesion count</td>
<td>Mean (SD)</td>
<td>66.5 (40.0)</td>
<td>71.5 (32.2)</td>
<td>61.5 (22.0)</td>
</tr>
</tbody>
</table>

Data was analysed with $^a$Fisher’s Exact test; $^b$Mann Whitney U Rank Test; $^c$Independent t-test.
Table 2. Comparison of treatment success at 6 and 12 weeks between treatment groups (n=36)

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin plus topical BPO (n=18)</td>
<td>Doxycycline plus topical BPO (n=18)</td>
</tr>
<tr>
<td>CASS at 6 weeks</td>
<td></td>
</tr>
<tr>
<td>Success n (%)</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>CASS at 12 weeks</td>
<td></td>
</tr>
<tr>
<td>Success n (%)</td>
<td>17 (94.4)</td>
</tr>
</tbody>
</table>

Data was analysed with Fisher’s Exact test. Only patients with complete follow-up data were included in the analysis. Success defined as achieving ‘clear’ (grade 0) or ‘almost clear’ (grade 1), or improvement in 2 grades from baseline to week 6 and 12.

In terms of CASS, percentage of clear or almost clear was higher in the doxycycline group at week 12 (83.3% vs 66.7%) with no significant difference between the two groups (p=0.443). (Table 3)

Table 3. Percentage of ‘clear’ or ‘almost clear’ according to CASS at 12 weeks between treatment groups (n=36)

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin plus topical BPO (n=18)</td>
<td>Doxycycline plus topical BPO (n=18)</td>
</tr>
<tr>
<td>CASS 0 or 1 at 12 weeks n (%)</td>
<td>12 (66.7)</td>
</tr>
</tbody>
</table>

Data was analysed with Fisher’s Exact test. Only patients with complete follow-up data were included in the analysis. CASS=Comprehensive Acne Severity Score; CASS ‘0’= clear, CASS ‘1’=almost clear

Our study also found a significant reduction in the mean number of inflammatory lesions from baseline to week 6 within the azithromycin group (27.4+13.9 vs 12.2+8.5, \( p<0.001 \)) and doxycycline group (23.9+12.4 vs 10.1+5.4, \( p<0.001 \)), and significant reduction in the mean number of non-inflammatory lesions from baseline to week 6 in azithromycin group (40.5+23.8 vs 19.1+12.4, \( p<0.001 \)) and in doxycycline group (40.4+17.5 vs 19.9+11.3, \( p<0.001 \)). Finally, total lesion counts also showed significant reduction from baseline to week 6 in azithromycin group (67.9+29.1 vs 31.3+18.8, \( p<0.001 \)) and in doxycycline group (64.3+21.2 vs 29.9+14.7, \( p<0.001 \)). (Table 4).

An overall reduction of 53.8% (SD=20.0) of inflammatory lesions at week 6 was observed compared to baseline. Specifically, there were mean reductions of 54.0% (SD=16.6) and 53.6% (SD=23.3) of inflammatory lesions in azithromycin group and doxycycline group, respectively. However, there was no statistical difference in mean changes of inflammatory lesions at week 6 between the treatment groups \( (p=0.948) \). Similarly, an overall reduction of 49.8% (SD=19.9) was observed for non-inflammatory lesions at week 6 compared to baseline. Specifically, there were mean reduction of 50.1% (SD=19.4) and 49.5% (SD=20.9) of non-inflammatory lesions in azithromycin and doxycycline group respectively. Again, there was no statistical difference in mean changes of non-inflammatory lesions at week 6 between the treatment groups \( (p=0.930) \). Mean reduction of total lesions was 53.2% (SD=17.5), with a decrease of 53.8% (SD=15.6) in azithromycin group and 52.6% (SD=19.6%) in doxycycline group. The reduction in total lesions percentage was not significant between the treatment groups \( (p=0.844) \) (Table 5).

Table 4. Comparison of acne lesion count from baseline to week 6 within treatment groups (n=36)

<table>
<thead>
<tr>
<th>Acne lesion count</th>
<th>Treatment groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Azithromycin plus topical BPO (n=18)</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>Inflammatory lesions</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Non-inflammatory lesions</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Total lesions</td>
<td>Mean (SD)</td>
</tr>
</tbody>
</table>

Data was analysed with paired t-test. Only patients with complete follow-up data were included in the analysis. **significant at \( p<0.001 \)
Table 5. Comparison of percentage change of acne lesion count from baseline to Week 6 between treatment groups (n=36)

<table>
<thead>
<tr>
<th>Change of acne lesions</th>
<th>Total</th>
<th>Treatment groups</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=36)</td>
<td>Azithromycin plus topical BPO (n=18)</td>
<td>Doxycycline plus topical BPO (n=18)</td>
</tr>
<tr>
<td>Inflammatory lesions (%)</td>
<td>Mean (SD)</td>
<td>-53.8 (20.0)</td>
<td>-54.0 (16.6)</td>
</tr>
<tr>
<td>Non-inflammatory lesions (%)</td>
<td>Mean (SD)</td>
<td>-49.8 (19.9)</td>
<td>-50.1 (19.4)</td>
</tr>
<tr>
<td>Total lesions (%)</td>
<td>Mean (SD)</td>
<td>-53.2 (15.6)</td>
<td>-53.8 (15.6)</td>
</tr>
</tbody>
</table>

Data was analysed with independent test. Only patients with complete follow-up data were included in the analysis. Percentage of change = \((\text{lesion count at week 6} - \text{lesion count at baseline}) / \text{lesion count at baseline}) \times 100\%

Significant reduction in the mean number of inflammatory lesions from baseline to week 12 was observed within the azithromycin group (27.4+13.9 vs 5.7+4.4, \(p<0.001\)) and doxycycline group (23.9+12.4 vs 3.4+3.1, \(p<0.001\)). There was also significant reduction in the mean number of non-inflammatory lesions from baseline to week 12 in azithromycin group (40.5+23.8 vs 8.3+6.2, \(p<0.001\)) and doxycycline group (40.4+17.5 vs 8.3+6.2, \(p<0.001\)). Finally, total lesions count also showed significant reduction from baseline to week 12 in azithromycin group (67.9+29.1 vs 13.9+9.4, \(p<0.001\)) and doxycycline group (64.3+21.2 vs 11.7+8.0, \(p<0.001\)) (Table 6).

There was an overall reduction of 81.8% (SD=13.2) of inflammatory lesions at week 12 compared to baseline. Specifically, there were mean reductions of 78.3% (SD=13.0) and 85.3% (SD=12.7) of inflammatory lesions in azithromycin and doxycycline group, respectively. However, there was no statistical differences in mean changes of inflammatory lesions, non-inflammatory lesions and total lesions at week 12 between the treatment groups (\(p=0.133\) vs \(p=0.852\) vs \(p=0.654\)) (Table 7).

Table 6. Comparison of acne lesion count from baseline to week 12 within treatment groups (n=36)

<table>
<thead>
<tr>
<th>Acne lesion count</th>
<th>Treatment groups</th>
<th>Azithromycin plus topical BPO (n=18)</th>
<th>Doxycycline plus topical BPO (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 12</td>
<td>P value</td>
</tr>
<tr>
<td>Inflammatory lesions</td>
<td>Mean (SD)</td>
<td>27.4 (13.9)</td>
<td>5.7 (4.4)</td>
</tr>
<tr>
<td>Non-inflammatory lesions</td>
<td>Mean (SD)</td>
<td>40.5 (23.8)</td>
<td>8.3 (6.2)</td>
</tr>
<tr>
<td>Total lesions</td>
<td>Mean (SD)</td>
<td>67.9 (29.1)</td>
<td>13.9 (9.4)</td>
</tr>
</tbody>
</table>

Data was analysed with paired t-test. Only patients with complete follow-up data were included in the analysis.

**significant at \(p<0.001\)

Table 7. Comparison of percentage change of acne lesion count from baseline to week 12 between treatment groups (n=36)

<table>
<thead>
<tr>
<th>Change of acne lesions</th>
<th>Total</th>
<th>Treatment groups</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=36)</td>
<td>Azithromycin plus topical BPO (n=18)</td>
<td>Doxycycline plus topical BPO (n=18)</td>
</tr>
<tr>
<td>Inflammatory lesions (%)</td>
<td>Mean (SD)</td>
<td>-81.8 (13.2)</td>
<td>-78.3 (13.0)</td>
</tr>
<tr>
<td>Non-inflammatory lesions (%)</td>
<td>Mean (SD)</td>
<td>-78.2 (12.7)</td>
<td>-77.7 (12.5)</td>
</tr>
<tr>
<td>Total lesions (%)</td>
<td>Mean (SD)</td>
<td>-80.2 (11.3)</td>
<td>-79.1 (10.3)</td>
</tr>
</tbody>
</table>

Data was analysed with independent test. Only patients with complete follow-up data were included in the analysis.

Percentage of change = \(((\text{lesion count at week 12} - \text{lesion count at baseline}) / \text{lesion count at baseline}) \times 100\%\)
Safety and tolerability

At 6 weeks, none of the subjects receiving azithromycin reported nausea while 14 (77.8%) from doxycycline group developed nausea, and the difference between treatment groups was statistically significant \( (p<0.001) \). After 12 weeks of treatment, 12 (66.7%) subjects from doxycycline group reported nausea \( (p<0.001) \), which is lesser than the percentage at 6 weeks (Table 8).

Discussion

Thirty-six subjects managed to complete the study and it was comparable to Kus et al (2005) which included 45 patients aged 18 to 40 suffering from moderate acne vulgaris.\(^20\) The age group of subjects in this study is comparable to Moravvej et al. (2012).\(^12\) Most of the previous similar studies included subjects aged 13-48 years with a sample size of 50 to 80.\(^12,16,18\)

According to the current findings, treatment was a success only in 11.1% of subjects in azithromycin group, as opposed to 22.2% of subjects in doxycycline group at 6 weeks. At 12 weeks, treatment was a success in 94.4% of subjects in azithromycin group, as opposed to 88.9% of subjects in doxycycline group. The difference was however not statistically significant \( (p>0.05) \). Additionally, both treatment groups showed more reductions in terms of total lesions, inflammatory lesions and non-inflammatory lesions at 12 weeks compared to 6 weeks of treatment with no significant difference between the treatment groups \( (p>0.05) \). There was no significant difference found in terms of percentage of lesions reductions following treatment between doxycycline or azithromycin groups at both 6 and 12 weeks as well.

Our current findings were similar to few other reported studies.\(^11,12,20,24\) In a randomized study with 50 patients (more than 16 years old) for 12 weeks done by Parsad et al. (2001), monthly pulse dosing of azithromycin 500mg 4 times each month was tested against doxycycline 100mg daily plus topical tretinoin 0.05%.\(^11\) Based on their results, pulse azithromycin plus topical tretinoin 0.05% was as effective as doxycycline 100mg daily plus topical tretinoin 0.05%. This was similar to Kus et al. (2005) where azithromycin with dosage of 500mg/day on 3 consecutive days per week in the first month, followed by 2 consecutive days per week in the second month and consecutively one day per week in the third month; were found to give significant and similar improvement to doxycycline twice a day for the first month and once a day for the second and third months.\(^20\) In another randomized, double-blind clinical trial, Babaienejad et al. (2011) compared the efficacy and safety of oral azithromycin 500mg daily, 4 consecutive days per month for 3 consecutive months and doxycycline, 100mg daily for 3 consecutive months.\(^24\) However, they did set the age as the influencing parameter. It

<p>| Table 8. Comparison of adverse effects at 6 and 12 weeks between treatment groups (n=36) |</p>
<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>6 Weeks</th>
<th>12 Weeks</th>
<th>P value</th>
<th>6 Weeks</th>
<th>12 Weeks</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Azithromycin plus topical BPO (n=18)</td>
<td>Doxycycline plus topical BPO (n=18)</td>
<td>P value</td>
<td>Azithromycin plus topical BPO (n=18)</td>
<td>Doxycycline plus topical BPO (n=18)</td>
<td>P value</td>
</tr>
<tr>
<td>Nausea</td>
<td>0 (0.0)</td>
<td>14 (77.8)</td>
<td>&lt;0.001**</td>
<td>0 (0.0)</td>
<td>12 (66.7)</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0 (0.0)</td>
<td>3 (16.7)</td>
<td>0.229</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>n/a</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>3 (16.7)</td>
<td>6 (33.3)</td>
<td>0.443</td>
<td>1 (5.6)</td>
<td>4 (22.2)</td>
<td>0.338</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3 (16.7)</td>
<td>4 (22.2)</td>
<td>1.000</td>
<td>1 (5.6)</td>
<td>1 (5.6)</td>
<td>1.000</td>
</tr>
<tr>
<td>Giddiness</td>
<td>1 (5.6)</td>
<td>0 (0.0)</td>
<td>1.000</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Data was analysed with Fisher’s Exact test or Chi square test. Only patients with complete adverse events follow-up data at 6 and 12 weeks were included in the analysis.
was concluded that although azithromycin is as effective as doxycycline in the treatment of moderate acne vulgaris, doxycycline is a better treatment option for patients above 18 years old. Another report by Moravvej et al. (2012) indicated similar efficacy between the two drugs in reducing the acne lesions too. Their 12 weeks study included 60 subjects with moderate facial acne and comparison was done between azithromycin 500mg/day, three times a week plus topical tretinoin versus doxycycline 100mg/day plus topical tretinoin.

Few studies reported azithromycin to be more effective than the other drug too. In a retrospective study by Fernandez-Obregon et al. (2000) involving 79 patients (13-48 years old), individuals who were intolerant to tetracycline, doxycycline, minocycline and erythromycin were treated with azithromycin 250mg three times a week. By 4 weeks, azithromycin was found to be significantly better. There were more than 80% reduction in inflammatory acne lesions (85.7%) versus an average of 77.1% for all other agents. In a different non-randomized study done by Singhi et al. (2003), 62 patients were treated with either daily dose of azithromycin 500mg for 3 consecutive days in a 10 days cycle plus topical erythromycin, with seven drug free days each cycle; or doxycycline 100mg/day with topical erythromycin over 12 weeks period. Azithromycin with topical erythromycin combination was found to be significantly better compared to doxycycline with topical erythromycin.

Kapadia and Talib (2004) treated acne patients with azithromycin 500mg 3 times weekly and found that 83% showed at least a 60% improvement in only 4 weeks and that the majority achieved 80% clearance in 12 weeks. In a study by Naieni et al. (2006), all 3 different azithromycin regimens - 5 consecutive days of treatment each month with 500mg on the first day and 250mg/day for another 4 days per month; 500mg/day for 4 consecutive days per month; and 250mg/day thrice weekly were effective in the treatment of acne vulgaris with no significant difference in their efficacies. This was a 12 weeks investigator blind, randomized study involving 58 moderate to severe acne patients.

On the other hand, Ullah et al. (2014) found that doxycycline worked better for acne with a significant difference at 12 weeks. It was a randomized study design with 386 patients of moderate acne (14-30 years old) comparing azithromycin 500mg/day, for 4 consecutive days monthly, and doxycycline 100mg/day. In this study however, no topical treatment was given to study subjects.

A large scale worldwide observational study of adherence with acne therapy by Dreno et al. (2010) reported that approximately 48% of Asian patients from Hong Kong, India, Philippines, and Singapore are likely to adhere poorly to their acne treatment regimen. 53% of Asian patients adhered poorly to systemic treatment. Thus, azithromycin could be a rational treatment because there is a possibility of better compliance with lower frequency dosing regimen. Based on our findings, azithromycin 250mg thrice weekly is as effective as doxycycline 100mg daily, hence suggesting this regimen could be used as an alternative for patients who are intolerant or contraindicated to doxycycline. This would also be more cost effective than the current Clinical Practice Guidelines on Management of Acne recommendation of 500mg three times per week, with potential lesser gastrointestinal side effect.

In terms of adverse effects, nausea was reported by the majority in the doxycycline group but none in the azithromycin group. However, both the study drugs were found tolerable, safe with no subjects withdrawing due to the adverse effects of the drugs by 6 and 12 weeks. Other reported adverse effects from this study include; diarrhoea, abdominal pain, vomiting, and giddiness. Most commonly reported adverse effects in patients receiving azithromycin 500mg of various dosing were, slight gastrointestinal upset and diarrhoea.

Limitations and recommendations
The main limitation of our study is small
sample size and single assessor, which may cause bias of assessment. Hence, a multi-centre study involving larger sample size would be needed. Further longer study up to 24 weeks is also helpful to determine the relapse rate of both group of patients.

**Conclusion**
This study demonstrated that in moderate to severe facial acne vulgaris, both low-dose oral azithromycin and doxycycline in combination with topical BPO are equally effective. Azithromycin can be considered as an alternative oral antibiotic for patients who are intolerant/allergic or contraindicated to doxycycline such as pregnant and lactating mothers.

**Conflict of Interest Declaration**
The authors have no conflict of interest to declare.

**Acknowledgement**
We would like to express our profound gratitude to Dr Muralitharan A/L Perumal and Dr Yap Soong Yiing from CRC Department, HTAR for their guidance and support in conducting this study. We would like to thank the Director General of Health Malaysia for his permission to publish this article.

**References**

Prevalence of Sexually Transmitted Infections (STIs) among Adolescents Attending Genitourinary Medicine Clinic Hospital Kuala Lumpur between 2014 and 2018

Vijayaletchumi Krishnasamy, Dip. STD/AIDS, Suganthi Thevarajah, MMed, Min Moon Tang, AdvMDerm

Department of Dermatology, Hospital Kuala Lumpur Kuala Lumpur, Malaysia

Abstract

Background

Adolescents, who aged between 10 and 19 years old, comprise about 20% of the world’s population. They are vulnerable to acquisition of sexually transmitted infections (STIs). Here, we aim to determine the demography and pattern of STIs among adolescents attending Genito-Urinary Medicine (GUM) Clinic, Hospital Kuala Lumpur (HKL).

Methods

This is a retrospective study on all adolescents attending GUM clinic between 2014 and 2018. Data was obtained from case notes and further analysed.

Results

A total of 111 adolescents attended GUM clinic between 2014 and 2018. The mean age was 18 years (range 12-19). The male to female ratio was 2.26:1. All patients were Malaysian. Only 2 were foreign nationals. The majority were Malays (85.3%) followed by Indians (11%) and Chinese (3.7%). About 46.8% were still schooling, 28.8% were employed and 23.4% were unemployed. About 8.3% had a history of substance abuse. The majority (67.6%) were heterosexual, about 17.1% were homosexual and 3.6% were bisexual. Nearly 95% engaged in unprotected sex. Majority (46%) had casual sex. The most frequent presenting symptoms for male and female adolescents were discharge (43.2%) followed by swelling/growth (23.4%). About 83% had confirmed STIs. The most common STIs among the male were gonorrhoea (44.1%), genital warts (23.4%) and non-gonococcal urethritis (14.7%). The most common STIs among the female were herpes genitalis (50%), genital warts (33.3%) and syphilis (8.3%). Six patients were infected with the human immunodeficiency virus (HIV).

Conclusion

The most common STI among adolescents between 2014 and 2018 was gonorrhoea for male and herpes genitalis for female.

Key words: Adolescent, Sexually transmitted infections, Gonorrhoea, Herpes genitalis, Genital warts, Syphilis

Introduction

Adolescents, defined as persons between 10 and 19 years old by WHO, are among of the most frequent group reported with STIs. Those who are sexually active account for approximately half of reported STI cases annually.1,2 It is estimated that about 333 million new cases of curable sexually transmitted infections occur worldwide each year, with the highest rates.
among 20-24 year-old followed by 15-19 year-old age group. In Malaysia, adolescents comprise of 18% of the total population. The improved surveillance system in Malaysia has reported an increasing trend of syphilis and gonorrhoea. The incidence rate of syphilis was reported at 3.46 per 100,000 population in 2011 but had tripled to 10.75 per 100,000 population in 2019. On the other hand, the incidence of gonorrhoea has doubled from 4.71 per 100,000 population in 2011 to 9.25 per 100,000 population in 2019. In 2018, about 3% of new HIV cases were reported among people age those aged between 13 and 19 years old in Malaysia. Adolescents are more likely to engage in high-risk sexual behaviour such as multiple partners or engaging in sexual activities without a condom. This is due in part to the fact that the prefrontal cortex, responsible for executive function, is still developing throughout adolescence. Furthermore, adolescents are less likely than adults to access to sexual health services due to confidentiality issues. These factors lead to a higher chance of exposure and a lower chance of diagnosis and treatment. From a biological perspective, adolescent females are particularly susceptible to STIs like Chlamydia trachomatis and human papilloma viruses due to lower production of cervical mucus and increased cervical ectopy. Therefore, if exposed to an STI, adolescent females are more likely than adults to get infected. STI guidelines from the CDC United States highlight that youth who are at highest risk of sexually transmitted infections include those in detention facilities, injection drug users, and teens with history of sexual molestation and males who have had anal sex with other males. Female victims of childhood sexual abuse are at increased risk for STIs possibly due to younger age at sexual initiation and unsafe sex practices. Sexually transmitted infections among adolescents in Malaysia is largely underreported. Thus there is limited data and studies on STIs in adolescents.

The aim of this study is to describe the demography and pattern of STIs among adolescents attending Genito-Urinary Medicine (GUM) Clinic, Hospital Kuala Lumpur (HKL).

Materials and Methods
This is a retrospective study on all adolescents attending GUM clinic between 2014 and 2018. Data was obtained from case notes and further analyzed.

Results
There were 111 adolescents who has attended Genitourinary Medicine clinic from the year 2014 till 2018 (Table 1). Majority were referred from the outpatient and emergency department. Five cases were from the Suspected Child Abuse and Neglect (SCAN) team. There were more males (69.3%) than females (30.6%). The mean age of these patients was 18 years and most of the adolescent were in the age group of 15 to 19 years (89%). The youngest male was 13 years while the youngest female was 14 years. Majority were Malaysian of which (85.3%) were Malays followed by Indians (11.1%) and Chinese (3.7%). Only one was married. There were 2 adolescents, unmarried presented to us during pregnancy. There were 2 single mothers. Less than half were still school going (46.5%), 28.8% were employed and 23.4% were unemployed. Eleven (1.3%) of them had history of substance abuse. These substances included marijuana, glue, amphetamines/methamphetamines, smoking and alcohol. Majority (67.6%) were heterosexual. About 17.1% and 3.6% were homosexuals and bisexuals respectively. About a tenth of the adolescents denied having any kind of sexual activity. Majority (95%) had engaged in unprotected sex. Those who used condom claimed to use them inconsistently.

The most common presentation to the GUM clinic was genital discharge (43.2%) followed by genital growths (23.4%). Following clinical assessment and laboratory investigations, 83% of adolescents were confirmed to have sexually transmitted infections. The most common STIs among the males were gonorrhoea (45.6%), genital warts (17.6%) and non-gonococcal
urethritis (17.6%), as shown in Table 2. The most common STIs among female adolescents were herpes genitalis (50%), genital warts (33.3%) and syphilis (8.3%). Non-STI causes that were diagnosed in this study included bacterial vaginosis, candidiasis, balanitis and molluscum contagiosum. Six male adolescents were diagnosed to have the human immunodeficiency virus (HIV).

**Table 1.** Demographic data and sexual behaviour of 111 adolescent attending GUM clinic Hospital Kuala Lumpur between 2014 and 2018

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Male n=76</th>
<th>Female n=35</th>
<th>Total n=111</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years (range)</td>
<td>18 (13-19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age group in years (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10-14</td>
<td>6</td>
<td>6</td>
<td>12 (10.8%)</td>
</tr>
<tr>
<td>15-19</td>
<td>70</td>
<td>29</td>
<td>99 (89%)</td>
</tr>
<tr>
<td>Ethnicity among Malaysian (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malay</td>
<td>65</td>
<td>28</td>
<td>93 (85.5%)</td>
</tr>
<tr>
<td>Chinese</td>
<td>3</td>
<td>1</td>
<td>4 (3.6%)</td>
</tr>
<tr>
<td>Indians</td>
<td>7</td>
<td>5</td>
<td>12 (10.8%)</td>
</tr>
<tr>
<td>Others</td>
<td>1</td>
<td>1</td>
<td>2 (1.8%)</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Student</td>
<td>34</td>
<td>18</td>
<td>52 (46.8%)</td>
</tr>
<tr>
<td>Employed</td>
<td>26</td>
<td>5</td>
<td>31 (28.0%)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>16</td>
<td>11</td>
<td>27 (24.0%)</td>
</tr>
<tr>
<td>Self employed</td>
<td>1</td>
<td>-</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>Sexual Orientation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterosexual</td>
<td>46</td>
<td>29</td>
<td>75 (67.5%)</td>
</tr>
<tr>
<td>Homosexual</td>
<td>19</td>
<td>-</td>
<td>19 (17.1%)</td>
</tr>
<tr>
<td>Bisexual</td>
<td>4</td>
<td>-</td>
<td>4 (3.6%)</td>
</tr>
<tr>
<td>Denied</td>
<td>6</td>
<td>7</td>
<td>13 (11.7%)</td>
</tr>
<tr>
<td>Type of sexual partner (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Casual</td>
<td>40</td>
<td>11</td>
<td>51 (46%)</td>
</tr>
<tr>
<td>Steady</td>
<td>25</td>
<td>17</td>
<td>42 (37.8%)</td>
</tr>
<tr>
<td>Sex worker</td>
<td>4</td>
<td>-</td>
<td>4 (3.6%)</td>
</tr>
<tr>
<td>No partner</td>
<td>6</td>
<td>7</td>
<td>13 (11.7%)</td>
</tr>
<tr>
<td>Number of sexual partner in the last 6 months (%)</td>
<td>1</td>
<td>45</td>
<td>24</td>
</tr>
<tr>
<td>&gt;1</td>
<td>24</td>
<td>5</td>
<td>29 (26%)</td>
</tr>
<tr>
<td>Numbers with documented substance abuse (%)</td>
<td>10</td>
<td>1</td>
<td>11 (1.3)</td>
</tr>
<tr>
<td>Condom usage (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>2 (1.8%)</td>
<td>1 (0.9%)</td>
<td>105 (89%)</td>
</tr>
<tr>
<td>Occasional</td>
<td>10 (3.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Always</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presenting symptoms (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genitalia pain</td>
<td>3</td>
<td>2</td>
<td>5 (4.5%)</td>
</tr>
<tr>
<td>Discharge</td>
<td>41</td>
<td>7</td>
<td>48 (43.2%)</td>
</tr>
<tr>
<td>Genital ulcers</td>
<td>10</td>
<td>11</td>
<td>21 (18.9%)</td>
</tr>
<tr>
<td>Swelling/ growth</td>
<td>18</td>
<td>8</td>
<td>26 (23.4%)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>2</td>
<td>3</td>
<td>5 (4.5%)</td>
</tr>
<tr>
<td>Contact</td>
<td>0</td>
<td>3</td>
<td>3 (2.7%)</td>
</tr>
<tr>
<td>Genital itch</td>
<td>2</td>
<td>1</td>
<td>3 (2.7%)</td>
</tr>
<tr>
<td>Scrotal swelling</td>
<td>4</td>
<td>-</td>
<td>4 (3.6%)</td>
</tr>
<tr>
<td>True sexually transmitted diseases at final diagnosis (%)</td>
<td>68</td>
<td>24</td>
<td>92 (82.8%)</td>
</tr>
</tbody>
</table>

**Table 2.** Pattern of Sexually Transmitted Infections (STI) in 92 adolescents

<table>
<thead>
<tr>
<th>Types of infections</th>
<th>Male n=68(%)</th>
<th>Female n=24(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genital warts</td>
<td>12 (17.6%)</td>
<td>8 (33.3%)</td>
</tr>
<tr>
<td>Herpes genitalis</td>
<td>5 (7.4%)</td>
<td>12 (50%)</td>
</tr>
<tr>
<td>Syphilis</td>
<td>10 (14.7%)</td>
<td>2 (8.3%)</td>
</tr>
<tr>
<td>Urethral discharge</td>
<td>Neisseria gonorrhoea (NG)</td>
<td>30(44.1)</td>
</tr>
<tr>
<td></td>
<td>Non gonococcal urethritis (NGU)</td>
<td>10 (14.7)</td>
</tr>
<tr>
<td></td>
<td>NG and Chlamydia trachomatis coinfection</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Epididymo-orchitis</td>
<td>4 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Vaginal discharge</td>
<td>Neisseria gonorrhoea</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td></td>
<td>Chlamydia trachomatis</td>
<td>1 (4.2)</td>
</tr>
</tbody>
</table>

**Discussion**

The increasing trend of sexually transmitted infections (STIs) among the young population is a significant public health problem. The magnitude of STI prevalence in those age 10 to 19 years is difficult to ascertain in our local setting as data tend to be aggregated with adults and rarely analysed as a distinct group. Neighbouring countries like Singapore had reported an 8% increase in STI among young people aged 10–19 years old from the year 2014 to 2015, with more than 90% of the cases being in the age group of between 15 and 19 years. Youth with acute STIs are at increased risk of HIV because of both non–condom-protected sexual behaviour and genital tract inflammation. Over one’s life span, each STI episode increases one’s susceptibility to HIV infection.

In our study there was a male preponderance amongst adolescents who had attended the GUM clinic. This was probably because majority of male adolescent were symptomatic. A large proportion of male adolescents in our cohort presented with urethral discharge and had NGU or gonorrhoea. Local studies showed that more upper secondary male students in Penang and Negeri Sembilan had engaged in sexual activities. In the Prevalence of HIV, STD, Drug Use, and Risk Behaviours in Adolescents and Young Adults (PHRAYA) study conducted in Thailand in 1999, it was shown that adolescents and young adults in Chiang Rai are...
at high risk of unprotected intercourse, being coerced to have sex, unwanted pregnancies, sexually transmitted diseases, and drug use. Sexual abuse during childhood or adolescence is often associated with the adoption of high-risk sexual behaviours including sex with multiple partners and prostitution, later in life. Interestingly, the male adolescents in our cohort had multiple sexual partners with a preference for casual partners when compared to female adolescents. This finding was similar to a study done in Thailand. Over the years there was a transition from sex workers to casual partners among the youth in Thailand. They tend to use less protection with casuals as compared with sex workers, probably under the impression that sexual activity with a casual contact may not pose a STI risk as compared to a sex worker.

Based on previous studies on sexual behaviour in Malaysia 15-20 years ago, the mean age at first sexual intercourse among Malaysia teens was 15 years. This was comparable to the studies from the Western countries for instance in US, where it was found that the majority had engaged in sexual activity by age 17. Initiation of sex at an earlier age would expose teens to longer periods of sexual activity thus exposing them to unintended pregnancies and STIs. In another study of urban females in US found that the median interval between first intercourse and first STI was 2 years. Although nearly 90% of our cohort were in the age group of 15 to 19 years, the youngest patients who presented with a STI were 13 and 14 years of age for male and female respectively. This shows that our adolescents may have engaged in sexual activities at much younger age and this should be reinvestigated again in our population.

About 1.3% of our adolescent cohort reported the use of recreational drugs. Adolescent drug use has been significantly associated with higher rate of STIs. The National Health and Morbidity Survey 2017 done in Malaysia reported that 3.4% of adolescents were current drug users. About 1 in 25 school students in Malaysia claimed to have used substances such as amphetamines, methamphetamines and marijuana. Studies have shown that prior substance use increases the probability of an adolescent initiating sexual activity, having more sexual partners, less consistent use of condoms, more sexually transmitted diseases, and greater prevalence of human immunodeficiency virus. The effectiveness of condom for prevention of non-viral STI has been well studied. It is disturbing to note that majority of the teens in our study did not use condoms during sexual intercourse. Inconsistent condom usage has been a major concern among the adolescents and youth in Malaysia and it has given rise to unintended adolescent pregnancies and STIs. The main reason for unprotected sex, however, is that men of all ages, including adolescents, do not like to use condoms. Adolescent girls are commonly disengaged from safe-sex practices as more often than not, the power dynamics within a couple are dominated by the male partner. This disparity provides for men to control or determine the use of protection i.e. condoms, birth control etc, especially with older partners. In addition, adolescent girls may have inadequate knowledge on the risk of STI and HIV infection via unprotected sex. Based on a local study done by Shiely et al, only 2% of women in their cohort used contraception to protect against STI or HIV.

According to a study in US, the lack of availability was a frequent cited barrier to condom usage. Other reasons given were cost of condom and the embarrassment associated with purchasing them. Zulkifli et al also reported similar findings whereby 72% of teens reported not using any kind of contraception at first intercourse (76% of boys, 61% of girls), despite the fact that condoms are freely available in convenient stores and pharmacies. Barriers for Malaysian teen and youth to access contraceptive information and methods include social or cultural taboos, legal restrictions, health care provider (HCP) attitudes, and healthcare systems. A teenager approaching a health care professional for contraception...
may sometimes get a judgemental or biased opinion regarding contraception. Long acting reversible contraception like intrauterine contraceptive device are normally inserted by trained medical personnel and require consent of parents or guardians for those less than 18 years. The cost of contraception services and methods is another potential barrier for adolescents. HCPs should counsel on available contraceptive options without bias to adolescents. Counselling must include the effectiveness, advantages and disadvantages. Adolescents should be informed that failure rates are the highest for user dependent methods (e.g. natural family planning, withdrawal, condoms, and oral contraceptives).

In view of these barriers and with heavy burden of STIs amongst the youth and adolescents, a condom availability program was started in some schools in United States for students to have free access to condoms. This is in addition to a comprehensive sexual education. Critics have argued that such programs would “promote” sexual activity but studies have shown the reverse. The rates of Chlamydia and gonorrhoea infection in US decreased significantly since the implementation of these programs. It has led to increased condom usage and improved sexual health. Hence, schools proved to be an excellent venue for provision of reproductive health services to teens. It should be considered in our local secondary schools. A robust and comprehensive scholastic approach to sex, in tandem with practical and discerning educators, can help mitigate risky sexual practices among students.

Studies have shown that confidentiality is a key concern among adolescents in seeking STI testing for fear of stigmatization, embarrassment in revealing sexual behaviour to medical providers and the fear of parents finding out. Homosexuality and bisexuality were only reported among the males in our cohort. A few have denied their sexual orientation or having had any partners despite being diagnosed with a STI. Fear of disclosure of their behaviour to the parents is one of the reasons for this denial especially in teens younger than 18 years. This brings us to the question of confidentiality which is a huge barrier to STI testing. It is important to for us to address this issue when working with adolescents. Female adolescents who had time alone with a medical provider during consultation were twice more likely to receive a STI screening than those whose parents were in the consultation room with them. This suggests that private discussions are important. To improve young people’s health, adolescent health services in Malaysia were introduced by the Ministry of Health Malaysia (MOH) since 1996 and were primarily available in health clinics and in schools through school health units (MOH, 2018c). These adolescent friendly clinics could be utilized to provide opportunistic STI screening for adolescents.

The comparisons of the STIs among adolescents with other countries are shown in Table 3. In the US, the most prevalent reported STI among adolescents between 14 and 19 years were genital warts and chlamydia. In Thailand the prevalence of STIs was 28% amongst pregnant teenagers attending antenatal care and the risk of acquiring STIs was significantly related to prior sexual contact and multiple partners. Spain noted a rising trend of STI cases among adolescents from 2012 to 2017 especially Chlamydia trachomatis infection, gonorrhoea and syphilis. Malaysian data in 2007 showed that the prevalence of chlamydia was highest in the age group of 15 to 19 years of age. In our setting Chlamydia infection is detected using Direct fluorescent antibody (DFA) test (MicroTrak Chlamydia trachomatis Direct Specimen Test, Trinity Biotech, Ireland). This assay has a sensitivity of 50% to 80% if performed on vaginal and urethral smear specimens collected from symptomatic individuals. Only 2 cases of Chlamydia were detected among the patients in our cohort. This is because DFA for chlamydia detection was no longer available during the end of the 2017. Symptomatic adolescents were treated presumptively based on the presence of leucocytes in gram stains done on urethral and
vaginal smears. Another reason for the small number of chlamydia infections detected was the refusal on speculum examination by parents and patients.

Our DFA was later replaced by Xpert CT/NG only in end of 2018. This is a qualitative in vitro PCR test for the automated detection and differentiation of genomic DNA from *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoea*. This assay aids in the diagnosis of chlamydia and gonorrhoeal obtained from urogenital sample like urine, urethral and vagina swabs, as well as swabs obtained from extra genital (pharynx and rectum) sites. Studies have shown that chlamydia and gonorrhoea infection in females are often asymptomatic and the best and non-invasive screening test to detect them would be nucleic acid amplification test.2,9,16,19,21

The burden of STIs is higher among HIV-infected young men who have sex with men (YMSM) than among HIV-uninfected YMSM. They are particularly at higher risk of syphilis infection, chlamydia and gonorrhoea specifically antibiotic resistant *Neisseria gonorrhoea* (NG). We would like to note that extra genital examination is very important especially in MSM with HIV and those on pre-exposure prophylaxis. Rectal *Chlamydia trachomatis* (CT) and NG testing, as well as pharyngeal NG testing, are recommended in YMSM. Studies have shown that 26.4% of extra genital CT infections and 63.2% of extra genital NG infections would have been missed if only urogenital examination was conducted. Another study found that patient reported exposure was not necessarily a reliable indicator for anogenital CT and NG screening in young black MSM. While reported anal sexual exposure predicted rectal infection, 19.4% of rectal infections would have been missed in men who denied receptive anal sex.

Genital herpes simplex virus (HSV) is also common among adolescents shown in our study and it is difficult to assess epidemiological trends because it is not a notifiable disease. Although HSV-2 typically causes genital herpes and HSV-1 typically causes orolabial herpes, several studies have shown that the prevalence of genital HSV-1 in adolescents has increased significantly. In USA, 60% of genital herpes are caused by HSV-1.20 The increase was postulated as result of the decreasing prevalence of orolabial HSV-1 in adolescents and thus a lack of HSV-1 antibodies upon sexual debut.20 The increase of HSV-1 anogenital infection is especially more prevalent among women and MSM.20

HPV infection is the second most common STI reported among male adolescents in our study. Again, there is not much local data of HPV in our local adolescents as it is not a notifiable disease. HPV vaccination had been integrated in the national school immunization program since 2010 and is given to all female students age 13 years. The exclusion of vaccination for male adolescents in the program probably accounts for the increasing numbers of anogenital warts in males.40 It has been proven that prophylactic administration of quadrivalent HPV vaccine is efficacious in preventing the development of external genital lesions associated with infection with HPV-6, 11, 16, or 18 in boys and men 16 to 26 years of age. Therefore, efforts should be made to introduce HPV vaccination for male students. An interesting local study done by Wong et al showed a low perceived susceptibility to HPV infection among boys.41 This is because mass media has selectively emphasized cervical cancer prevention in women without revealing the consequences of HPV infection in males. The public should be made aware that HPV infection in men can be associated with penile, oral and anal cancer and the benefits of vaccination should be highlighted to boys or men.41

Sexual coercion or non-consensual sexual activity is something that we should bear in mind when managing female adolescents as we have SCAN team. A significant minority of cases have been pressured or forced into non-consensual sexual activity by their peers or adults. Female victims of childhood sexual abuse are at increased risk for STI possibly due
to younger age at sexual initiation and unsafe sex practices.\textsuperscript{1,16}

We cannot generalize the findings of this study to the entire adolescent population because most of the adolescents who had attended the GUM clinic were symptomatic. Evidence has shown that most STIs are asymptomatic therefore substantial number of infections are missed especially in young MSM and females.\textsuperscript{2,16,20,38}

Some adolescents may have sought advice or treatment at general practitioners or alternative medicine centers. Ideally, a rapid, cost-effective screening method which is non-invasive should be used to diagnose STIs in adolescents.\textsuperscript{8,16,20,42} Rapid point of care testing is the most ideal method as patients could be screened and treated in the same day, hence reducing loss to follow up.\textsuperscript{20,42}

Table 3. Comparisons of STI among adolescents in different countries

<table>
<thead>
<tr>
<th>Author, year, country</th>
<th>Age in years</th>
<th>Sexual behaviour</th>
<th>Prevalence of STI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study, Malaysia</td>
<td>13-19</td>
<td>Homosexual 17.1% Casual 51% &gt;1 Partner 26.1%</td>
<td>Male: NG 45.6%, HPV 17.6% NGU 17.6%, HSV 7.4% Female: HSV 50%, HPV 33.3%</td>
</tr>
<tr>
<td>Vives N et al\textsuperscript{34} 2020, Spain</td>
<td>13 to 19 years</td>
<td>CT (13.4%)</td>
<td>Gonorrhoea (7.0%)</td>
</tr>
<tr>
<td>Mean age</td>
<td>17.7</td>
<td>18.3</td>
<td>18.5</td>
</tr>
<tr>
<td>Heterosexual female</td>
<td>87.8%</td>
<td>39.3%</td>
<td>16.7%</td>
</tr>
<tr>
<td>Heterosexual male</td>
<td>6.7%</td>
<td>23.1%</td>
<td>13.1%</td>
</tr>
<tr>
<td>Homosexual</td>
<td>1.6%</td>
<td>18.8%</td>
<td>60.7%</td>
</tr>
<tr>
<td>Unknown</td>
<td>3.8%</td>
<td>18.8%</td>
<td>9.5%</td>
</tr>
<tr>
<td>HIV</td>
<td>2.0%</td>
<td>2.8%</td>
<td>8.5%</td>
</tr>
</tbody>
</table>

Ayerdi Aguirrebengoa et al\textsuperscript{43} 2020, Spain

<table>
<thead>
<tr>
<th>%/(n)</th>
<th>MSM 39.8% (149)</th>
<th>Heterosexual 22.7% (85)</th>
<th>Women 37.4% (140)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonorrhoea</td>
<td>30.2 (45))</td>
<td>22.4(19))</td>
<td>12.2(17)</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>10.1 (15))</td>
<td>25.9 (22)</td>
<td>19.3 (27)</td>
</tr>
<tr>
<td>Syphilis</td>
<td>0.1(15)</td>
<td>1.2(1)</td>
<td>1.4(2)</td>
</tr>
<tr>
<td>HIV</td>
<td>7.4(9)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Park JJ, et al\textsuperscript{42} 2017, Korea

<table>
<thead>
<tr>
<th>Mean ± SD</th>
<th>Substance abuse 8.4% &gt;1 partner 25%</th>
<th>Prevalence of STI 28.0% (CT 19.8%, NG 1.7%, TVS 1.7%, HSV 0.8%, HPV 0.8%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.1 ± 1.5</td>
<td>-</td>
<td>CT 13.9% NG 1.7% TVS 0.8% HSV 0.4% Syphilis 0.8% HIV 0</td>
</tr>
</tbody>
</table>

Asavapiriyanont et al \textsuperscript{33}, 2016 Thailand

<table>
<thead>
<tr>
<th>Age of first sexual contact (years)</th>
<th>Mean + SD 15.38±1.81 &gt;1 partner 48.2%</th>
</tr>
</thead>
</table>

Forhan et al\textsuperscript{21}, 2009, USA

| 14-19 | NA | HPV 18.3% CT 3.9% |

Bunnel et al\textsuperscript{19} 1999, USA

| 14-19 | >1 partner 72% | Females with STI 40% CT 27%, HSV 14%, gonorrhoea 6% TVS 3% |

USA – United States of America; NG – Nesseria gonorrhoea; CT - Chlamydia trachomatis; HPV – human papilloma virus; NGU – non gonococcal urethritis; HSV – herpes simplex virus; HIV- human immunodeficiency virus; MSM – men who have sex with men; TVS – Trichomonas vaginalis; STI – sexually transmitted infections; SD – standard deviation
Conclusion
Sexually transmitted infections are an ongoing concern among our adolescents. We have managed STIs in those as young as 13 years of age. The most common STI among adolescents in our cohort between 2014 and 2018 was gonorrhoea in male and herpes genitalis in females. STI preventive efforts for adolescents should encompass contributions, cooperation and support from all parties including parents, schools, health care providers and social media.

Conflict of Interest Declaration
All authors have no financial/conflict of interest to disclosed.

Acknowledgement
The authors would like to thank the Director of Health Malaysia for permission to publish this paper.

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27. Abdul Mutalip MH, Mishkin K, Paiwai F, Sulaiman J, Yoop N. Factors Associated with Sexual Intercourse, Condom-Use, and Perceived Peer Behaviors Among...


ORIGINAL ARTICLE

Characteristics of Sexually Transmitted Infections in Genito-Urinary Medicine Clinic, Sarawak General Hospital between 2018 and 2020

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Abstract

Background
Sexually transmitted infections (STIs) are common worldwide. This study aims to determine the patterns of STIs among attendees in the Genito-Urinary Medicine (GUM) clinic of Sarawak General Hospital (SGH).

Methods
This is a retrospective study. Medical records of new cases referred to GUM clinic, SGH between the year 2018 and 2020 were reviewed. Demography data, diagnosis, and clinical characteristics of STIs were reviewed and analysed using SPSS software.

Results
There was a total of 225 patients with newly diagnosed STIs. Their mean age was 30.9 years old. There were 124 (55.1%) males and 101 (44.9%) females. Nearly half (46.7%) of the patients were Malay, followed by Sarawak indigenous groups (33.3%), and Chinese (18.7%). Most patients (n=119, 52.9%) were single at the time of diagnosis. Three quarters (73.3%) of the patients were heterosexual, while 47 (20.9%) patients were homosexual or bisexual, and missing data in the remaining 5.8%. Anogenital wart was the commonest STI (49.8%), followed by syphilis (n=91, 40.4%), genital herpes (n=24,10.7%) and gonorrhoea (n= 15, 6.7%). The commonest symptoms were genital growth (n= 107, 47.6%), followed by pelvic discharge (n=22, 9.8%).

Conclusion
The most common STIs in our study are anogenital warts, syphilis, genital herpes and gonorrhea. Effective national sexuality education in Malaysia is paramount in reducing premarital sex and STIs. Human Papillomavirus (HPV) vaccines are effective to reduce genital warts and HPV related malignancies.

Key words: Sexual transmitted disease, Syphilis, Anogenital warts

Introduction
STIs are very common with 1 million new cases every day worldwide in the year 2016.¹ Sexual transmitted infections can be caused by viral, bacterial or parasites. According to WHO, the commonest STIs are chlamydia, gonorrhoea, syphilis and trichomoniasis which contribute to 376 million new cases in males and females aged between 15 and 49 years in 2016.² On the other hand, viral STIs such as Herpes Simplex Virus...
(HSV) infection and Human Papillomavirus (HPV) infections had been reported as high as well, with estimated cases of 417 and 291 million, respectively in the same year. STIs can increase the risk of acquisition and transmission of the Human Immunodeficiency Virus (HIV). STIs can lead to a wide range of complications such as pelvic inflammatory diseases, cancers, ectopic pregnancies and infertility. Furthermore, untreated STIs can have poor maternal and fetal outcomes. Therefore, STIs should be treated promptly. However, many symptomatic patients are reluctant to seek treatment due to social stigmatisation, needless to say for those asymptomatic patients. The true incidence of STIs is largely unknown, as not all STIs need mandatory reporting including genital herpes. Perhaps under-reporting of STIs among general practitioner further jeopardise the true incidence of STIs. Younger generations tend to have earlier sexual exposure with a higher percentage of teenage pregnancies in Sabah and Sarawak compared to Peninsular Malaysia. There is also an increasing number of men having sex with men (MSM) and a change in sexual preference such as oral sex as well. As a result, the presentations and disease patterns of STIs have been changed. However, there is limited local data on the STIs among our local population. This study aims to determine the patterns of STIs among attendees in the Genito-Urinary Medicine clinic of Sarawak General Hospital (SGH) from the year 2018-2020.

Materials and Methods
This retrospective study was done in Genito-Urinary Medicine (GUM) clinic, SGH. SGH is a tertiary hospital in East Malaysia and received referrals from Kuching and its surrounding cities in southern Sarawak. A team of dermatologists, dermatology fellows and senior medical officers manage the clinic and provide care for patients with STIs. Patient records will be kept in a designated area in the clinic to maintain patient confidentiality.

In this study, all medical records of new cases referred to the GUM clinic, SGH between January 2018 and December 2020 were retrieved. Demography data, diagnosis, and clinical characteristics of STIs were reviewed and analysed using SPSS software version 26.0.

Results
There were 245 new cases referred to GUM clinic, Sarawak General Hospital between the year 2018 to 2020. Of these, 225 patients were diagnosed with STIs. The remaining 20 patients were diagnosed with non-STIs such as vaginal candidiasis, screening test and other dermatoses. We analysed the data from all 225 patients diagnosed with STIs during our study periods. The age of the STI patients ranged widely from 3-88 years old with a mean of 30.94 +/-13.52. Most patients were in the age group of 20-29 years old (n=165,73.3%), followed by those aged <20 (n=21,9.3%) and 40-49 (n=19,8.4%). There were 124 (55.1%) male and 101 (44.9%) female patients with a ratio of 1.2:1 in our study population. For the ethnic group, 105 (46.7%) of the patients were Malay, followed by Sarawak Indigenous groups (n=75, 33.3%), and Chinese (n=42, 18.7%). There were only 2 (0.9%) and 1 (0.4%) of the study populations were foreigners and Indians respectively. Most of the patients (n=119, 52.9%) were single at the time of diagnosis. Ninety-five (42.2%) of them were married with the remaining 9 (4%) and 2 (0.9%) of the patients were divorcees and widowed, respectively.

In terms of sexual orientation, 165 (73.3%) of the patient were heterosexual, while the remaining 39 (17.3%) were homosexual and 8 (3.6%) of the patients were bisexual. Among our study population, 115 (51.1%) of them were employed, 37 (16.4%) were housewives and 26 (11.6%) of them were students. Another 9 (4%) patients were unemployed, 7 (3.1%) were retirees and 5 (2.2%) of the remaining were self-employed. Our sources of referral were mainly inter-department referral from our centre (n=106,47.1%), government clinic and district hospital (n=98, 43.6%), blood bank (n=14, 6.2%) and general practitioner (n=7, 3.1%).
A total of 172 (76.4%) patients were symptomatic whereas the remaining 53 (23.6%) were asymptomatic at the time of diagnosis. Most of the symptomatic patients presented with growth at anogenital area (n=107, 47.6%), followed by pelvic/urethral discharge (n=22, 9.8%), cutaneous skin lesions (n=20, 8.9%), genital ulcer (n=10, 4.4%), painful lesion (n=9, 4%) and pruritus (n=4, 1.8%). Asymptomatic patients were mainly diagnosed via asymptomatic screening (n=22, 9.8%), blood donation screening (n=14, 6.2%), antenatal screening (n=12, 5.3%), and contact tracing (n=5, 2.2%).

Among the 225 patients with STIs, anogenital warts were the commonest reported STI, diagnosed in 112 (49.8%) of the patients. Another 91 (40.4%) patients were diagnosed with syphilis, 24 (10.7%) patients diagnosed with genital herpes, followed by gonorrhoea (n=15, 6.7%), and trichomoniasis (n=2, 0.9%). A total of 19 (8.4%) patients had concomitant 2 different STIs at the time of presentation. Among the patients with STIs, 50 (22.2%) of them had concomitant HIV infection, with another 7 (3.1%) had hepatitis B infection and 8 (3.6%) had hepatitis C infection. Further analysis of the trend of STI cases revealed that a total of 100 patients with STIs had been reported in our centre in the year 2018. This number had been reduced to 77 cases in 2019 and 48 cases in the year 2020. The total number of cases in the individual STI group showed a similar reducing trend except for genital herpes in which 5 cases were reported in 2018 and the reported cases increased significantly to 11 cases in the year 2019 before it was reduced to 8 cases in 2020 (Figure 1).

For the treatment of anogenital warts, 74 (66.1%) of patients received liquid nitrogen (LN) spray alone, whereas 24 (21.4%) of them received LN sprays in combination with other treatment modalities like imiquimod and podophyllin. Another 5 (4.5%) and 4 (3.6%) patients received imiquimod and podophyllin local application alone, respectively. One (0.9%) patient underwent electrocautery, and another patient (0.9%) underwent surgical removal of warts (table 2). There were 3 (2.7%) patients with anogenital warts resolved without active treatment. All patients with syphilis received intramuscular benzathine penicillin as the standard of treatment.

Table 1. Demographic data and clinical presentation of new STI cases in GUM clinic, SGH between the year 2018-2020

<table>
<thead>
<tr>
<th>Variables</th>
<th>Frequency, n=225</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>21</td>
<td>9.3</td>
</tr>
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<td>20-29</td>
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<td>73.3</td>
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<tr>
<td>40-49</td>
<td>19</td>
<td>8.4</td>
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<tr>
<td>50-59</td>
<td>6</td>
<td>2.7</td>
</tr>
<tr>
<td>&gt;60</td>
<td>13</td>
<td>5.8</td>
</tr>
<tr>
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<td>225</td>
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</tr>
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<tr>
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<td>124</td>
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<tr>
<td>Female</td>
<td>101</td>
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<tr>
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<td>165</td>
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<tr>
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<tr>
<td>Employment</td>
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<tr>
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<tr>
<td>Housewife</td>
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<tr>
<td>Students</td>
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<td>11.6</td>
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<td>Retirees</td>
<td>7</td>
<td>3.1</td>
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<tr>
<td>Missing data</td>
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<td>11.6</td>
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<td>Presenting symptoms</td>
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<tr>
<td>Symptomatic</td>
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<td>76.4</td>
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<tr>
<td>Growth</td>
<td>107</td>
<td>47.6</td>
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<tr>
<td>Discharge</td>
<td>22</td>
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<tr>
<td>Skin Lesions</td>
<td>20</td>
<td>8.9</td>
</tr>
<tr>
<td>Genital Ulcer</td>
<td>10</td>
<td>4.4</td>
</tr>
<tr>
<td>Pain</td>
<td>9</td>
<td>4.0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>4</td>
<td>1.8</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>52</td>
<td>23.6</td>
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<tr>
<td>Asymptomatic Screening</td>
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<td>9.8</td>
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<tr>
<td>Blood donation screening</td>
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<tr>
<td>Antenatal Screening</td>
<td>12</td>
<td>5.3</td>
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<tr>
<td>Contact Screening</td>
<td>5</td>
<td>2.2</td>
</tr>
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</table>
Intramuscular ceftriaxone in combination with azithromycin or doxycycline was given to patients with gonorrhoea infection whereas acyclovir was given for all patients with genital herpes infection except one who was diagnosed with resolved genital herpes with no evidence of recurrence.

Table 2. Treatment modalities among patients with anogenital wart in GUM Clinic SGH, year 2018-2020

<table>
<thead>
<tr>
<th>Anogenital Wart</th>
<th>Frequency, n</th>
<th>Percent/%</th>
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</thead>
<tbody>
<tr>
<td>LN Spray</td>
<td>74</td>
<td>66.1</td>
</tr>
<tr>
<td>Combination Therapy</td>
<td>24</td>
<td>21.4</td>
</tr>
<tr>
<td>Imiquimod</td>
<td>5</td>
<td>4.5</td>
</tr>
<tr>
<td>Podophyllin</td>
<td>4</td>
<td>3.6</td>
</tr>
<tr>
<td>Electrocautery</td>
<td>1</td>
<td>0.9</td>
</tr>
<tr>
<td>Surgical Excision</td>
<td>1</td>
<td>0.9</td>
</tr>
<tr>
<td>Observation</td>
<td>3</td>
<td>2.7</td>
</tr>
<tr>
<td>Total</td>
<td>112</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Discussion

Our study showed that the majority of the STI patients are from the age group of 20-29 with a male to female ratio of 1.2:1. This finding is consistent with previous studies on the prevalence of STIs. This group of patients are of reproductive age. Inadequate treatment will lead to deleterious effects among females and during their pregnancies. On the other hand, untreated STIs increase the risk of HIV infection. Both AIDS and STDs have a major demographic, economic, social, and political impact. Therefore, prompt diagnosis and treatment of these curable STIs and HIV are fundamental to minimise their impact on country developments and health.

Prevalence of STIs

The WHO report in the year 2016 on the prevalence of 4 common STIs showed that trichomoniasis had the highest prevalence, especially in females, followed by chlamydia, gonorrhoea and syphilis. A study done in Chiang Mai, Thailand in 1997 showed the prevalence of chlamydial infection (16.9%), gonococcal infection (14.4%) and condyloma acuminata (4.6%) among commercial sex workers. Our study showed that the highest number of STIs among attendees of our GUM clinic were anogenital warts followed by syphilis, genital herpes, and gonorrhoea. This finding is consistent with the other study done by Hariyadurai HR et al. in Hospital Kuala Lumpur (HKL). The common STIs along the GUM clinic attendees in HKL were warts (30.2%), syphilis (21.7%), gonorrhoea 13.8% and primary herpes (11.4%). However, our study will likely underestimate the true prevalence of gonorrhoea, chlamydia and trichomoniasis for a few reasons. Firstly, many patients with STIs are reluctant to seek treatment at government hospitals due to the social stigmata and lack of confidentiality. They tend to receive treatment at private clinics or hospitals. A prevalence study done in 1998 showed that 77% of the STI notification were done by private clinics and hospitals. On the other hand, those who seek treatment at government facilities are mostly treated at the health clinics due to easy access. Basic investigations and treatments are readily available in these health clinics.

Moreover, most specialist clinics in tertiary
hospitals do not accept walk-in consultation. Patients are required to have an initial assessment at the health clinics before they are scheduled for an appointment to receive treatment at the specialist clinic if needed. This forms a barrier to the treatment of STIs by dermatologists among the local population. Thirdly, the lack of high sensitivity tests such as the Nucleic Acid Amplification Test (NAAT) for gonorrhoea, chlamydia and trichomoniasis is the other factor for the low prevalence of these diseases in our centre. In our centre, smear for gonococcal and culture with chocolate agar are commonly used in cases of suspected gonorrhoea. Posterior vaginal wet mount microscopies are done for cases suggestive of trichomoniasis. These tests had lower sensitivity to diagnose STIs and highly depend on the sampling method as well.\textsuperscript{11}

There is no molecular test available to diagnose chlamydia infection in our centre. Centers for Disease Control and Prevention (CDC) has recommended NAAT in cases of suspected Neisseria gonorrhoea, Chlamydia trachomatis and Trichomonas vaginalis infection given its higher sensitivity and specificity when compared to the other methods\textsuperscript{12}. The high number of anogenital warts in our clinic is due to a variety of treatment modalities that are available only in the GUM clinic such as liquid nitrogen spray, imiquimod and podophyllin application.

**Trend of STD Referral in GUM clinic, SGH**

In our study population, the total number of STIs cases were reducing in trend from the year 2018 to 2020. There were 100 STI Patients seen in the GUM clinic in 2018 and the number reduced to 77 and 48 patients, respectively, in 2019 and 2020. The reducing GUM referral is unlikely due to the reducing incidence of STIs in our local population. According to the Ministry of Health, Malaysia report in the year 2016-2019, the 2 notifiable diseases, namely gonorrhea and syphilis, continue to see an increasing incidence, especially among male patients.\textsuperscript{13} Malaysia has started STI friendly clinics in selected government health clinics since June 2016.\textsuperscript{14} These primary healthcare facilities offer various point-of-care testings and treatments for STIs thus the STIs referral to GUM clinic in the hospital is significantly reduced. The cases were further reduced in the year 2020 largely due to the Covid-19 pandemic announced by WHO on March 2020.\textsuperscript{15} With the movement control order and strict social activities including the closure of the entertainment centers such as pubs and karaoke centers, the cases of STIs had been estimated to be reduced. On the other hand, patients with STI may not seek treatment during the pandemic in the fear of COVID-19 infection.

**STIs among patients with HIV and MSM**

In our study, 50 (22.2 \%) and 47 (20.9\%) of the patients were HIV positive and homosexual/bisexual, respectively. Among this group, 96% of the HIV positive patients and 97.4\% of the non-heterosexual patients were male \(p=0.000\) (table 3). For the past decades, the HIV cases in Malaysia has been commonly transmitted via sharing needle but more recently sexual contact had become the main mode of transmission of the HIV according to the local data.\textsuperscript{16} In the Malaysia key population estimation report 2018, It is estimated that there is a total of 220,000 MSM in Malaysia. This represents 2.2\% of the total adult male population in Malaysia.\textsuperscript{17} The Integrated Biological and Behavioural Surveillance (IBBS) 2014 report revealed that HIV prevalence among MSM substantially increased over the years. Increased alcohol consumption prior to sex and reduced condom used had been shown to be significantly associated with HIV prevalence among MSM.\textsuperscript{18}

**Table 3. Distribution of HIV infection and sexual orientation according to gender**

| HIV (n=225) | | Sexual Orientation (n=212*) |
|------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|            | Positive (n=50) | Negative (n=175) | \(p\)-Value  | Homosexual/ Bisexual (n=47) | Heterosexual (n=165) | \(p\)-Value  |
| Female     | 2 (4\%)         | 99 (56.6\%)     | 0.000         | 46 (97.9\%)      | 98 (59.4\%)      | 0.000         |
| Male       | 48 (96\%)       | 76 (43.4\%)     |              | 47 (100\%)       | 165 (100\%)      |              |
| Total      | 50 (100\%)      | 175 (100\%)     |              | 47 (100\%)       | 165 (100\%)      |              |

\*3 missing data on sexual orientation
The incidence of STIs among this population is expected to be increased as well. Malaysia National Strategic Plan for Ending AIDS 2016-2030 aimed to end AIDS epidemic by the year 2030. The strategies include prompt detection and treatment of HIV among high-risk populations and decentralize testing and treatment to accredited primary health centres. The Harm Reduction Programme will be intensified among injecting drug users. To reduce sexual transmission of HIV and STIs, mapping of the geographic and local hotspots for HIV transmission will be conducted. A National Task Force on Mitigation of HIV through Sexual Transmission will look into innovative and effective ways of addressing the changing sexual transmission scenarios, particularly the increasing use of mobile devices and social media for the sex trade. These strategies will be implemented between 2016 to 2030 as part of the national efforts to reduce HIV and STI cases.

**Premarital Sex and Sexuality Education**

Our study showed that 52.9% of the patients were single. This indicates an alarmingly high rate of premarital sex among the local population. Therefore, innovative, and effective sexuality educations are fundamental among teenagers in secondary schools to advocate correct sexual behaviours and minimise high-risk sexual activities. Johari Talib et al. reported that 90% of the university students agreed that sexuality education has not been taught in Malaysian schools. The same study also concluded that informal information given by most of the teachers were vague thus not useful in term of sexuality education. Khalaf ZF et al. reported that Malaysian multicultural society, lack of community involvement as some of the barriers to national sexuality education. Respondents in this study believed that school-based sexuality education is not easily accomplished in Malaysia. Therefore, campaigning to raise the awareness of families, teachers, community leaders, religious authorities and policymakers are essential to establish an effective national sexuality education in Malaysia.

**HPV Vaccination**

Vaccinations are helpful to prevent Human Papillomavirus (HPV) Infections which can potentially lead to anogenital warts and malignancies. HPV 6, 11 contribute up to 90% of genital warts. Moreover, 4.5% of all cancer cases are attributable to HPV every year and present with vulva, vagina, anus, penis, and oropharynx cancer. HPV 16, 18, 33, and 58 were commonly detected HPV types from the cervical samples among females in Malaysia. There are three HPV vaccines available at the moment, 2vHPV (HPV 16, 18), 4vHPV (HPV 6, 11, 16, 18), and 9vHPV (HPV 6, 11, 16, 18, 31, 33, 45, 52, 58). Only 4vHPV and 9vHPV protect against HPV type 6 and 11 that are commonly associated with anogenital warts. Both 2vHPV and 4vHPV protect against HPV 16 and HPV 18 infections which are the commonest HPV types implicated in the majority of cervical malignancies. 9vHPV provide extra protection towards other HPV types such as HPV 31,33,45,52,58 that contribute to cervical malignancies as well. A study in Sweden reported a substantially reduced risk of invasive cervical cancer at the population level after quadrivalent HPV vaccination.

Giuliano AR et al. reported that the 9vHPV vaccine did not prevent disease related to vaccine HPV types detected at baseline, but significantly reduced cervical, vulvar, and vaginal diseases related to other vaccine HPV types. In the global health sector strategy on sexually transmitted infections 2016-2021 which aim toward ending STIs, WHO advocated the implementation of prophylactic HPV vaccination to eliminate cervical cancer and genital warts. HPV vaccination has been incorporated in our national immunization program in 2010 for all female students who are 13 years of age at government schools, with the aim of three doses completion rate of 95%. However, vaccination among boys will be required to reduce the incidence of HPV related warts and cancers in male patients. To date, the vaccination is not offered for male students under the national immunisation programme.

**Conclusion**

The most common STIs in our study are
anogenital warts, syphilis, genital herpes and gonorrhea. HIV and MSM are common especially among male patients in our study cohort. With the strategies endorsed under the national strategies plan to end AIDS epidemic by 2030, the incidences of STIs are expected to be reduced. STI-friendly clinics in primary care settings help to provide quality and prompt treatment of STIs in the effort to reduce transmission. National Sex education programmes require collaboration between government, private sector and religious authorities to improve the quality and efficacy of sex education among school children and young adults. HPV vaccination for both adolescent male and female students is recommended to reduce HPV related diseases and malignancies.

Conflict of Interest Declaration

The authors have no conflict of interest to be declared.

Acknowledgement

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References

ORIGINAL ARTICLE

Oral Lichenoid Reactions and Contact Sensitization: A 5-year Review in the Department of Dermatology, Hospital Kuala Lumpur, Malaysia

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Abstract

Background
Oral lichen planus is an idiopathic autoimmune inflammatory condition and oral lichenoid reactions are lesions that resemble oral lichen planus clinically and histopathologically, but develop secondary to various underlying causes. Oral lichenoid reactions have been reported to be caused by contact allergy to dental materials. This study aims to describe the characteristics of patients with a clinical and/or histopathological diagnosis of oral lichen planus who underwent patch testing in Hospital Kuala Lumpur, Malaysia.

Methods
This is a 5-year retrospective study of patients who had oral lichen planus and had undergone patch testing at the Department of Dermatology, Hospital Kuala Lumpur, Malaysia between January 2015 and December 2019. Patch tests were performed with European Baseline Series and relevant extended series, which include dental and metal series as well as patients’ own products. Patch test results were recorded according to the International Contact Dermatitis Research Group recommendation.

Results
There were 41 patients with oral lichen planus who underwent patch test. The median age was 56 (range 21 to 73) with 70.7% of patients being female. There were 29 (70.7%) patients who developed at least one positive reaction. The most frequent sensitizing allergens were nickel sulfate (34.1%), gold(I)sodium thiosulphate dihydrate (22.0%), fragrance mix I (19.5%), cobalt chloride (14.6%), Peru balsam (12.2%) and sodium tetrachloropalladate (II) hydrate (12.2%). Current relevance was recorded in 16 patients (39.0%) and of these patients, 12 of them had positive patch test reactions to allergens found in dental materials such as dental fillings, dental implants, orthodontic braces, dentures and dental crowns.

Conclusion
Contact sensitization was detected in about 70% of our patients with oral lichen planus. The most common sensitizing allergen was nickel sulfate. Current relevance was found mainly towards dental materials.

Key words: Allergic contact dermatitis, Patch test, Oral lichen planus, Oral lichenoid reactions, Oral lichenoid lesions, Oral lichenoid diseases, Lichen planus-like lesions, Oral lichenoid tissue reactions

Introduction
Lichen planus is an inflammatory disease of unknown aetiology that primarily affects the skin and oral mucosa. Apart from oral mucosa, other mucous membranes that can be involved include the genitalia, esophagus...
and conjunctiva. Cutaneous lichen planus is characterized by erythematous-violaceous, polygonal, shiny and symmetrical papules with the presence of whitish streaks on the surface known as Wickham striae. Oral lichen planus usually presents in two ways, either as painful and erythematous erosions and ulcerations or as painless radiating white papules or patches on the buccal mucosa. These lesions may also involve the lips, tongue and palate.

Oral lichenoid reactions are lesions that resemble oral lichen planus clinically and histopathologically but develop secondary to various underlying causes. There are several synonyms that have been used to describe oral lichenoid reactions and these include oral lichenoid lesions, oral lichenoid diseases, lichen planus-like lesions and oral lichenoid tissue reactions. These lesions can be caused by exogenous factors such dental restoration materials and systemic medications, whereas others may be due to systemic diseases such as graft-vs-host disease (GVHD), systemic lupus erythematosus or malignant tumours. Patch test plays an important role in diagnosing oral lichenoid reactions related to contact allergy, especially from dental materials.

This study aims to describe the characteristics of patients with a clinical and/or histopathological diagnosis of oral lichen planus who underwent patch testing in Hospital Kuala Lumpur, Malaysia.

Materials and Methods
This is a 5-year retrospective study of patients who had oral lichen planus and had undergone patch testing at the Department of Dermatology, Hospital Kuala Lumpur, Malaysia between January 2015 and December 2019. Patch tests were performed with European Baseline Series and relevant extended series from Chemotechnique Diagnostics using IQ chambers™. Extended series used include dental screening series, metal series, cosmetic series, and plastic and glue series. Patients were also tested with their own products, which include toothpaste and mouthwash. Toothpaste was tested “as is”. Mouthwash was diluted with water to 10% (w/w).

Patches were applied to the patients and removed after 48 hours. Initial reading was done at 48 hours and final reading was recorded at 96 hours after patch application. The parameters studied include positive patch test reactions and the source of allergens. Readings were recorded according to the International Contact Dermatitis Research Group recommendation.

Results
There were 41 patients with oral lichen planus who underwent patch test. The demographic data is shown in Table 1. The median age was 56 (range 21 to 73) and the majority of patients (70.7%) were female. In addition to the oral lichen planus, cutaneous involvements were found in 5 patients. These patients had involvement of the trunk (3 patients), upper and lower limbs (1 patient) and lower limbs only (1 patient). Twenty-four (58.5%) patients had dental procedures done which include dental fillings, crown, bridges, implant, dentures and orthodontic braces. The diagnosis of oral lichen planus was confirmed histopathologically in 31 patients (75.6%), whereas the rest of the patients had no biopsy, inconclusive biopsy results or the biopsy results were not available. All patients were referred to our centre from dental departments in hospitals based in Klang Valley areas.

More than half of the patients (53.7%) had symptoms of six months or less, 8 patients (19.5%) had symptoms between 6 months to 1 year and the rest (26.8%) had symptoms lasting more than 1 year. All patients described symptoms of pain and discomfort, especially when eating spicy foods.

There were 29 (70.7%) patients who developed at least one positive reaction. As shown in Table 2, the most frequent sensitizing allergens were nickel sulfate (34.1%), gold (I) sodium thiosulphate dihydrate (22.0%), fragrance mix I (19.5%), cobalt chloride (14.6%), Peru balsam (12.2%) and sodium tetrachloropalladate (II) hydrate (12.2%). Current relevance was recorded.
in 16 patients (39.0%) and of these patients, 12 (75%) of them had positive patch test reactions to allergens found in dental materials such as dental amalgam, dental implants, orthodontic braces and dental crowns. Four (25%) of these patients had current relevance attributed to their own toothpastes.

Table 1. Characteristics of 41 patients who underwent patch test for oral lichen planus

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n=41</th>
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</thead>
<tbody>
<tr>
<td>Median age in years (range)</td>
<td>56 (21-73)</td>
</tr>
<tr>
<td>Male:Female ratio</td>
<td>1:2.4</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td>19 (46.3)</td>
</tr>
<tr>
<td>Indian</td>
<td>15 (36.6)</td>
</tr>
<tr>
<td>Malay</td>
<td>6 (14.6)</td>
</tr>
<tr>
<td>Others</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Presence of cutaneous involvement, n (%)</td>
<td>5 (12.2)</td>
</tr>
<tr>
<td>Oral lichen planus confirmed by histopathological examination, n (%)</td>
<td>31 (75.6)</td>
</tr>
<tr>
<td>Series used, n (%)</td>
<td></td>
</tr>
<tr>
<td>European Baseline</td>
<td>41 (100.0)</td>
</tr>
<tr>
<td>Dental</td>
<td>41 (100.0)</td>
</tr>
<tr>
<td>Metal</td>
<td>15 (36.6)</td>
</tr>
<tr>
<td>Cosmetics</td>
<td>3 (7.3)</td>
</tr>
<tr>
<td>Plastic and glue</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Own products</td>
<td>15 (36.6)</td>
</tr>
</tbody>
</table>

Table 2. Sensitization pattern of current cohort

<table>
<thead>
<tr>
<th>Positive Patch Test</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nickel sulfate</td>
<td>14 (34.1)</td>
</tr>
<tr>
<td>Gold(I)sodium thiosulphate dihydrate</td>
<td>9 (22.0)</td>
</tr>
<tr>
<td>Fragrance mix I</td>
<td>8 (19.5)</td>
</tr>
<tr>
<td>Cobalt chloride</td>
<td>6 (14.6)</td>
</tr>
<tr>
<td>Peru balsam</td>
<td>5 (12.2)</td>
</tr>
<tr>
<td>Sodium tetrachloropalladate (II) hydrate</td>
<td>5 (12.2)</td>
</tr>
<tr>
<td>Palladium chloride, formaldehyde, mercury</td>
<td>4 each (9.8)</td>
</tr>
<tr>
<td>Colophony, MCI/MI</td>
<td>3 each (7.3)</td>
</tr>
<tr>
<td>Thiuram mix, potassium dichromate, textile dye mix, butylphenol formaldehyde resin</td>
<td>2 each (4.9)</td>
</tr>
<tr>
<td>Epoxy resin, neomycin, Quaternium-15, methylisothiazolinone, fragrance mix II, carbonyl mercury ammonium chloride, triethyleneglycol dimethacrylate, amalgam, BIS-GMA, MDB-GN, thimerosal, 2-Hydroxyethyl methacrylate</td>
<td>1 each (2.4)</td>
</tr>
</tbody>
</table>

MC/I/MI - methylchloroisothiazolinone/methylisothiazolinone; BIS-GMA - Bisphenol A glycol dimethacrylate; MDB-GN- methylidibromoglutaronitrile

Discussion

Contact sensitization was detected in about 70% of our patients with oral lichen planus. The 3 most common sensitizing allergens were nickel sulfate, gold sodium thiosulphate and fragrance mix. These findings were similar to studies conducted in other countries (Table 3). Other metals that were also found as common sensitizers in our study include cobalt chloride and palladium.

The high number of positive reactions to metal allergens in our study can be explained by the presence of metal in dental restoration materials. Most metals found in dentistry are in the form of alloys. Alloys are mixtures of metals and non-metals. They are preferred as pure metals do not have the appropriate physical properties to function as dental restoration materials. Metal-ceramic alloy has been used in dental restoration materials since the 1950s. The durability of these alloys was proven by studies. Nearly 90% of metal-ceramic crowns and 80.2% of metal-ceramic fixed partial dentures were still in function after 10 years. Nickel, gold, cobalt and palladium are present in dental restoration materials in variable combinations with ceramic and other metals to optimize their clinical performance, aesthetics and physical properties. This possibly explains why these metals were found as top sensitizing allergens in our study.

Metal alloys used in dentistry can be divided into noble and base metal alloys. Noble metals are gold, palladium, iridium, ruthenium, and platinum. Base metals in dentistry are further divided into two main systems, which are nickel based and cobalt based. Alloys in both systems contain chromium as their second largest constituent. Other base metal used in dentistry include titanium. Adverse effects due to these metals are chiefly caused by corrosion, which results in release of metal ions and subsequent metal-protein or metal-cell interactions.

The most common sensitizing allergen found in our study was nickel sulfate. Nickel is widely used in dental restoration materials as it is cheaper compared to metals such as gold and possesses better mechanical properties to gold when combined with other metals. Nickel...
is found in alloys such nickel-chromium-beryllium, nickel-chromium and nickel-high chromium alloys. Beryllium was used in the past with nickel as it facilitates casting and enhanced porcelain bonding but due to the increased corrosion especially at low pH, this alloy is no longer recommended. As nickel is a highly sensitizing metal, there is a need for other affordable metal alloys that are free of nickel yet confer similar properties as nickel containing alloys. An alternative to nickel containing alloys is chromium-cobalt alloys, which have a high biocompatibility and since they are nickel-free, they can be used in patients who are known to be allergic to nickel.

The relevance of contact sensitization to nickel and oral eruptions is however controversial as it is abundant in our environment and sources of exposure can be unrelated to the dental restoration materials. Nickel allergy presenting as oral eruption alone is thought to be rare. Exposure to nickel during treatment of with orthodontics braces is thought to confer tolerance in nickel insensitive patients. In nickel sensitive patients however, exposure to nickel via orthodontic implants have shown conflicting findings. Studies have shown exacerbation of dermatitis together with lip swelling and burning after fixation of orthodontic implants in previously nickel sensitized individuals. On the other hand, there were also patients who were nickel-sensitive but developed lower incident of oral contact reactions following orthodontic implants, which is thought to be due to the development of tolerance. With this in mind, determining the relevance of nickel in causing oral lichenoid reactions requires careful consideration and interpretation. Often times, current relevance can only be made retrospectively when there is improvement of lesions upon removal of the suspected dental materials that contain nickel as a constituent.

The second most common allergen in our study is gold sodium thiosulphate. Gold is used in dental restorations because it is easily malleable and is highly resistant to corrosion. It is also inert and is fairly nonreactive with other metals. Gold alloys as dental restoration materials comprised of over 70% of gold predominated until the price of gold skyrocketed in the mid-1970s. Subsequently, the demand for lower cost of metal alloys paved the way for the use of cheaper metal alloys such as nickel. The gold-platinum-palladium alloys were the first to be used successfully for metal-ceramic restorations; however their used decreased after more economical alloys were developed with significantly better mechanical properties. Gold dental alloy that is still used nowadays has a reduced gold content, typically in the range of 35 to 50%, which is less costly.

The clinical features of intra-oral contact allergy related to gold exposure are not specific, although lichenoid reactions appear to be the most common manifestation of gold contact allergy in the oral mucosa. Patients with oral lichenoid reactions have been found to have an increased frequency to patch test positivity to gold compared to patients undergoing evaluation of other dermatitis not affecting the oral lesions. Other manifestations of gold allergy in the oral cavity include non-specific stomatitis and burning mouth syndrome. Additionally, studies have also shown that there is a statistically significant and dose-dependent relationship between contact allergy and the number of dental gold restorations. Metallic gold (foil) and trivalent auri chloride were previously used for patch testing but they are no longer recommended today. At present, monovalent gold salts in the form of gold sodium thiosulfate in petrolatum is used as the gold allergen in patch test. It is also recommended that patch test reading for gold allergy is extended to day 7 as the development of a positive reaction may be delayed. In dentistry, gold is mostly alloyed with other metals such as palladium, platinum and silver and therefore it is important to patch test these metals as well.

Fragrances are also common allergens in our study as evidenced by the high sensitization to fragrance mix I and Peru Balsam. Fragrance mix I contains eight fragrances, consisting
of seven defined chemicals (amyl cinnamal, cinnamal, cinnamyl alcohol, eugenol, geraniol, hydroxycitronellal and isoeugenol) and oakmoss absolute (Evernia prunastri extract).\textsuperscript{19} Peru Balsam is the balsam obtained from the bark of Myroxylon balsamum (L.) Harms var. pereirae (Royle) Harms tree and contain allergenic ingredients such as isoeugenol, eugenol and cinnamyl alcohol, but there are also other unknown chemicals in Peru Balsam that can cause contact allergy.\textsuperscript{20} Fragrances are used as flavouring agents in food products and oral hygiene products such as toothpaste and mouthwash.\textsuperscript{21} flavourings are added to toothpaste as they make the toothpaste more pleasant to use and at the same time freshen the breath. Eugenol is also used in dentistry in the form of zinc oxide eugenol cement due to its anti-inflammatory and antibacterial properties and this has been shown to cause oral lichenoid reaction.\textsuperscript{22}

Apart from containing fragrance allergens listed above, toothpaste can also contain carvone. Carvone is used as a flavoring agent in toothpaste and chewing gum and it is one of the main constituents of spearmint oil. Carvone gives out a mint flavor and hence is an ingredient of most toothpastes.\textsuperscript{23} Carvone is available as an allergen in the dental screening series used at our centre. In our study, we only had one patient who was found to have positive patch test reaction to carvone. Interestingly, a study in Sweden has found that 57\% of patients with carvone allergy had oral lichenoid reactions and this over-representation of oral lichenoid reactions is not connected with concomitant contact allergy to gold or mercury.\textsuperscript{24} These findings were also found in few other similar studies.\textsuperscript{25-27}

As fragrances and carvone present in toothpaste may be the causative allergens causing oral lichenoid reactions, patch testing to patient’s own toothpaste should strongly be considered. However, there is currently no consensus on patch testing to toothpaste. Irritant reaction is deemed to be common when patch testing using undiluted toothpaste due to the presence of abrasives and detergents. Diluting the toothpaste on the other hand will reduce its irritant potential but may cause false negative reaction. As a starting point, a semi-open test or closed patch test with the undiluted toothpaste can be performed. If a positive patch test reaction to an undiluted toothpaste developed, it should be followed with retesting and/or testing a dilution series (e.g. undiluted, 40\% pet or water and 20\% pet or water) and/or control testing.\textsuperscript{28}

All of our patients complained of pain or discomfort especially after eating spicy foods. Around 70\% of them sought medical attention within 1 year of onset of symptoms. This suggests that oral lichen planus negatively impacts their quality of life, prompting them to seek treatment early. This is especially true in Malaysia whereby spicy foods, which form part of our normal diet, may exacerbate or perpetuate this condition. Therefore, it is imperative that the cause of oral lichenoid reactions is assessed carefully. In order to distinguish contact allergy from other causes of oral lichenoid reactions, we recommend that patch test is performed in all patients who presented with oral lichen planus.

As with other cases of contact allergy, avoidance of the causative allergen remains the pivotal part of management. Treatment of oral lichenoid reactions related to contact allergy to dental restoration materials includes removal, replacement or recovering of fillings in direct contact with the lesions.\textsuperscript{29} Upon removal, improvement can be expected within 1 to 6 months.\textsuperscript{30} The criteria for replacement of restorations vary considerably in different practices. In some studies, the replacement of restorations was undertaken only in cases of a positive patch test, while others replaced all restoration in contact with the lesion, irrespective of the patch test result.\textsuperscript{30} Despite a negative patch test, improvement can still be observed after removal of the dental restoration materials in close proximity to the oral lichenoid lesions. This is because these lesions may be due to the irritant effect of the dental restoration materials...
as well. However, results from a positive patch test is still useful in providing guidance on the types of replacement restoration materials.

For contact allergy related to fragrances, patient should be advised to avoid foods and oral hygiene products that contains fragrances and flavourings. Although difficult to achieve, studies have shown that avoidance of fragrance allergens in these patients gave better control of their lesions than what they had achieved previously. Due to the widespread presence of these allergens in our foods, complete avoidance may not be possible and occasional adjunctive therapy (such as topical steroids) may be required. Apart from cinnamon derivatives, the most common flavourings used in toothpaste are derivatives extracted from the main varieties of mint, such as spearmint, peppermint, menthol and carvone, as they produce sensation of freshness. One study showed a dramatic improvement in a patient with oral lichen planus when spearmint oil was avoided. Therefore, in patients with oral lichenoid reactions showing positive patch test reaction to fragrance, we may empirically recommend alternative-flavoured toothpaste that uses flavourings derived from fruit extracts instead such as orange, banana, strawberry and pineapple.

There are several limitations to this study. This is a single centre study and our findings may not be representative of the Malaysian population as a whole. We did not follow up these patients after the patch test is completed. We are not aware of the progress of the patients after the patch test results were revealed and the measures taken for these patients. We did not perform delayed reading after 5 days and patients with late positive patch reactions might have been missed. We also did not repeat the patch test with 40% or 20% dilution in patients who had positive patch test reaction to undiluted toothpaste and this could pose a risk of a false positive patch test reaction. In the future, we will extend our readings to day 7 for patients tested with dental screening series and offer a repeat patch test with serial dilutions of toothpaste at 20% and 40% for patients who develop a positive patch test to their toothpaste. Future studies should also include follow-up these patients after completion of their patch tests, in order to evaluate whether avoidance of causative allergens has resulted in improvement of their symptoms.

### Table 3. Oral lichen planus and oral lichenoid reactions: a review of the literature

<table>
<thead>
<tr>
<th>Author</th>
<th>Study period</th>
<th>No of patients</th>
<th>Positive reaction</th>
<th>Top 3 allergens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Our study, Malaysia</td>
<td>2015 - 2019</td>
<td>41</td>
<td>70.7%</td>
<td>Nickel sulfate, gold sodium thiosulphate, fragrance mix</td>
</tr>
<tr>
<td>Torge et al</td>
<td>USA 2000 - 2004</td>
<td>59</td>
<td>55.9%</td>
<td>Potassium dicyanoaurate, fragrance mix, gold sodium thiosulphate</td>
</tr>
<tr>
<td>Khamaysi et al</td>
<td>Israel 2000 - 2004</td>
<td>17</td>
<td>35.3%</td>
<td>Gold sodium thiosulphate, nickel sulphate, mercury</td>
</tr>
<tr>
<td>Kim et al</td>
<td>South Korea 2004 - 2011</td>
<td>24</td>
<td>75.0%</td>
<td>Nickel sulfate, gold sodium thiosulphate, potassium dichromate</td>
</tr>
<tr>
<td>Lomaga et al</td>
<td>Canada 2006 - 2007</td>
<td>24</td>
<td>66.7%</td>
<td>Nickel sulfate, fragrance mix, cobalt chloride</td>
</tr>
</tbody>
</table>

### Conclusion

Contact sensitizations were detected in about 70% of our patients with oral lichen planus and the most common sensitizing allergen was nickel sulfate. Current relevance was found mainly towards metals in dental restoration materials. Apart from metals, other source of exposure to contact allergens included fragrances as part of the ingredients in oral hygiene products. Patch test should be considered in all cases of oral lichen planus. Studies evaluating the trends of contact allergens in oral lichen planus would help in determining the appropriate dental restoration materials in our population.

### Conflict of Interest Declaration

All authors have no financial/conflict of interest to disclosed.

### Acknowledgement

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20. de Groot AC. Myroxylon pereirae resin (balsam of Peru) - A critical review of the literature and assessment of the significance of positive patch test reactions and the usefulness of restrictive diets. Contact Dermatitis 2019;80:335-53.


ORIGINAL ARTICLE

A Prospective Case Control Study Comparing Serum Vitamin D Levels in Patients with and without Alopecia Areata

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Abstract

Background
Alopecia areata (AA) is the most common cause of non-scarring alopecia.\(^1\) Many studies reported decreased serum vitamin D levels in patients with AA compared to healthy subjects.\(^1-8\) This study aimed to assess the prevalence of vitamin D deficiency in patients with AA compared to patients without AA. The secondary objective was to determine the correlation between vitamin D deficiency with disease severity and the pattern of AA.

Methods
This research was a case control study involving patients with AA from the dermatology clinic in Hospital Raja Permaisuri Bainun. All the subjects and controls were age, sex and Fitzpatrick skin type matched. Serum vitamin D (25-hydroxyvitamin D) (25 OHD) levels were obtained and analysed by the chemiluminescence immunoassay method. AA severity was assessed by Severity of Alopecia Tool (SALT) score.

Results
A total of 50 subjects, out of which 25 patients with AA and 25 controls, were recruited. The median serum vitamin D level was 54.15 nmol/L (IQR 139) in the AA group and 53.79 nmol/L (IQR 64.47) in the control group. However, the difference was not statistically significant (\(p=0.823\)). The prevalence of vitamin D deficiency was higher in the AA group (12%) compared to the control group (4%), but it was not statistically significant (\(p=0.304\)). There was no statistical significance in serum vitamin D levels with disease severity (SALT score) (\(p=0.171\)) and pattern of AA (\(p=0.657\)).

Conclusion
There was no statistical difference in the prevalence of vitamin D deficiency between patients with and without AA. There was no correlation between serum vitamin D levels with disease severity and pattern of AA. Further studies using a larger sample size is needed to justify measuring serum vitamin D levels in patients with AA.

Key words: Alopecia areata, Vitamin D, SALT score, Malaysia

Introduction
Alopecia areata (AA) is a common form of non-scarring hair loss.\(^1\) AA usually presents as patches of hair loss on the scalp, but it may also involve any areas of hair-bearing skin.\(^2\) AA is an organ-specific autoimmune disease exemplified by T-cell infiltrate and cytokine production around anagen-stage hair follicles.\(^3\) AA affects about 1-2% of the general population.
population, with an estimated lifetime risk of 1.7%. There is a higher prevalence in younger (21-40 years old) patients, but no significant difference in incidence exists between males and females. AA can profoundly affect a patient’s quality of life, resembling the degree seen in other diseases, such as psoriasis and atopic dermatitis. Vitamin D is a secosteroid hormone that is vital for calcium homeostasis and bone health. Vitamin D is also implicated in certain cancers, cardiovascular health and immune system.

Literature data suggest that vitamin D may be involved in the pathogenesis of AA due to its immunomodulatory effects. It has been shown that Vitamin D Receptors (VDRs) are strongly expressed in hair follicles. The lack of VDRs reduced epidermal differentiation and the growth of hair follicles. Some studies reported decreased serum vitamin D levels in AA in comparison to healthy subjects. A significant negative correlation between Severity of Alopecia Tool Score (SALT score) and serum vitamin D was found in several studies. However, data concerning the correlation between vitamin D and clinical disease parameters were inconsistent. A study by Ghafoor R et al. showed that serum vitamin D levels were significantly lower in patients with AA than healthy controls. Yilmaz et al., however, did not find any correlation between serum vitamin D concentrations in 42 patients with AA and the extent of hair loss, number of patches, disease duration and nail involvement. Erpolat et al. conducted a case control study on 41 AA patients and found no statistically significant difference in the serum vitamin D levels between AA patients and healthy controls. Therefore, the vitamin D levels among patients in Malaysia with AA is not known.

The findings of our study may justify incorporating vitamin D supplements as adjunct therapy on top of the standard therapy. Our primary objective was to compare vitamin D deficiency in patients with or without AA. Secondary objectives were to assess the prevalence of vitamin D deficiency in patients with AA and determine the correlation of vitamin D deficiency with disease severity in patients with AA.

Materials and Methods

Study design and subject recruitment
This was a prospective case control study conducted at the dermatology clinic of Hospital Raja Permaisuri Bainun Ipoh, Perak, Malaysia, between the period of May 2020 and November 2020. AA patients aged 12 years old and above were recruited into the study by a convenient sampling method. Exclusion criteria included pregnancy/lactating females; patients on oral vitamin D supplementation/topical vitamin D analogues, patients with other types of alopecia (such as tinea capitis, androgenic alopecia, trichotillomania, scarring alopecia, traction alopecia, telogen effluvium), patients with BMI>25 (as vitamin D deficiency was associated with obesity) and patients with other systemic autoimmune diseases (e.g. vitiligo, rheumatoid arthritis, diabetes mellitus, thyroid disorder, lupus erythematosus etc.).

AA patients were interviewed to obtain demographic data, which consisted of their age, gender, ethnicity, Fitzpatrick skin phototype, education level, family history of AA, duration of the disease, presence of comorbidities, smoking and drinking habits, dietary restrictions and clothing practices.

Diagnosis of AA was based on clinical findings and dermatoscopy (to look for exclamation mark hairs, coudability, yellow dots, black dots, short vellus hair). Clinical data and clinical variables were documented. The duration of disease, site of involvement, severity assessment for scalp involvement (SALT score) and pattern of hair loss was recorded. Patients were asked to recall their 3-day diet history, which would subsequently be analysed for its vitamin D content using Nutritionist Pro™ Software of the United States Department of Agriculture (USDA) Standard Reference Database, First DataBank, Inc., San Bruno, California.

The sun exposure index (SEI) was calculated
using the formula: hours of sun exposure per week multiplied by the fraction of BSA (body surface area involvement using the Wallace Rule of Nines chart) exposed to sunlight. Subjects in the control group were selected randomly among patients and hospital staff without alopecia. The controls were matched to age, sex and Fitzpatrick skin type. Similar exclusion criteria were applied to the control group. Control subjects were assessed clinically with detailed history and thorough examination. A total of 50 subjects were recruited with 25 AA patients and 25 healthy controls into each arm, respectively.

**Serum vitamin D sampling and analysis**

Three millilitres (ml) of venous blood was obtained from all subjects and transferred to a Lithium Heparin tube. Samples were collected and sent to the biochemical pathology laboratory in Hospital Raja Permaisuri Bainun Ipoh. The samples were centrifuged and transported to the biochemical pathology laboratory in Hospital Putrajaya. The blood samples were analysed by chemiluminescence immunoassay method through Beckham DXI analyser to measure serum total Vitamin D (25 -hydroxyvitamin D) (25OHD) levels. Clinical decision values were defined as deficient (<25 nmol/L), insufficient (25-75 nmol/L), sufficient (76-250 nmol/L) and possible intoxication (>250 nmol/L).

**Sample size calculations**

The sample size of this study was calculated based on a systematic review and meta-analysis by Lee S *et al.*\textsuperscript{15} This sample size was calculated using Power and Sample Size Calculation version 3.1.2 with alpha = 0.05 and power = 80%. The sample size calculated was 46 (i.e. 23 subjects with AA and 23 subjects in the control group).

**Data analysis**

The Statistical Package for Social Sciences for Windows version 22.0 (SPSS, Chicago, IL, USA) was used to perform the statistical analysis. The data normality was checked by the Shapiro-Wilk test. The computed significance levels for age, BMI, vitamin D level, vitamin D category and vitamin D intake are > 0.05). Therefore, normality cannot be assumed, and a non-parametric test was performed. The descriptive data were expressed as median and inter quarter range, or frequency and percentage. Mann-Whitney test was used for the analysis of the difference between two study group means. Because of the small sample size of SALT 4 and SALT 5, and Ophiasis, Totalis and Universalis, they were collapsed into one single group, respectively (Naidu & Baddireddy 2020).\textsuperscript{19} Kruskal Wallis H test was used to determine the difference between the three study groups means; *p*<0.05 was considered statistically significant.

**Ethical approval**

This study was registered with the National Medical Research Registry (NMRR-20-41-52526). Ethical approval for the study was obtained from the Medical Research and Ethics Committee, Ministry of Health, Malaysia.

**Results**

Table 1 shows the demographic and clinical characteristics of subjects with AA and controls. A total of 50 subjects were recruited, with 25 AA patients and 25 healthy controls in each arm, respectively. There was no significant difference (*p>*0.05) between the two groups regarding age, sex, BMI, race, education, comorbidities, smoking habits, alcohol intake, diet, Fitzpatrick skin type, medications, family history with AA and family history of autoimmune diseases.

The median vitamin D level was slightly higher in the AA group compared to the control group, although the difference was not statistically significant (54.15 nmol/L vs 53.79 nmol/L, *p*=0.823). The median vitamin D intake was higher in the control group (7.86 mcg; IQR: 34.9) compared to the AA group (6.65 mcg; IQR: 44), but the difference was not statistically significant (*p*=0.503). The median SEI was higher in the AA group (7.86 mcg; IQR: 34.9) compared to the control group (220.5; IQR: 209.8) compared to the control group (146.16; IQR: 863.7) even though the difference was not statistically significant (*p*=0.823). Vitamin D deficiency was higher in the AA group (12%) compared to the control group.
group (4%), while vitamin D insufficiency was found in 76% of AA patients and 92% in the control group. However, the results were not statistically significant (p=0.304). (Table 2)

Table 1. Demographic characteristics and clinical characteristics of subjects with and without alopecia areata (n = 50)

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Subject (AA) n = 25</th>
<th>Control n = 25</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in years)</td>
<td>29 (25)</td>
<td>29 (22)</td>
<td>0.938c</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>11 (44 %)</td>
<td>9 (36 %)</td>
<td>0.773b</td>
</tr>
<tr>
<td>Female</td>
<td>14 (56 %)</td>
<td>16 (64 %)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>23 (5.1)</td>
<td>22 (5.1)</td>
<td>0.839c</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malay</td>
<td>7 (28 %)</td>
<td>7 (28 %)</td>
<td>1.000a</td>
</tr>
<tr>
<td>Chinese</td>
<td>9 (36 %)</td>
<td>9 (36 %)</td>
<td></td>
</tr>
<tr>
<td>Indian</td>
<td>9 (18 %)</td>
<td>9 (18 %)</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>1 (4 %)</td>
<td>0 (0 %)</td>
<td>0.450a</td>
</tr>
<tr>
<td>Secondary</td>
<td>15 (60 %)</td>
<td>13 (52 %)</td>
<td></td>
</tr>
<tr>
<td>Tertiary</td>
<td>9 (36 %)</td>
<td>12 (48 %)</td>
<td></td>
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<tr>
<td>Comorbid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7 (28 %)</td>
<td>3 (12 %)</td>
<td>0.289#</td>
</tr>
<tr>
<td>No</td>
<td>18 (72 %)</td>
<td>22 (88 %)</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>4 (16 %)</td>
<td>4 (16 %)</td>
<td>1.000a</td>
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<tr>
<td>No</td>
<td>20 (80 %)</td>
<td>20 (80 %)</td>
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<tr>
<td>Ex-smoker</td>
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<td>1 (4 %)</td>
<td></td>
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<tr>
<td>Alcohol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7 (28 %)</td>
<td>3 (12 %)</td>
<td>0.289#</td>
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<tr>
<td>No</td>
<td>18 (72 %)</td>
<td>22 (88 %)</td>
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<tr>
<td>Diet</td>
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<tr>
<td>Vegetarian</td>
<td>2 (8 %)</td>
<td>0 (0 %)</td>
<td>0.490#</td>
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<tr>
<td>Non-vegetarian</td>
<td>23 (92 %)</td>
<td>25 (100 %)</td>
<td></td>
</tr>
<tr>
<td>Fitzpatrick</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type III</td>
<td>9 (36 %)</td>
<td>9 (36 %)</td>
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<tr>
<td>Type IV</td>
<td>7 (28 %)</td>
<td>7 (28 %)</td>
<td></td>
</tr>
<tr>
<td>Type V</td>
<td>9 (36 %)</td>
<td>9 (36 %)</td>
<td></td>
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<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8 (32 %)</td>
<td>12 (48 %)</td>
<td>0.387#</td>
</tr>
<tr>
<td>No</td>
<td>17 (68 %)</td>
<td>13 (52 %)</td>
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<tr>
<td>Family history AA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1 (4 %)</td>
<td>0 (0 %)</td>
<td>1.000#</td>
</tr>
<tr>
<td>No</td>
<td>24 (96 %)</td>
<td>25 (100 %)</td>
<td></td>
</tr>
<tr>
<td>Family history Autoimmune</td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>2 (8 %)</td>
<td>2 (8 %)</td>
<td>1.000#</td>
</tr>
<tr>
<td>No</td>
<td>23 (92 %)</td>
<td>23 (92 %)</td>
<td></td>
</tr>
</tbody>
</table>

*Chi-Square test; *Fisher’s exact test; *Mann-Whitney test

Table 2. Vitamin D level and deficiency in case and control group

<table>
<thead>
<tr>
<th>Vitamin D level (nmol/L)</th>
<th>Subject (AA) n = 25 Median (IQR)</th>
<th>Control n = 25 Median (IQR)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D intake (mcg/mcg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sun Exposure index (SEI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D categories</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Deficient &lt; 25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insufficient 25-75</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sufficient 76-250</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Mann-Whitney test; *Chi-Square test

The association of SALT score with vitamin D level was obtained by Kruskal-Wallis statistic and was interpreted as a chi-square value. There was no statistically significant association between SALT score and vitamin D levels (p=0.171). (Table 3)

Table 3. Association of SALT scores with vitamin D level

<table>
<thead>
<tr>
<th>SALT subclass (n=25)</th>
<th>n (%)</th>
<th>Median (IQR)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>18 (72 %)</td>
<td>54.56 (32.5)</td>
<td>0.171a</td>
</tr>
<tr>
<td>S2</td>
<td>2 (8 %)</td>
<td>34.42 (0)</td>
<td></td>
</tr>
<tr>
<td>S3-S5</td>
<td>5 (20 %)</td>
<td>42.78 (43.13)</td>
<td></td>
</tr>
</tbody>
</table>

*Kruskal-Wallis test

A similar analysis was performed for the association of AA patterns with vitamin D levels. The result showed no statistically significant difference between the pattern of AA with vitamin D levels (p=0.657). (Table 4)

Table 4. Association of pattern scores with vitamin D level

<table>
<thead>
<tr>
<th>Pattern subclass (n=25)</th>
<th>n (%)</th>
<th>Median (IQR)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1 (patchy: single)</td>
<td>6 (24 %)</td>
<td>44.62 (37.29)</td>
<td>0.657*</td>
</tr>
<tr>
<td>P2 (patchy: multiple)</td>
<td>15 (60 %)</td>
<td>54.16 (30.65)</td>
<td></td>
</tr>
<tr>
<td>P3 (ophiasis, totalis and universalis)</td>
<td>4 (16 %)</td>
<td>43.49 (35.66)</td>
<td></td>
</tr>
</tbody>
</table>

*Kruskal-Wallis test

Discussion

Vitamin D can be obtained from 3 sources: endogenous synthesis in the skin induced
by ultraviolet B (UVB) radiation, dietary intake, and vitamin D supplementation.\textsuperscript{3,13,14} 7-dehydrocholesterol is the precursor molecule in the skin which absorbs UVB light and converts to vitamin D3(cholecalciferol). Vitamin D3 binds to vitamin D3 binding protein and is transported to the liver where it is hydroxylated to 25-hydroxyvitamin D (calcidiol) (25(OH)D). Calcidiol is then converted to 1,25-dihydroxyvitamin D3 (calcitriol) in the kidney by 1-α hydroxylase.\textsuperscript{13,14} The optimal level for 25-hydroxyvitamin D (25OHD), the most stable and reliable parameter to evaluate vitamin D status, starts at 30 ng/ml, although the level of 25OHD required to maintain optimum immune system homeostasis has yet to be established.\textsuperscript{20}

The active form of vitamin D (1,25-hydroxyvitamin D) acts by binding to specific vitamin D receptors found in the nucleus of target cells.\textsuperscript{7} Vitamin D Receptor (VDR) is highly expressed in the key structures of hair follicles, and it is vital for the maintenance of the normal hair cycle. It has been demonstrated that a lack of VDRs reduces the growth of hair follicles. Therefore, with the role of vitamin D and VDR in the hair cycle, it is hypothesised that vitamin D deficiency may have a role in AA.\textsuperscript{1,2}

A study conducted in Malaysia on vitamin D status in Malaysian men found that the prevalence of vitamin D deficiency was 0.5% and insufficiency was 22.7%, respectively.\textsuperscript{21} Numerous studies have shown that vitamin D insufficiency was common in tropical countries, including Vietnam, Malaysia, and Indonesia.\textsuperscript{21} The prevalence of vitamin D deficiency among Malaysian adolescents aged 13 years was 78.8%.\textsuperscript{22}

In our study, there was no significant difference in terms of the median vitamin D level between the AA and control group, even though the level was slightly higher in the AA group. A study by Nassiri \textit{et al.}\textsuperscript{23} found no statistically significant difference in serum vitamin D levels between AA cases and controls (ordinal odds ratio:0.49 (0.18-1.34 and 95%CI, \textit{p}=0.16). Erpolat \textit{et al.}\textsuperscript{18} also reported similar findings with mean serum vitamin D levels of 8.1 ng/ml in AA patients compared to 9.8 ng/ml in healthy controls, which was not statistically significant (\textit{p}=0.05). In contrast, numerous studies reported high statistically significant lower vitamin D levels in cases compared to control. Aksu Cerman \textit{et al.}\textsuperscript{3} reported significantly lower mean serum vitamin D levels in AA patients (11.84±6.18 ng/ml) than healthy controls (23.57±9.03 ng/ml) (\textit{p}<0.001). A study conducted by Bhat \textit{et al.}\textsuperscript{4} found a statistically significant difference in the mean serum vitamin D levels of AA patients (16.6±5.9 ng/ml) as compared to the control group (40.5±5.7 ng/ml) (\textit{p}<0.001).\textsuperscript{4} Similar findings of high statistically significant lower vitamin D levels in AA cases compared to control was also reported in studies conducted by Sidappa \textit{et al.}\textsuperscript{5}, Mahamid \textit{et al.}\textsuperscript{7}, Rehman \textit{et al.}\textsuperscript{8}, and Yilmaz \textit{et al.}\textsuperscript{17}

Our study revealed that Vitamin D deficiency and insufficiency was high in both AA (12%, 76%) and control group (4%, 92%). This finding was consistent with recent studies, which showed vitamin D insufficiency was commonly found in tropical countries such as Vietnam, Malaysia, and Indonesia.\textsuperscript{21} A study conducted by Kok-Yong Chin \textit{et al.}\textsuperscript{21} found that the prevalence of vitamin D deficiency (<30 nmol/L) was 0.5% and insufficiency (30-50 nmol/L) was 22.7% among Malaysian men. The result of higher vitamin D deficiency and insufficiency in both groups in our study compared to Kok-Yong Chin \textit{et al.}\textsuperscript{21} The discrepancy might be due to different definitions of vitamin D deficiency and insufficiency used in the study. Another study conducted in Malaysia by Moy \textit{et al.}\textsuperscript{23} found that vitamin D insufficiency was observed in 67.9% of participants among Malay adults in Malaysia. Another study conducted by Rahman \textit{et al.}\textsuperscript{24} in Malaysia also showed a high prevalence of inadequate serum vitamin D levels among postmenopausal Malaysian women. A total of 73.3% of Malay postmenopausal women and 12.2% of Chinese postmenopausal women had insufficient serum vitamin D levels (<50 nmol/L).\textsuperscript{24}

In our study, there was no statistical difference in the prevalence of vitamin D deficiency between AA and the control group even though vitamin
D deficiency was higher in the AA group than the control group (12% vs 4%, p>0.05). This observation could be due to a small sample size leading to insignificant results. Erpolat et al.\textsuperscript{18} also reported higher vitamin D deficiency in the AA group compared to control (93.8% vs 85.3%), but the difference was not statistically significant (p>0.05). Numerous studies reported a significantly higher prevalence of vitamin D deficiency in AA compared to the control group. Suchana et al.\textsuperscript{1} reported 83.3% of vitamin D deficiency in the AA group compared to the control group (53.3%; p=0.01). Bakry et al.\textsuperscript{2} found that 83.3% in the AA group versus 23.3% in the control group had deficient serum vitamin D levels (p<0.001). Similar findings were reported by Aksu Cerman et al.\textsuperscript{3} and Naidu et al.\textsuperscript{19}.

Our study did not find any statistically significant correlation between serum vitamin D levels and SALT scores. Suchana et al.\textsuperscript{1} found that patients with more severe SALT scores tend to have lower serum vitamin D levels, with an inverse correlation (r=-0.026, p=0.89); however, the results were not statistically significant. Naidu et al.\textsuperscript{19} also showed slightly lower serum vitamin D levels as the SALT score progressed, but the difference was not statistically significant (p=0.06). Various studies, as reported by Yilmaz et al.\textsuperscript{17}, d’Ovidio et al.\textsuperscript{20}, El-Mongy et al.\textsuperscript{25} and Darwish et al.\textsuperscript{26} found no significant correlation between serum vitamin D levels with disease severity. However, this contradicts numerous other studies that found that serum vitamin D levels showed a significant negative correlation with disease severity.\textsuperscript{2,3,4,5,6,8} Aksu Cerman et al.\textsuperscript{3} found a significant inverse correlation between disease severity and serum vitamin D levels in AA patients (r=-0.730; p<0.001). Bhat et al.\textsuperscript{4} also reported a significant negative correlation between SALT score and vitamin D levels (r=-0.730; p<0.001).\textsuperscript{4} Similar findings of significant inverse correlation between SALT score and vitamin D levels were reported by Sidappa et al.\textsuperscript{5}, Gade et al.\textsuperscript{6}, and Rehman et al.\textsuperscript{8}.

Regarding the correlation of serum vitamin D levels with the pattern of disease, our study did not find any correlation between different patterns of AA with serum vitamin D levels. This finding was similar to a study conducted by El-Mongy et al.\textsuperscript{25}, which reported no statistical significance between serum vitamin D levels and disease pattern (p=0.14). Similar findings were reported in studies conducted by Yilmaz et al.\textsuperscript{17}, d’Ovidio et al.\textsuperscript{20} and Nassiri et al.\textsuperscript{27}. In contrast, a study conducted by Bakry et al.\textsuperscript{2} showed a gradual decline of serum vitamin D levels from patchy AA to Alopecia totalis/universalis. Serum vitamin D levels of alopecia totalis/universalis patients were significantly lower when compared to patchy AA (p<0.001) and ophiasis (p<0.05). Rehman et al.\textsuperscript{5} also reported similar findings where serum vitamin D levels negatively correlated with the pattern of AA (r=-0.273, p=0.004).

The median SEI in the AA group was higher than the control group, although the result was not statistically significant (SEI: 220.50 vs 146.16, p>0.05). A study conducted by Bingley et al.\textsuperscript{28} among 93 adults in Hawaii showed low serum vitamin D levels despite adequate sun exposure, suggesting variable responsiveness to UVB radiation among individuals.\textsuperscript{28} A study conducted on 167 Malaysians by Wong et al.\textsuperscript{29} on sun exposure among healthy adults in a health facility showed a mean SEI of 160±144, lower than the median SEI of 220.5 in the AA group from our study.\textsuperscript{29} Although Malaysia is a tropical country with adequate sunlight throughout the year, a low SEI among Malaysians can be attributed to sun avoidance to achieve a fairer skin tone, which is deemed more desirable, and escape the tropical heat. Other factors include the choice of clothing, with most Asians dresses modestly due to influence by tradition, culture, or religion, which limits the amount of sunlight that reaches the skin.\textsuperscript{29} The primary cause of vitamin D deficiency is inadequate exposure to sunlight.\textsuperscript{30}

The median vitamin D intake was lower in the AA group compared to the control group, although it was not statistically significant. Vitamin D intake was low in both groups, which correlates to low serum vitamin D levels in both groups.
The finding could be attributed by very few foods that naturally contain or are adequately fortified with vitamin D. As examples, food sources that are naturally high in vitamin D include cod liver oil, salmon, sardines, tuna, shitake mushrooms and egg yolks. The recommended vitamin D intake is 600 IU/day (15 mcg) for adults aged 19-50 years old, and at least 600-800 IU/day (15-20 mcg) for adults aged 50-70 years old and above 70 years old, respectively. However, for serum vitamin D level to rise above 30 ng/ml (75 nmol/L), one may require 1500-2000 IU/day (38 mcg-50 mcg) of supplemental vitamin D.  

Limitations

The limitations of this study include a relatively limited sample size. As this study was conducted from a single centre in Malaysia, larger studies involving multiple centres may be more representative of the population in Malaysia. In addition, as the patients were not followed up with vitamin D supplementation and repeated serum vitamin D levels, it was hard to conclude if vitamin D supplementation may be beneficial as an adjunctive treatment for patients with AA.

Conclusion

There is no significant statistical difference in vitamin D levels between patients with AA and without. However, the prevalence of vitamin D insufficiency was high in both AA and control groups. There is also no correlation between serum vitamin D levels with severity and pattern of disease.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

Acknowledgement

This study was funded with a research grant from the Dermatological Society of Malaysia. We would like to thank all the staff from the departments of dermatology and pathology of Hospital Raja Permaisuri Bainun, Ipoh and Hospital Putrajaya, and Suria Junus, the statistical supervisor. We also wish to thank the Director-General of Health Malaysia for permission to publish this article.

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ORIGINAL ARTICLE

A Study Assessing the Practices and Motivation for Seeking Tattoo Removal

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²Sparsha Skin Care Clinic, Mandya, Karnataka, India

Abstract

Background
As the number of patients getting tattooed is increasing, so is the number of patients seeking removal of tattoos. The primary objective of this study was to assess the reasons as to why patients got tattoos and also seek tattoo removal. The secondary objective was to study the demographics and the knowledge they had regarding tattoo removal.

Methods
A cross sectional study was done among 250 consecutive patients who attended the Dermatology centre seeking tattoo removal. A questionnaire was used to fill in the details.

Results
167 males and 83 females were included in the study. Majority of patients were in the age group of 21 to 30 years (43.8%) followed by 31-40 years (26.7%). 56.6% of patients had got tattoos in the third decade and 35.1% in the second decade. 52.6% of those seeking tattoo removal had got their tattoos from amateur artists, village fairs or roadside tattoo shops. 45.8% did not have a specific reason for getting a tattoo and were decorative tattoos. 34.7% had names of their beloved or family members. 29.5% were seeking removal for professional reasons and 23.1% due to changes in relationship status.

Conclusion
Patients seek tattoo removal mainly for professional reasons, changes in personal relationships when they have name tattoo and due to complications. Most of the patients were in the third decade of life. It is important to educate school going children ang youngsters regarding the permanent nature of tattoo and its complications.

Key words: Tattoo, Laser removal, Awareness

Introduction
Tattooing is a common and popular form of body decoration especially among younger individuals. Tattoo is a permanent change brought about in the skin by injection of a dye molecule into the dermal layer. Tattoos may be decorative, medical or accidental depending on whether the dye was introduced intentionally or by accident.¹ Medical tattoos are done for cosmetic camouflage in vitiligo, permanent hair loss, scars and areola reconstruction after surgery.² Tattoos are part of the cultural heritage of various tribes. It used to be an indicator of social status or a victory.³ With modernisation, tattoo has become more of a fashion statement.
There are limited studies regarding the motivation for tattoos and for reasons requesting its removal.\textsuperscript{3,4}

The objective of this study was to evaluate what motivated the participants to get tattoo and why they were seeking the removal.

**Materials and Methods**

**Study design**

A cross sectional descriptive study was conducted between Jan 2019 and Jan 2021. A sample of 250 consecutive patients who attended the centre seeking removal of tattoos were included in the study. Written informed consent was taken from the participants to use their data. Patients who did not consent were excluded from the study.

**Methods**

A questionnaire in the language known to the patient was used to collect the data regarding the demography, education, age at which tattoo was done, reason for the tattoo, amateur or professional, site and number of tattoos, if they were aware that the tattoo was permanent, why they were seeking tattoo removal and if they had tried other methods of removal. The responses were coded from 1 to 5 according to questions and entered in excel sheet. Approval was taken from institutional ethics committee.

Data was entered in excel sheet and analysed using SPSS software. Results were expressed in percentage.

**Results**

Out of 250 participants in the study, 167 were males (66.5%) and 83 were females (33.1%). The analysis of demographic data showed that 110 of participants were in third decade (43.8%), 67 in the fourth decade (26.7%), and with almost equal number of participants in remaining age groups (Table 1).

The number of participants from the urban area was slightly higher than the rural. (57.4%). Among the participants, one hundred and seven were graduates, (50.6%), 77 had studied up to higher primary level (30.7%) and 46 were either illiterates or dropped out of primary school (18.3%). Majority of patients 142 (83.7%) patients had got their first tattoo in the third decade (56.6%) and 88 in second decade (35.1%).

Professional tattoos were seen in one hundred and seventeen (46.6%) (Figure 1) and 132 had amateur tattoos (52.6%) (Figure 2). Majority of the participants (71%) from rural areas had amateur tattoos whereas 61% of those from urban areas had professional tattoos. Single tattoo was seen among 210 participants (83.7%). A large number of participants (45.8%) did not have a specific motive to get a tattoo, it was for decorative purpose. 74 of them had a tattoo to symbolise a romantic relationship and 13 (5.2%) for a family member.

Only 18 (7.2%) were under the influence of alcohol at the time of tattooing. Decorative tattoos (46.6%) were the most common, followed by names of friends or family members (34.7%), (Figure 3) and 26 (10.4%) had inspirational and religious quotes. (Figure 4) Forearm was the most common site for tattoo in 113 (45.0%), followed by chest in 73 (29.1%), shoulder and neck in 38 (15.1%), bindi and lower back in 9 each (3.6%). Only 35 participants (13.9%) were not aware about the permanent nature of the tattoo. 74 wanted tattoo removed for professional reasons (29.5%), 58 due to separation from partners (23.1%), 43 due to tattoo reactions (17.1%), 31 due to family pressure (12.4%) and 29 due to regret (11.6%).

<table>
<thead>
<tr>
<th>Age in years</th>
<th>Number</th>
<th>Percentage %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>24</td>
<td>9.6</td>
</tr>
<tr>
<td>20-30</td>
<td>110</td>
<td>43.8</td>
</tr>
<tr>
<td>30-40</td>
<td>67</td>
<td>26.7</td>
</tr>
<tr>
<td>40-50</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>&gt;50</td>
<td>24</td>
<td>9.6</td>
</tr>
</tbody>
</table>

![Table 1. Age of the patients seeking tattoo removal](image-url)
As high as 85% of those who wanted tattoo removal for professional reasons were educated higher primary and above and 86% were men. Most common reason for women seeking removal was separation from partners (38%) followed by pressure from family members in 18%. 69.7% of reactions were in men and 30.3% in women. (Figure 5) Local measures like application of lime (Figure 6), cuts, burning with candles and incense stick was tried by 33 participants (13.1%), before consulting specialists.

Table 2. Reasons for seeking tattoo removal

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regret</td>
<td>29</td>
<td>11.6</td>
</tr>
<tr>
<td>Professional advancement</td>
<td>74</td>
<td>29.5</td>
</tr>
<tr>
<td>Separation from partner</td>
<td>58</td>
<td>23.1</td>
</tr>
<tr>
<td>Reactions</td>
<td>43</td>
<td>17.1</td>
</tr>
<tr>
<td>Family pressure</td>
<td>31</td>
<td>12.4</td>
</tr>
<tr>
<td>Religious obligations</td>
<td>15</td>
<td>6.0</td>
</tr>
</tbody>
</table>

Figure 1. Professional black tattoo

Figure 2. Amateur tattoo

Figure 3. Tattoo of beloved’s name

Figure 4. Types of tattoo

Figure 5. Granulomatous reaction to tattoo

Figure 6. Irritant contact dermatitis due to application of lime to remove tattoo
Discussion
Tattooing has become a common form of body decoration. Being sported by supermodels and popstars, they provide a lot of appeal to the youngsters.\(^5\)

In the study by Thakur et al. of the tattoo practices in North eastern India, more than 50% patients seeking tattoo removal had got their tattoos in school-going age which they attributed to emotional immaturity and influence of fashion. Studies by Varma et al and Ltrielle et al also published that majority of participants got tattoos in second decade.\(^5,6\) However in our study only 35.1% had got tattoos before the age of 20 years, but majority (56.5%) of patients got their tattoos in third decade. Few of the participants were not aware about the permanency of the tattoo and majority of them were less than 20 years of age. Knowledge among students regarding the safety, permanency and side effects of tattoos is insufficient.\(^7\) Preventive education in school regarding the permanency of tattoo, possible effects on future employment, risks and complications may help to reduce underage tattooing. Most of them being amateur tattoos, there was obviously no explanation given to the participants about the permanent nature or possible side effects by tattoo artists.

Most of the participants (45.8%) in the study did not have a specific motive for getting a tattoo, it was for decorative purpose. Our study conforms with similar findings of other studies where most of the tattoos are often applied impulsively.\(^5,6\) 34.7% of participants had names tattooed for sentimental reasons, out of which 85% had their partners’ names. More women had tattooed their partners’ names (39.7%) than men which was 24.5%.

52.6% had amateur tattoos in our study which is much lower than the study from Eastern India where 94.3% of tattoos were amateur which can be explained by the cultural heritage of tattooing among tribes in North Eastern India.\(^3\) No significant difference was noted in the level of education and the place of tattoo. Higher proportion of people from rural areas had amateur tattoos (70.7%), compared to 60.13% of those from urban areas who had professional tattoos. This can be explained by the more number of tattoo parlours in urban areas with a lot of advertisements. Also functions like fairs where amateur tattoo artists are in plenty, are not common in urban areas.

The most common reason for removal of tattoos was for employment prospects (74 patients). According to the revised tattoo policy by Indian Army, only tattoos on inner aspect of forearm and dorsum of the hand are permissible. Candidates belonging to tribal communities/from tribal areas, as declared by the Government of India Scheduled Castes and Scheduled Tribes Orders Act/Lists (amended and modified from time to time), are permitted to have permanent body tattoos on any part of the body, as per existing customs and traditions of the said tribe to which a candidate belongs.\(^9\) Though there are no open policies and guidelines regarding tattoo in any other government sector In India, people applying for Civil services and railways job also sought tattoo removal. 23% were seeking removal of name tattoos due to changes in relationship status. Couples frequently tattoo the names of their partners to show their affection which is regretted when the relationship ends.\(^4\)

Other reasons were family pressure and religious issues. 17% of patients had tattoo reactions like allergic contact dermatitis (commonly to red colour). This is similar to previous reported studies, where allergic reactions are found more frequently to red colour.\(^10\) According to study by Thakur et al to be eligible for armed force jobs was the most common reason for tattoo removal (49.5%), followed by regret (21.7%), elder or school pressure (14.2%), personal (12.7%) and unsightly appearance such as hypertrophic scarring in tattoo (1.9%).\(^3\) Similar results were published from a study in Western India.\(^4\) These were quite different from Western studies.

According to Varma et al the reasons for seeking tattoo removal were improvement of self-esteem (48 patients), followed by social reasons (24 patients), family pressure (13 patients),
improving potential for employment (12 patients) and a change of partner (4 patients). The reasons also varied according to the age of the patients. Teenagers sought removal mainly due to regret and familial pressure. In the third decade professional eligibility was the most common reason. In those over the age of 30 separation from partners and regret were the reason why they sought removal frequently. Thirty-three patients had tried various methods of tattoo removal like application of lime, soda, burning with incense sticks, scraping with blade which had resulted in infection and scars.

The limitation of this study is that it is a hospital-based study done only on individuals seeking tattoo removal at a single centre. Recall bias and selection bias have to be considered before projecting the results to the community.

Conclusion
Patients seeking tattoo removal which was once done enthusiastically is increasing. Counselling about the permanent nature of tattoo and the significant cost involved in their removal may hinder the impulsive nature in few. Physicians should be aware about the different methods of tattooing, tattoo removal and complications associated with tattoos. Education about the tattoo regulations especially among those seeking to join the armed forces is important. The tattoo artists should also involve in counselling the patients, so potential side effects like regret and seeking removal immediately may be reduced.

Conflict of Interest Declaration
The authors have no conflict of interest to declare.

Acknowledgement
Nil

References
A Comparative Study of Licochalcone A Moisturiser versus Topical Hydrocortisone in Treating Mild-to-Moderate Atopic Dermatitis

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Abstract

Background
Topical corticosteroids are the mainstay of treatment for patients with atopic dermatitis. However, adverse effects associated with long-term steroid use often limit its use. This interventional study compared the efficacy of a proprietary moisturiser containing licochalcone A, omega-6 fatty acids, and ceramide 3 against 1% hydrocortisone cream in treating patients with mild-to-moderate atopic dermatitis.

Methods
Patients with mild-to-moderate atopic dermatitis affecting either the cubital fossa or popliteal fossa symmetrically were given twice-daily applications of the moisturiser and hydrocortisone on opposite sides of the body and monitored for a total of three weeks in a non-randomised half body, double-blind study. Hydrocortisone was switched to aqueous cream after two weeks, whereas the application of the moisturiser continued until study completion. The assessment of SCORing Atopic Dermatitis (SCORAD) index and Dermatology Life Quality index was performed at baseline and every subsequent follow-up visit to measure patients’ response to treatment.

Results
The licochalcone A (LA) moisturiser and 1% hydrocortisone (HC) cream both demonstrated significant reduction in sign and symptom scores after only 1 week of treatment (percentage of reduction in sign and symptom scores: 52.8% [LA] vs 58.5% [HC]). Further reduction in mean sign and symptom scores for both treatments was observed at week 2 (61.3% [LA] vs 56.8% [HC]) and also at week 3 when HC was switched to aqueous cream (70.5% [LA] vs 63.5% [HC→aqueous cream]) (p<0.001 vs baseline within the same treatment arm at weeks 1, 2 and 3). When comparing the mean difference in SCORAD index for both individual as well as total skin signs and symptoms between LA and HC (i.e. inter-arm comparison), there was no significant difference between the two treatments for all the assessed parameters. Patients reported improvements in itching, sleeplessness, and overall quality of life over the course of treatment.

Conclusion
The licochalcone A moisturiser can be considered as an effective steroid-sparing alternative to topical corticosteroids in managing mild-to-moderate atopic dermatitis.

Key words: Atopic dermatitis; Eczema; Emollient; Licochalcone A; Omega-6 fatty acids; Ceramide 3

Introduction
Atopic dermatitis (AD, also known as atopic eczema) is a chronic, recurring inflammatory skin condition. The prevalence of AD is most common in childhood with up to 90%
of children developing AD by the age of 5 years. Although most children achieve disease resolution by adulthood, 10–30% of patients do not, and a smaller percentage develop symptoms as adults. Classic signs and symptoms of AD include dry skin, itching, erythema, erosions, lichenification, oozing and crusting. As AD is often associated with elevated immunoglobulin E (IgE) levels, patients may also present with comorbid conditions related to IgE sensitisation such as asthma, allergic rhinitis, and food allergy. Therefore, AD imposes a substantial physical and psychological burden that can negatively impact the quality of life (QoL) of patients and their family.

The aetiology of AD remains unknown, but it has been postulated that the disease is caused by a complex interaction of genetic, immunological, and environmental factors that leads to altered epidermal barrier function. Potential triggering factors that can worsen AD include aeroallergen (e.g. dust, pollen, animal dander), physical irritants (e.g. soaps, detergents, disinfectants), food, as well as patient and environmental factors (e.g. stress, pollution, heat).

The management of AD relies on efficient control of flares by treating acute inflammatory symptoms and restoring skin barrier function. Currently, topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) are the mainstay of treatment for disease flares, along with the use of moisturisers to improve skin hydration, maintain barrier integrity, and prevent new flare-ups. Although TCS is associated with severe adverse effects (AEs) such as skin atrophy, telangiectasia and hypertrichosis, these AEs can be lessened when the duration and strength of TCS is used appropriately. However, TCS is often underutilised owing to patients and/or their carers’ steroid phobia, leading to poor treatment adherence and subsequent treatment failure.

The aforesaid drawbacks have thus driven the search for effective steroid-sparing agents that could be used in the treatment of AD. This study compared the efficacy of a moisturiser containing licochalcone A, omega-6 fatty acids and ceramide 3 against 1% hydrocortisone cream for the treatment of mild-to-moderate AD in a small population of Malaysian patients.

**Materials and Methods**

**Study design and patient population**

This three-week, non-randomised half body, double-blind, interventional study was initiated to compare the efficacy of a cortisone-, fragrance-, colourant- and paraben-free moisturiser containing licochalcone A, omega-6 fatty acids and ceramide 3 (LA; Eucerin® Acute Care Cream) against that of 1% hydrocortisone (HC) in the treatment of mild-to-moderate AD. The active ingredients in LA were 0.025% licochalcone A, 12% omega-6 fatty acids, 0.05% ceramide 3, and 10% glycerin, while HC contained 1% cortisol (acetate salt of hydrocortisone).

The study was carried out at the dermatology clinic of University Malaya Medical Centre (UMMC), Kuala Lumpur, Malaysia between November 2018 and March 2019. Thirty patients aged between 1 and 80 years, who were diagnosed with mild-to-moderate AD based on the United Kingdom working party diagnostic criteria and the modified Hanifin and Rajka criteria, and not on any systemic or topical treatment, were enrolled in the study; mild-to-moderate AD was defined by the SCOring Atopic Dermatitis (SCORAD) index score range of 1–50. To qualify for study enrolment, patients were also required to have symmetrical involvement of skin lesions on both flexural area of the body (left and right cubital or popliteal fossa). Patients with skin infection and known allergies to any ingredients of the study interventions were excluded.

On recruitment, patients were given two white containers labelled A and B. The content of containers A and B was applied, twice-daily, on affected areas of the right and left sides of patients’ bodies, respectively. The containers containing the topical agents were prepared and given to the patients by a doctor not involved in assessing the patients, while the post treatment
clinical outcome was assessed by a different dermatologist. Container A was filled with LA while container B was first filled with HC for two weeks, and then with a lipid-based topical formulation cream (AQ) for the remaining week of the study. The switch from HC to AQ was carried out to assess whether symptom control can be maintained by AQ (a non-active agent) once disease remission has been induced, without the knowledge of the patient and the investigators. Oral antihistamine, systemic steroid or immunosuppressant were not used by any of the patients during the study period. Patients were required to provide written consent and were free to withdraw from the study at any time.

**Study assessments**

Clinical outcome post treatment was documented by digital photography and assessed by a modified form of SCORAD. The intensity of the disease (i.e. erythema, oedema, excoriation, lichenification, oozing/crusting, and dryness) was assessed on the right and left sides of patients’ bodies and the corresponding scores were documented. Area of involvement and subjective symptoms were not included when assessing the right and left affected areas. Subjective symptoms, such as itch and sleeplessness, were assessed at each follow-up visit throughout the study duration (i.e. weeks 1, 2 and 3). QoL was assessed by Dermatology Life Quality Index (DLQI), a patient-rated questionnaire comprising 10 questions concerning patients’ perception of AD’s impact on different aspects of their health-related QoL. Adverse events were recorded.

**Statistical analysis**

Continuous variables were presented as mean (standard deviation), while categorical variables were presented as frequencies and percentages. Changes in the SCORAD index of LA- and HC-treated areas were analysed by paired t-test. A p-value of <0.05 was considered statistically significant.

**Ethics approval statement**

This study was approved by the Medical Research Ethics Committee of University Malaya Medical Centre (approval number: 42866; 16 June 2018) and was conducted according to the principles of the Declaration of Helsinki.

**Results**

**Patient characteristics**

A total of 30 patients were enrolled in the study, with 73.3% being younger than 12 years of age and 83.3% have had AD for less than 10 years (mean duration: 8.35\pm9.2 years). Many of these patients have a family history of atopic diseases, particularly asthma (30%) and AD (30%), as well as a personal history of asthma (30%) and food allergy (30%) (Table 1).

**Table 1. Patient demographics and characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>1–6 years</td>
<td>12 (40.0)</td>
</tr>
<tr>
<td>7–12 years</td>
<td>10 (33.3)</td>
</tr>
<tr>
<td>&gt;12 years</td>
<td>8 (26.7)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>19 (63.3)</td>
</tr>
<tr>
<td>Female</td>
<td>11 (36.7)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>Malay</td>
<td>21 (70.0)</td>
</tr>
<tr>
<td>Chinese</td>
<td>9 (30.0)</td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>12 (40.0)</td>
</tr>
<tr>
<td>Food allergy</td>
<td>3 (10.0)</td>
</tr>
<tr>
<td>Drug allergy</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>AD</td>
<td>9 (30.0)</td>
</tr>
<tr>
<td><strong>Medical history</strong></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>9 (30.0)</td>
</tr>
<tr>
<td>Food allergy</td>
<td>9 (30.0)</td>
</tr>
<tr>
<td>Drug allergy</td>
<td>1 (3.3)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>2 (6.7)</td>
</tr>
</tbody>
</table>

**Changes in signs and symptoms associated with AD**

Both LA and HC resulted in a progressive improvement of patients’ mean SCORAD index for total skin signs and symptoms at each follow-up. Compared with the baseline values within the same treatment arm, both treatments showed comparable reduction in mean sign and symptom scores after one week of treatment.
initiation (LA: 52.8% vs HC: 58.5% [percentage of reduction from baseline in mean SCORAD index]). At week 2, however, LA showed a greater reduction in mean sign and symptom scores compared with HC (LA: 61.3% vs HC: 56.8%), an observation that continued into week 3 of the study (LA: 70.5% vs HC→AQ: 63.5%). The mean differences between the baseline SCORAD index value and that calculated at subsequent follow-up visits were all significant (p<0.001 for both treatments) (Figure 1). Nonetheless, when comparing the mean difference in SCORAD index for total skin signs and symptoms between LA and HC (i.e. inter-arm comparison), there was no significant difference between the two treatments (LA vs HC at baseline, p=0.972; LA vs HC at week 1, p=0.669; LA vs HC at week 2, p=0.701; LA vs HC at week 3, p=0.442).

Additionally, when individual symptoms (i.e. erythema, oedema, crusting, excoriation, lichenification and dryness) were analysed separately, a comparison between LA and HC also showed no significant difference in SCORAD score reduction for all the assessed parameters (Figure 2). As such, LA was shown to be non-inferior to standard topical steroid therapy in resolving AD symptoms, especially skin erythema, oedema, crusting, excoriation, lichenification and dryness within the first week of treatment (Figure 3). Of note, one patient developed a flare-up of AD after the application of LA.

Figure 1. Mean SCORAD index for total skin signs and symptoms after three weeks of treatment with LA and HC

![Figure 1](image)

*Figure 2. Inter-arm comparison of disease intensity, as indicated by individual AD symptoms, after three weeks of treatment with LA and HC

![Figure 2](image)
Figure 3. Clinical response shown by patients with AD following treatment with AC and HC

Impervement in itching and sleeplessness
Patients reported reduced skin itching throughout the study for both treatments. LA afforded a greater mean score reduction throughout the study, with a mean difference...
of 2.04±1.53 at week 1, 2.48±2.12 at week 2, and 2.84±2.06 at week 3. Meanwhile, HC showed a mean score reduction of 1.96±1.79, 2.37±2.02, and 2.64±2.16 at weeks 1, 2, and 3, respectively (p<0.001 vs baseline for all data points). Additionally, both treatments showed reduced mean score for sleeplessness over a period of three weeks. The application of either LA or HC resulted in a mean score reduction of 1.96±1.97 at week 1, 2.62±1.52 at week 2, and 3.26±2.05 at week 3 (p<0.001 vs baseline for all data points).

Improvement in overall quality of life
At baseline, 60% of patients felt that AD had a very large effect on their QoL (mean score: 13.00±4.06). However, after three weeks of treatment with either LA or HC, only 12% of the study participants reported the same degree of disease impact (mean DLQI score: 6.44±5.86; mean difference: -6.64±5.86), with close to half of the study population expressing small to no effect at all (48%). DLQI mean scores and the improvement in QoL throughout the study duration are shown in Table 2 and Table 3, respectively.

Table 2. DLQI scoring of patients receiving either LA or HC over a period of 2 weeks

<table>
<thead>
<tr>
<th>DLQI</th>
<th>Baseline</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean score</td>
<td>13.00±4.06</td>
<td>8.74±5.16</td>
<td>7.00±4.48</td>
<td>6.44±5.86</td>
</tr>
<tr>
<td>Difference in mean score</td>
<td>-4.62±3.93</td>
<td>-6.00±4.67</td>
<td>-6.64±5.86</td>
<td></td>
</tr>
</tbody>
</table>

(p<0.001 vs baseline)

Table 3. Impact of AD on QoL as measured by DLQI

<table>
<thead>
<tr>
<th>Impact on QoL</th>
<th>Baseline</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No effect at all (0–1)</td>
<td>-</td>
<td>2 (7.4)</td>
<td>4 (14.3)</td>
<td>6 (24.0)</td>
</tr>
<tr>
<td>Small effect (2–5)</td>
<td>-</td>
<td>6 (22.2)</td>
<td>8 (28.6)</td>
<td>6 (24.0)</td>
</tr>
<tr>
<td>Moderate effect (6–10)</td>
<td>10 (33.3)</td>
<td>7 (25.9)</td>
<td>8 (28.6)</td>
<td>9 (36.0)</td>
</tr>
<tr>
<td>Very large effect (11–20)</td>
<td>19 (63.3)</td>
<td>12 (40.0)</td>
<td>8 (29.6)</td>
<td>3 (12.0)</td>
</tr>
<tr>
<td>Extremely large effect (21–30)</td>
<td>1 (3.3)</td>
<td>-</td>
<td>-</td>
<td>1 (4.0)</td>
</tr>
</tbody>
</table>

Discussion
Patients in this study were mostly children of Malay ethnicity with atopic background and a family history of atopic disease, which matched the patient demographic of another cross-sectional study that reported the prevalence and management of AD in Malaysian children. Incidentally, the same study also revealed that parents generally preferred TCS, specifically hydrocortisone, over nonprescription drugs in AD management. TCS and TCI, along with moisturisers, are the mainstay of treatment for AD in patients requiring pharmacological intervention. However, the side effects associated with the persistent use of corticosteroids limit its use. These risks, although mostly unfounded, have spurred efforts to seek alternative steroid-sparing anti-inflammatory topical agents for the management of AD.

This study demonstrated that the topical application of LA, a moisturiser containing licochalcone A, omega-6 fatty acids and ceramide 3, was an effective and safe therapy that is non-inferior to standard topical steroid therapy for the treatment of mild-to-moderate AD. These results were consistent with previous studies that demonstrated the efficacy of licochalcone A-based moisturisers, compared with 1% HC creams, in improving the clinical manifestations of AD.

Licohalcone A is a flavonoid extracted from the Chinese liquorice root, Glycyrrhiza inflata. In vitro studies showed that licochalcone-A extracts exhibited potent antibacterial, anti-inflammatory, and immunomodulatory activities. Clinical studies have also confirmed the efficacy of licochalcone A-containing formulation in reducing erythema and skin irritations (i.e. dryness, itching, and burning sensation). Additionally, LA also contains ceramide which improves skin barrier function and prevents transepidermal water loss in patients with AD. Taken together, the findings from this study provide new evidence to support the efficacy of licochalcone A as an anti-inflammatory agent in the management of mild-to-moderate AD.

Itching is a major criterion of AD and is often worse at night, leading to a persistent itch-scratch cycle that can affect sleep and QoL.
considerable impact of sleep insufficiency on mood, health, and development (particularly in growing children), achieving lasting itch relief with minimal treatment-related side effects is an important goal in the management of AD.\textsuperscript{22,23} The management of AD with either LA or HC can lead to considerable improvement in patients’ overall QoL, as shown by the gradual reduction in mean DLQI scores throughout the study period.

**Strengths and limitations**

In this study, the side-by-side comparison of treatment efficacy in the same patient reduces the risk of potential errors that could be attributed to individual treatment response differences. However, we acknowledge that this study has a relatively small sample size and a short study period.

**Conclusion**

This study demonstrated that a proprietary moisturiser containing licochalcone A, omega-6 fatty acids and ceramide 3 as its active ingredients was non-inferior to 1% hydrocortisone cream in resolving symptoms associated with acute AD. Therefore, it may serve as a valuable steroid-sparing therapeutic alternative in the treatment of AD.

**Conflict of Interest Declaration**

The authors declare no conflict of interest.

**Acknowledgement**

Medical writing assistance was provided by MIMS Medica Sdn Bhd, and complied with Good Publication Practice 3 ethical guidelines (Battisti et al. *Ann Intern Med.* 2015; 163: 461–4). Medical writing assistance for this article has been funded by Beiersdorf (Malaysia) Sdn Bhd.

**References**

ORIGINAL ARTICLE

The Clinical Characteristics of Inpatients: An Audit in the Department of Dermatology Hospital Kuala Lumpur Between 2016 and 2020

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Department of Dermatology, Hospital Kuala Lumpur

Abstract

Background

Although Dermatology is primarily a non-acute, outpatient-centered clinical specialty, some of them require in-patient care for intensive skin management. We aim to describe the demographic data, clinical characteristics, and outcomes of Dermatology inpatients in Hospital Kuala Lumpur (HKL).

Methods

This is a retrospective study on all dermatology inpatients in HKL between 2016 and 2020. Data was obtained from admission records and further analyzed.

Results

A total of 1567 patients were admitted to the Dermatology ward between 2016 and 2020 accounted for 2292 admissions. The mean age was 45 years (range 8-93). The male to female ratio was 1.16:1. The majority were Malaysian (99.2%). Most Malaysian were Malays (60%) followed by Chinese (19.3%) and Indian (17.1%). About 91% of the admissions were arranged from the dermatology clinic. The mean length of stay was 5.06 days (range 0-63). About 20% of the patients required multiple admissions. The main dermatological diagnosis requiring inpatient care were non-infective dermatoses (60.4%) which included eczematous dermatoses, autoimmune dermatoses, psoriasis, cutaneous adverse drug reactions, inflammatory and non-inflammatory dermatoses. This was followed by cutaneous infections (24.5%) and drug allergy testing & drug provocation tests (7.9%). About 3% of patients were transferred to other departments for further intensive management, and the rest were discharged home well. No mortality occurred in the Dermatology ward.

Conclusion

The Dermatology ward HKL managed 2292 admissions between 2016 and 2020. The three main dermatological diagnoses requiring intensive skin management were eczematous conditions, cutaneous infections, and autoimmune dermatoses.

Key words: Dermatology, Inpatients, Eczema, Cutaneous infection, Autoimmune dermatoses

Introduction

Skin is the outermost part of the human body and is subject to a spectrum of skin disorders. Despite being the largest organ, dermatology is primarily a non-acute, outpatient-centered clinical specialty. However substantial number of patients still require in-patient care for intensive skin management, advanced nursing care and multispecialty referral. Hospitalization improved patients’ dermatologic disorders and
their quality of life. The Massachusetts General Hospital was the first hospital to develop its first dermatology ward in the United States in 1870. This initiative has led to the development of inpatient services at many academic institutions. To date, inpatient dermatology is available in the United States (US), the United Kingdom (UK), Brazil, South Africa, Eastern India.

With the progression and advancement of therapy, the number of patients requiring inpatient treatment has reduced. In the US and UK, many Dermatology programs have reduced or abolished inpatient services, whereby patients admitted with dermatological conditions are managed by non-dermatologists. Psoriasis, cutaneous drug reactions, immunobullous dermatoses, infected ulcers and skin infections remains the main cause of hospitalization worldwide. In Malaysia, only Hospital Kuala Lumpur and Hospital Raja Permaisuri Bainun in Ipoh provide inpatient dermatology services with their designated dermatology wards at present. Being the largest hospital in Malaysia, the Department of Dermatology Hospital Kuala Lumpur (HKL) is a tertiary referral center for patients with complex dermatological disorders and sexually transmitted infections. The dermatology ward, situated at level 1 of the Administration and Financial Block (Bangunan Pentadbiran dan Kewangan) of Hospital Kuala Lumpur, has a maximum capacity of 32 beds. All patients admitted to the ward were seen by consultant dermatologists and dermatology trainees daily.

This study aims to describe the demographic data, clinical characteristics and outcome of Dermatology inpatients in Hospital Kuala Lumpur between 2016 and 2020.

Materials and Methods
This is a retrospective study on all dermatology inpatients in HKL between 2016 and 2020. The ward admission record books were retrieved and reviewed. All patients admitted to the Dermatology ward were included into statistical analysis. Data collected included demographics, source of admission, types of dermatoses, number of admissions, length of stays and their outcomes. Both quantitative and qualitative data were examined using Microsoft Excel and further analysed through statistical approach.

Results
There was a total of 1567 patients admitted to the Dermatology ward in Hospital Kuala Lumpur during the study period, involving 2292 admissions and 2661 diagnoses were made with an average of 458 admissions per year between 2016 and 2020. Although dermatology ward has a maximum capacity of 32 beds, the bed occupancy by patients with pure dermatological diseases were intermittently affected by temporary lodging of patients from other specialities during the study period of 2016 to 2020. These includes patients from the Department of Urology and others due to temporary closure of the respective wards for renovation and upgrading works. In addition, the strike of pandemic COVID-19 has led to a massive increase of in-patient demand for COVID-19 in Hospital Kuala Lumpur. As a result, the bed number catered purely for dermatological diseases has reduced to a maximum 10 beds since March 2020 to date. The demographic characteristics of in-patients with pure dermatological diseases are illustrated in Table 1. The youngest patient admitted to the Dermatology ward was 8 years old and the oldest was 93 years old. The mean age was 45 years with a male to female ratio of 1.16:1. Nearly half of the patients (49.4%) were aged between 20-49 years old, and about a third of them (31.3%) were between 50-69 years.

Among the Malaysian inpatients, the Malays contributed to 60.1%, followed by Chinese 19.3%, Indians 17.1% and others, 1.7%. Forty (1.7%) patients were foreigners, most of them were Indonesians, 23 (1.0%). The majority of patients admitted were male, 1232 (53.8%). Most patients (90.7%) were admitted from the dermatology clinic and 143 (6.2%) were transferred from the department of medicine or other hospitals to the dermatology ward. Only 3.1% of patients were admitted from
the Department of Accident and Emergency. About 19.4% of the patients required multiple admissions, of which 11 (0.7%) of them had more than 10 admissions. The average length of stay was 5.06±4.95 days with the longest stay of 63 days. About 4.3% required an inpatient stay of more than 2 weeks.

Table 1. The demographic data of 1567 patients admitted to Dermatology ward Hospital Kuala Lumpur between 2016 and 2020

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n=1567 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>45.04±18.79</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1232 (53.8)</td>
</tr>
<tr>
<td>Female</td>
<td>1060 (46.2)</td>
</tr>
<tr>
<td>Mean length of stay (days)</td>
<td>5.06±4.95</td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td></td>
</tr>
<tr>
<td>0-7</td>
<td>1903 (83.0)</td>
</tr>
<tr>
<td>8-14</td>
<td>284 (12.4)</td>
</tr>
<tr>
<td>15-21</td>
<td>63 (2.7)</td>
</tr>
<tr>
<td>22-28</td>
<td>18 (0.8)</td>
</tr>
<tr>
<td>More than 28 days</td>
<td>18 (0.8)</td>
</tr>
<tr>
<td>No recurrent admission</td>
<td>1263 (80.6)</td>
</tr>
<tr>
<td>Recurrent admission (No)</td>
<td></td>
</tr>
<tr>
<td>2 to 5</td>
<td>271 (17.3)</td>
</tr>
<tr>
<td>6 to 10</td>
<td>22 (1.4)</td>
</tr>
<tr>
<td>11 to 15</td>
<td>5 (0.3)</td>
</tr>
<tr>
<td>16 to 20</td>
<td>6 (0.4)</td>
</tr>
<tr>
<td>Number of admissions per year</td>
<td></td>
</tr>
<tr>
<td>2016</td>
<td>483 (21.1)</td>
</tr>
<tr>
<td>2017</td>
<td>482 (21.0)</td>
</tr>
<tr>
<td>2018</td>
<td>437 (19.1)</td>
</tr>
<tr>
<td>2019</td>
<td>494 (21.6)</td>
</tr>
<tr>
<td>2020</td>
<td>396 (17.3)</td>
</tr>
<tr>
<td>Malaysian - Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Malay</td>
<td>1377 (60.1)</td>
</tr>
<tr>
<td>Chinese</td>
<td>443 (19.3)</td>
</tr>
<tr>
<td>Indian</td>
<td>392 (17.1)</td>
</tr>
<tr>
<td>Others</td>
<td>40 (1.7)</td>
</tr>
<tr>
<td>Source of admission</td>
<td>Dermatology clinic 2079 (90.7)</td>
</tr>
<tr>
<td></td>
<td>Department of Medicine 121 (5.28)</td>
</tr>
<tr>
<td></td>
<td>Accident &amp; Emergency 70 (3.1)</td>
</tr>
<tr>
<td></td>
<td>Other hospitals 10 (0.43)</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
</tr>
<tr>
<td>Discharge home</td>
<td>2229 (97.3)</td>
</tr>
<tr>
<td>Transfer of care</td>
<td>63 (2.7)</td>
</tr>
</tbody>
</table>

As shown in Table 2, the main dermatological diagnosis requiring inpatient care were non-infective dermatoses (60.4%) followed by infective dermatoses (24.5%), drug allergy testing and drug provocation tests (7.9%) and cutaneous malignancy (1.1%). A hundred and sixty-five (6.1%) patients had other non-dermatological diagnoses. Eczematous dermatoses were the most frequent non-infective conditions that required admission in our cohort. These included severe atopic dermatitis, severe contact dermatitis, infected discoid eczema, idiopathic photodermatitis etc. The main autoimmune dermatoses managed in dermatology ward HKL was pemphigus followed by cutaneous vasculitis. Psoriasis, cutaneous adverse drug reactions, other inflammatory and non-inflammatory dermatoses were other non-infective dermatoses that were managed in the ward. The type of psoriasis that required hospitalization included extensive plaque psoriasis, erythrodermic psoriasis, generalized or severe localized pustular psoriasis and severe acute psoriatic arthropathy. There was a total of twenty-nine patients admitted for management of cutaneous malignancies, with the majority being mycosis fungoides, followed by extramammary Paget’s disease.

A hundred and thirty patients were admitted for cutaneous adverse drug reactions, of which almost half (51 patients) were due to drug-induced epidermal necrolysis namely Steven Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), as shown in Table 3. This was followed by eighteen patients with acute generalized exanthematous pustulosis (AGEP), fourteen with drug rash with eosinophilia and systemic symptoms (DRESS) and seven with fixed drug eruptions (FDE).

Infective dermatoses accounted for nearly a quarter of the total admissions, with more than half of them being bacterial infection 378 (57.8%) as shown in Table 4. This was followed by fungal infections 113 (17.3%) and viral infection 105 (16.1%). About 8% of patients were electively admitted for drug allergy skin tests and drug provocation test.
Most patients 2229 (97.3%) were discharged home after treatment and 63 (2.7%) were transferred to other units for further management. There was no mortality occurred in the dermatology ward for the past 5 years.

**Table 2.** The Main types of dermatoses leading to admission to Dermatology ward Hospital Kuala Lumpur between 2016-2020

<table>
<thead>
<tr>
<th>Clinical diagnosis</th>
<th>n=2661 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non infective dermatoses</td>
<td>1608 (60.4)</td>
</tr>
<tr>
<td>Eczematous dermatoses</td>
<td>687 (42.7)</td>
</tr>
<tr>
<td>Autoimmune dermatoses</td>
<td>478 (29.7)</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>215 (13.4)</td>
</tr>
<tr>
<td>Cutaneous adverse drug reactions</td>
<td>130 (8.1)</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>86 (5.3)</td>
</tr>
<tr>
<td>Non inflammatory</td>
<td>12 (0.7)</td>
</tr>
<tr>
<td>Cutaneous infections</td>
<td>654 (24.5)</td>
</tr>
<tr>
<td>Bacterial infection</td>
<td>378 (57.8)</td>
</tr>
<tr>
<td>Fungal</td>
<td>113 (17.3)</td>
</tr>
<tr>
<td>Viral</td>
<td>105 (16.1)</td>
</tr>
<tr>
<td>Mycobacterium</td>
<td>35 (5.4)</td>
</tr>
<tr>
<td>Parasites</td>
<td>23 (3.5)</td>
</tr>
<tr>
<td>Drug allergy testing and drug provocation tests</td>
<td>209 (7.9)</td>
</tr>
<tr>
<td>Cutaneous malignancy</td>
<td>29 (1.1)</td>
</tr>
<tr>
<td>Mycosis Fungoides</td>
<td>22</td>
</tr>
<tr>
<td>Extramammary Paget's Disease</td>
<td>4</td>
</tr>
<tr>
<td>Anaplastic Large Cell Lymphoma</td>
<td>1</td>
</tr>
<tr>
<td>Gorlin Syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Sezary Syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Other non dermatological diagnosis</td>
<td>161 (6.0)</td>
</tr>
</tbody>
</table>

**Table 3.** The detailed diagnosis of Non-Infective dermatoses that were managed in Dermatology ward Hospital Kuala Lumpur between 2016-2020

<table>
<thead>
<tr>
<th>Type</th>
<th>n=1608</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eczematous dermatoses</td>
<td>687</td>
</tr>
<tr>
<td>Eczema – non erythrodermic</td>
<td>277</td>
</tr>
<tr>
<td>Erythrodermic eczema</td>
<td>204</td>
</tr>
<tr>
<td>Contact dermatitis</td>
<td>133</td>
</tr>
<tr>
<td>Photodermatitis</td>
<td>36</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>18</td>
</tr>
<tr>
<td>Seborrhoeic dermatitis, radiation recall dermatitis, pompholyx, nodular prurigo, lichen simplex chronicus etc</td>
<td>19</td>
</tr>
</tbody>
</table>
Table 4. The detailed diagnosis of Infective dermatoses that were managed in Dermatology ward Hospital Kuala Lumpur between 2016-2020

<table>
<thead>
<tr>
<th>Type of infective dermatoses</th>
<th>n=654</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial infections</td>
<td></td>
</tr>
<tr>
<td>Cellulitis</td>
<td>215</td>
</tr>
<tr>
<td>Infected ulcer</td>
<td>62</td>
</tr>
<tr>
<td>Infected stasis eczema</td>
<td>41</td>
</tr>
<tr>
<td>Abscess</td>
<td>12</td>
</tr>
<tr>
<td>Infected lymphostasis verrucosa cutis</td>
<td>9</td>
</tr>
<tr>
<td>Ecthyma</td>
<td>7</td>
</tr>
<tr>
<td>Furunculosis</td>
<td>5</td>
</tr>
<tr>
<td>Folliculitis</td>
<td>4</td>
</tr>
<tr>
<td>Impetigo</td>
<td>3</td>
</tr>
<tr>
<td>Infected Biopsy Wound</td>
<td>3</td>
</tr>
<tr>
<td>Infected Wound</td>
<td>3</td>
</tr>
<tr>
<td>Syphilis</td>
<td>2</td>
</tr>
<tr>
<td>Thrombophlebitis</td>
<td>2</td>
</tr>
<tr>
<td>Infected pressure sore</td>
<td>2</td>
</tr>
<tr>
<td>Others (actinomycosis, bullous impetigo, paronychia, gangrene, infected bursitis, genital ulcer, gonorrhoea, erysipelas)</td>
<td>8</td>
</tr>
<tr>
<td>Fungal infections</td>
<td>113</td>
</tr>
<tr>
<td>Intertrigo</td>
<td>41</td>
</tr>
<tr>
<td>Tinea</td>
<td>36</td>
</tr>
<tr>
<td>Onychomycosis</td>
<td>17</td>
</tr>
<tr>
<td>Candidiasis</td>
<td>12</td>
</tr>
<tr>
<td>Sporotrichosis</td>
<td>3</td>
</tr>
<tr>
<td>Chromoblastomycosis</td>
<td>2</td>
</tr>
<tr>
<td>Pityriasis versicolor</td>
<td>1</td>
</tr>
<tr>
<td>Eumycetoma</td>
<td>1</td>
</tr>
<tr>
<td>Viral infections</td>
<td>105</td>
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<tr>
<td>Eczema herpeticum</td>
<td>30</td>
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<tr>
<td>Herpes Zoster</td>
<td>29</td>
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<tr>
<td>Genital herpes</td>
<td>27</td>
</tr>
<tr>
<td>Herpes Simplex</td>
<td>11</td>
</tr>
<tr>
<td>Viral Wart</td>
<td>4</td>
</tr>
<tr>
<td>Varicella zoster</td>
<td>1</td>
</tr>
<tr>
<td>Hand Foot Mouth Disease</td>
<td>1</td>
</tr>
<tr>
<td>Viral Exanthem</td>
<td>2</td>
</tr>
<tr>
<td>Mycobacterium infections</td>
<td>35</td>
</tr>
<tr>
<td>Leprosy</td>
<td>32</td>
</tr>
<tr>
<td>Mycobacterium other than tuberculosis</td>
<td>2</td>
</tr>
<tr>
<td>Cutaneous tuberculosis</td>
<td>1</td>
</tr>
<tr>
<td>Parasite infections</td>
<td>23</td>
</tr>
<tr>
<td>Scabies</td>
<td>21</td>
</tr>
<tr>
<td>Head Lice</td>
<td>1</td>
</tr>
<tr>
<td>Elephantias</td>
<td>1</td>
</tr>
</tbody>
</table>

Discussion

In-patient care is crucial for a small cohort of patients with severe and extensive skin diseases when topical treatment is complicated. Inpatient admission allows regular clinical and laboratory monitoring, parenteral therapies, advanced nursing care and multispecialty referrals. These include those with blistering diseases (e.g., toxic epidermal necrolysis/ Stevens-Johnson Syndrome, pemphigus, bullous pemphigoid), those who are frail and disabled as well as those with systemic involvement (e.g., connective tissue diseases, drug reaction eosinophilia with systemic symptoms, cutaneous vasculitis) who require close monitoring.

Patients who are ill with their underlying dermatosis complicated with a secondary infection will require intravenous antibiotics, pain management, intravenous fluids and nutritional support which is suboptimal when managed in an outpatient setting. Intensive topical treatment and education in the ward will help to improve the disease severity. Educational sessions including strategies to raise patient motivation are vital to maintaining improvement as shown by Masson Regnault et al. In addition, drug allergy testing and drug provocation test which are laborious and time consuming could be performed comfortably in the dermatology ward in regions where allergy is a sub-specialty of interest under dermatology. If these patients do not develop systemic reactions during the tests, they could be discharged after close observation for 6-8 hours in the ward. Otherwise, observation could be extended overnight if reactions occurred during the tests.

Understanding the incidence of skin diseases is fundamental in making decisions regarding allocating resources for clinical care and research, especially with the introduction of the Malaysian Diagnosis Related Group (Malaysian DRG) in the Strategic Framework of the Medical Programme by the Ministry of Health (MOH) for the year 2021-2025. Population-based studies are essential in this respect as an important platform to prepare healthcare system towards evidence-based budget allocation system. Our inpatient services encompass medical Dermatology only at present, not aesthetic or dermato-surgery. Our
study has a male to female ratio of 1.16:1 which is similar to that of Sen et al\textsuperscript{2} in Eastern India and Garcia-Doval et al\textsuperscript{9} in Spain, in contrast to that of Bertanha et al\textsuperscript{1} in Brazil, which has a lower male to female ratio, 1:1.72. Like Sen et al\textsuperscript{2} and Bertanha et al\textsuperscript{1}, the mean age in our study of 45.04±18.79, which is much younger than that of García-Doval et al\textsuperscript{9} and Krisner et al\textsuperscript{10} in the United States. This could be explained by the pattern of dermatoses that contributed to the hospitalization. The prevalence of cutaneous malignancies is more prevalent with advanced age. The inpatient dermatology unit in García-Doval et al\textsuperscript{9} and Krisner et al\textsuperscript{10} comprises of dermato-surgery, photochemotherapy and skin grafting which cater more to cutaneous malignancy. Specialized dermatology-related procedures like photopheresis, total skin electron beam therapy, Mohs micrographic surgery, skin grafting surgeries, etc are yet to be expanded in our setting.

Like other studies shown in Table 5, the main reasons for hospitalization in our cohort were non-infective dermatoses followed by infective dermatoses. Eczematous dermatosis was the most common indication of admission. This was similar to that in Brazil, Australia and South Africa wherein eczema or dermatitis accounted for 17.5-46.6\% of the dermatology in-patient care. This is in contrast with García-Doval et al\textsuperscript{9} where 36\% of inpatients were surgical dermatology cases. Inpatient management of atopic dermatitis is effective in improving disease severity and should be considered an important treatment option for patients with severe atopic dermatitis.\textsuperscript{7} Only about 1\% of our patients were admitted for cutaneous malignancy, far lower than the Spain\textsuperscript{9} and Brazil\textsuperscript{1} data. Most of the advanced cutaneous malignancies in HKL were managed at the Department of Plastic and Reconstruction as well as the Department of Oncology.

Infective dermatoses was the second most common dermatoses in our cohort. This is consistent with other studies i.e. Sen et al\textsuperscript{2} in India, Garcia-Doval et al\textsuperscript{9} in Spain, Krisner et al\textsuperscript{11} in the US. Drug-induced dermatosis is the second most common cause of admissions after eczematous dermatosis and papulosquamous disease for Jessop et al\textsuperscript{11} in South Africa and García-Doval et al\textsuperscript{9} in Spain.

Our cohort has the shortest length of stay of 4.82±4.60 compared to other cohorts. Most patients experienced short-term benefits from inpatient care and were discharged well. The in-patient care services in medical dermatology i.e. the setting up of a designated dermatology ward could be expanded to other dermatology centers in Malaysia.

The limitation of our study was stemmed from the nature of the data source. We could not assess the complexity of each admission as well as the determining factors of the length of stay. Our patients may have suboptimal control of co-morbidities or develop complications from the treatment which resulted in a prolonged stay in the ward. The treatment modalities and procedures done during admission were also not captured from the admission book. Future audits on Dermatology inpatients should focus on the aspects mentioned above as well as the cost of inpatient Dermatology care.

Conclusion
The Dermatology ward HKL managed 2292 admissions between 2016 and 2020. The three main dermatological diagnoses requiring intensive skin management were eczematous conditions, cutaneous infections and autoimmune blistering diseases. Standalone dermatology inpatient services may be expanded to other Department of Dermatology of major public hospitals in Malaysia.

Conflict of Interest Declaration
The authors have no conflict of interest to declare.

Acknowledgment
We would like to thank the Director General of Health Malaysia for the permission to publish this article.
### References


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### Table 5. Comparison of international data on Dermatology In-patient

<table>
<thead>
<tr>
<th>Study, year, Country</th>
<th>No of patients</th>
<th>M:F ratio</th>
<th>Mean age (years)</th>
<th>Diagnosis requiring admission</th>
<th>Average length of stay (days)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current study, Malaysia</td>
<td>1567</td>
<td>1.16:1</td>
<td>45.04±18.79</td>
<td>Eczematous dermatoses 35.8%, autoimmune dermatoses 18.0%, psoriasis 8.1%, bacterial infection 14.2%, drug induced dermatoses 4.8%, fungal infection 4.1%, viral infection 3.9%, malignancy 1.2%</td>
<td>4.82±4.60</td>
<td>Discharged 97.3% Transfer of care (2.7%)</td>
</tr>
<tr>
<td>Sen et al 2016 Eastern India</td>
<td>375</td>
<td>1.66:1</td>
<td>45.5±2</td>
<td>Immunobullous disorders 24.3%; Erythroderma/ Dermatitis 26.7%; infective disorders 19.5%; drug reaction 10.7%; CTD 3.2%; Malignancy 0.53%</td>
<td>22.16±15.73</td>
<td>Discharged 83.2% Transferred of care 2.13%</td>
</tr>
<tr>
<td>de Paula Samorano-Lima et al 2014, Brazil</td>
<td>3308</td>
<td>1:1.14</td>
<td>42.8±23.6</td>
<td>Eczema/dermatitis (17.5%), cutaneous infections (15.9%), immunobullous diseases (11.0%), connective tissue diseases (9.6%), psoriasis (9.2%).</td>
<td>13</td>
<td>3.7% transferred to ICU, 2.5% died</td>
</tr>
<tr>
<td>Bale et al 2014, Australia</td>
<td>97</td>
<td>1.27:1</td>
<td>42</td>
<td>Dermatitis or eczema (37%), ulcers (12%)</td>
<td>10</td>
<td>N/A</td>
</tr>
<tr>
<td>Bertanha et al 2016 Brazil</td>
<td>16,399</td>
<td>1:1.72</td>
<td>43.9±22.1</td>
<td>Eczematous dermatoses 18.1%; cutaneous infection 13.1%; erythematous squamous dermatosis 6.9%; malignancy 6.1%</td>
<td>N/A</td>
<td>No mortality</td>
</tr>
<tr>
<td>García-Doval et al 2002 Spain</td>
<td>1048</td>
<td>1.05:1</td>
<td>66</td>
<td>Neoplasms 36%; infection 15%; psoriasis 10%; dermatitis 6%; drug reaction 5%</td>
<td>7(5-10)</td>
<td>0.76% mortality</td>
</tr>
<tr>
<td>Jessop S et al 2002 South Africa</td>
<td>133</td>
<td>N/A</td>
<td>34.1</td>
<td>Atopic dermatitis 33.1%; Other forms of dermatitis 13.5%; Psoriasis 15.8%; Severe drug reactions 7.5%; Leg ulcer 5.3%; Skin infection 5.3%; Bullous disease 4.5%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Kirsner et al 2000 US</td>
<td>345</td>
<td>NA</td>
<td>60.7</td>
<td>Psoriasis (25%), chronic wounds (23%), dermatitis (11%), infections or infestations (10%), connective tissue diseases (9%), Immunobullous diseases (7%), drug reaction (3%)</td>
<td>6.1±0.2</td>
<td>N/A</td>
</tr>
</tbody>
</table>
ORIGINAL ARTICLE

The Effect of Narrowband Ultraviolet B Phototherapy on Vitamin D Status in Psoriasis Patients with Skin Phototype III, IV and V

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²Dermatology unit, Department of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Wilayah Persekutuan Kuala Lumpur, Malaysia

Abstract

Background
Narrowband ultraviolet-B (NBUVB) is an effective treatment option for psoriasis. Vitamin D insufficiency is common in psoriasis patients. We assessed the effect of NBUVB on vitamin D levels amongst psoriasis patients with skin phototype III, IV and V.

Methods
Psoriasis patients planned for NBUVB phototherapy were enrolled in a prospective cohort study in Hospital Putrajaya and Hospital Kuala Lumpur from May 2020-December 2020. NBUVB phototherapy was given twice weekly for 12 weeks. Serum 25 (OH)D level was measured at baseline and at week 12.

Results
A total of 21(63.6%) male and 12(36.4%) female patients aged 18-66 years participated. Majority were Fitzpatrick skin phototype (FSP) IV (66.7%) followed by FSP V (21.2%) and FSP III (12.1%). Serum 25(OH)D increased significantly (p<0.001) from 52.09±21.43 nmol/L at baseline to 72.80±19.56 nmol/L at week 12 with the most increment seen in skin type V. There was also a significant improvement seen in Body Surface Area (BSA) involvement after 12 weeks of phototherapy (p<0.001). There was no correlation seen between BSA at week 12 with serum 25(OH)D and percentage of serum 25(OH) D increment.

Conclusion
NBUVB phototherapy increases the level of serum 25(OH)D in psoriasis patients with darker skin types while simultaneously clearing psoriasis.

Key words: 25-hydroxyvitamin D; Fitzpatrick skin phototype; Psoriasis; Narrowband Ultraviolet-B; Phototherapy

Introduction
Psoriasis is an immune-mediated inflammatory skin disease which occurs worldwide and is estimated to affect around 2.0% to 3.0% of the world’s population.¹² Epidemiological evidence demonstrated variable prevalence of psoriasis amongst different ethnic groups and population.³ The Malaysian Psoriasis Registry recorded a total of 21,735 psoriasis patients aged ≥18 years.
from January 2007 through December 2018.\textsuperscript{4}

Narrowband ultraviolet-B (NBUVB) phototherapy is an effective and safe treatment for psoriasis. NBUVB reverses several pathologic alterations in psoriasis which ultimately causes reduction in T-lymphocytes and dendritic cells.\textsuperscript{5} Inhibition of maturation, differentiation and migration of dendritic cells are caused by activation of vitamin D. The epidermis plays an important role in vitamin D synthesis but is also a target tissue for activated vitamin D and its analogues. The active form of vitamin D, 1,25 dihydroxyvitamin D [1,25(OH)₂D] produced by hydroxylation in the liver and kidney suppresses growth and induces differentiation of keratinocytes, thus reducing psoriasis severity. The radiation wavelength of NBUVB (from 311 to 313 nm), lies within the action spectrum responsible for cutaneous vitamin D₃ production.\textsuperscript{5} Psoriatic lesions respond well to narrowband ultraviolet B phototherapy.\textsuperscript{6} NBUVB positively affects vitamin D status\textsuperscript{7,8,9,10} and this could partly account for the beneficial effect of phototherapy in psoriasis.

Skin phototype determines response to UVB radiation, with a greater rate of vitamin D₃ synthesis in lighter skin tones as melanin absorbs UVB irradiation.\textsuperscript{11} Therefore, people with naturally darker skin are at greater risk of vitamin D deficiency. Increase in serum vitamin D₃ levels as well as improvement in Psoriasis Area and Severity Index (PASI) have been demonstrated after NBUVB therapy.\textsuperscript{8,9,10}

Our study was conducted to assess the effect of NBUVB on vitamin D levels amongst psoriasis patients of darker skin types (Fitzpatrick skin phototype III, IV or V), its association with improvement in body surface area (BSA) affected by psoriasis as well as the correlation between cumulative NBUVB dose and the improvement in serum 25(OH)D.

Materials and Methods
An observational cohort study was performed. The study population was psoriasis patients planned for NBUVB phototherapy at the Dermatology Clinics of Hospital Putrajaya and Hospital Kuala Lumpur who fulfilled the inclusion and exclusion criteria during the study period from May 2020 to December 2020. Inclusion criterion was psoriasis patients aged 18 and above with Fitzpatrick skin phototype III, IV or V. Patients with renal or hepatic disease, previous skin malignancy, on vitamin D or calcium supplements were excluded. Psoriasis severity was defined by percentage of BSA affected by psoriasis based on the Malaysian Clinical Practice Guideline for the Management of Psoriasis Vulgaris; mild ≤10%, moderate >10%-30% and severe >30%.\textsuperscript{12}

Serum 25(OH)D was measured at baseline prior to NBUVB therapy and after 12 weeks of therapy. NBUVB was delivered using either Daavlin 3 Series or MEDLight N-LINEpro cabins. Irradiation protocol was based on the patient’s skin type. The irradiation dose started at 0.3J/cm\textsuperscript{2} and was increased by 20% on each subsequent visit till just perceptible erythema appeared on uninvolved skin. If symptomatic erythema (burning, pain) developed, phototherapy was stopped till the erythema settled. On restarting therapy, the irradiation dose was decreased by 20%. The dose delivered for each session was documented in a standard form. Phototherapy was given twice weekly on non-consecutive days for 12 weeks. Each phototherapy session was approximately between 10 to 15 minutes. The genitals were shielded and eyes were protected with UV safety glasses. If any patient had a gap in his/her phototherapy session of more than a week, the date for serum 25 (OH)D was postponed appropriately.

Serum 25(OH)D levels were obtained using UniCelDxI 800 Access Immunoassay System which is a chemiluminescent based automated analyser, that accurately and precisely measures 25(OH)D. Levels of 25-OH vitamin D3 were graded as: deficient <25 nmol/L, insufficient 25–74 nmol/L, and normal 75–250 nmol/L.\textsuperscript{13} Sample size estimation was calculated using two population means formulae.\textsuperscript{14} Mean
difference in vitamin D levels pre and post NBUVB phototherapy was based on the results of Ryan et al.\textsuperscript{9} Serum vitamin D prior to NBUVB therapy was 23±37 nmol/L, the level post treatment increased to 59± 80.0 nmol/L. A minimum sample size of 30 was needed to be able to reject the null hypothesis with probability (power) 0.8 and 10% drop out rate. The Type I error probability in rejecting the null hypothesis is 0.05. Data analysis was performed using IBM SPSS Statistics for Windows Version 22.0.

Comparison of the differences between two sets of normally distributed numerical data was analysed using paired t-test, while the Wilcoxon SignedRank test was used if the data was not normally distributed. Pearson or Spearman rank correlations, where appropriate, were calculated. All probability values are two-sided, and a level of significance of less than 0.05 (\textit{p-value} < 0.05) was considered as statistically significant.

This study was conducted in compliance with ethical principles outlined in the Declaration of Helsinki and Malaysian Good Clinical Practice Guidelines. Data collection was commenced after obtaining Medical Research and Ethics Committee approval (Approval Ref : KKM/NIHSEC/P20-798(12).

\textbf{Results}

A total of 33 subjects were recruited, 30 patients completed 12 weeks of NBUVB phototherapy. Three patients defaulted treatment and follow up due to logistical difficulties caused by the COVID-19 pandemic. There were 12 (36.4%) male patients and 21 (63.6%) female patients with a male to female ratio of 4:7. The patients’ mean age was 37.00±12.52, with a range of 18–66 years. The majority of patients were Malay 29 (87.9%) followed by Chinese 3 (9.1%) and Indian 1 (3.0%). There were 4 (12.1%) patients with Fitzpatrick skin phototype (FSP) III, 22 (66.7%) with FSP IV, and 7 (21.2%) with FSP V. Duration of disease ranged between 2 and 34 years with a median of 12 years. The mean body surface area (BSA) at baseline was 30.39±22.07%. The majority of patients, 16 (48.5%) had minimal sun exposure having spent less than 1 hour under the sun per week. Milk consumption was notably low with only a median value of 1 cup per week. Table 1 shows the demographic and clinical characteristics of the study population.

\textbf{Table 1. Demographic and clinical characteristics of the study population (n=33)}

<table>
<thead>
<tr>
<th>Parameters</th>
<th>n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, (years), mean±SD</td>
<td>37.0±12.5</td>
</tr>
<tr>
<td>Age, (range)</td>
<td>18 - 66</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>21 (63.6)</td>
</tr>
<tr>
<td>Female</td>
<td>12 (36.4)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Malay</td>
<td>29 (87.9)</td>
</tr>
<tr>
<td>Chinese</td>
<td>3 (9.1)</td>
</tr>
<tr>
<td>Indian</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>Fitzpatrick skin phototype</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>4 (12.1)</td>
</tr>
<tr>
<td>IV</td>
<td>22 (66.7)</td>
</tr>
<tr>
<td>V</td>
<td>7 (21.2)</td>
</tr>
<tr>
<td>Duration of psoriasis, (years)</td>
<td>8.0 (12.0)*</td>
</tr>
<tr>
<td>Duration of psoriasis (range)</td>
<td>2-34</td>
</tr>
<tr>
<td>Total body surface area (BSA), (%)</td>
<td>30.4±22.1</td>
</tr>
<tr>
<td>Total BSA (range)</td>
<td>5-80</td>
</tr>
<tr>
<td>Psoriasis Severity</td>
<td></td>
</tr>
<tr>
<td>Mild (&lt;10% BSA)</td>
<td>5 (15.2)</td>
</tr>
<tr>
<td>Moderate (10-30 BSA)</td>
<td>16 (48.5)</td>
</tr>
<tr>
<td>Severe (&gt;30% BSA)</td>
<td>12 (36.4)</td>
</tr>
<tr>
<td>Sun exposure, (hours per week)</td>
<td></td>
</tr>
<tr>
<td>&lt; 1 hour</td>
<td>16 (48.5)</td>
</tr>
<tr>
<td>1-2 hours</td>
<td>11 (33.3)</td>
</tr>
<tr>
<td>&gt; 2 hours</td>
<td>6 (18.2)</td>
</tr>
</tbody>
</table>

\*Median (IQR)

Serum 25(OH)D and psoriasis severity at baseline and after 12 weeks of NBUVB therapy is tabulated in Table 2. At baseline, 2(6.7%) patients were 25(OH)D deficient, 23(76.7%) patients had insufficient levels and 5(16.7%) had normal 25(OH)D levels. The mean 25(OH)D level at baseline was 52.09±21.43 nmol/L. After 12 weeks of NBUVB therapy, 16(53.3%) patients achieved normal 25(OH)D levels whilst 14(46.7%) had insufficient levels. None of the patients were 25(OH)D deficient. There was a statistically significant difference between baseline and week 12 serum 25(OH)D values (52.09±21.43 vs 72.80±19.56,
Psoriasis severity measured as BSA significantly improved with NBUVB. Median value for baseline BSA was 20 (30%) vs 15 (13%) at week 12 with \( p \text{ value} = <0.001 \).

### Table 2. Serum 25(OH)D and psoriasis severity at baseline and after 12 weeks of NBUVB therapy (n = 30)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Week 12</th>
<th>( p \text{ value} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum 25(OH)D, mean±SD</td>
<td>52.1±21.4</td>
<td>72.8±19.6</td>
<td>&lt;0.001( ^{a} )</td>
</tr>
<tr>
<td>Deficient (&lt;25nmol/L), n (%)</td>
<td>2 (6.7)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Insufficient (25-74nmol/L), n (%)</td>
<td>23 (76.7)</td>
<td>14 (46.7)</td>
<td>&lt;0.001( ^{a} )</td>
</tr>
<tr>
<td>Normal(75-250nmol/L), n (%)</td>
<td>5 (16.7)</td>
<td>16 (53.3)</td>
<td></td>
</tr>
<tr>
<td>Psoriasis severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total body surface area, %</td>
<td>20 (30.0)</td>
<td>15 (13.0)</td>
<td>&lt;0.001( ^{a} )</td>
</tr>
<tr>
<td>Mild, n (%)</td>
<td>5 (16.7)</td>
<td>11 (36.7)</td>
<td></td>
</tr>
<tr>
<td>Moderate, n (%)</td>
<td>16 (53.3)</td>
<td>17 (56.7)</td>
<td>0.002( ^{c} )</td>
</tr>
<tr>
<td>Severe, n (%)</td>
<td>9 (30.0)</td>
<td>2 (6.7)</td>
<td></td>
</tr>
<tr>
<td>Fitzpatrick Skin phototype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III (n =4), median(IQR)</td>
<td>50.9 (25.0)</td>
<td>58.8 (28.3)</td>
<td>0.144( ^{c} )</td>
</tr>
<tr>
<td>IV (n =21), mean±SD</td>
<td>50.5±21.8</td>
<td>72.6±21.8</td>
<td>&lt;0.001( ^{a} )</td>
</tr>
<tr>
<td>V (n =5), mean±SD</td>
<td>56.7±27.7</td>
<td>79.9±8.1</td>
<td>0.109( \text{a} )</td>
</tr>
</tbody>
</table>

Data was analysed with: \( ^{a} \) Paired t test, \( ^{b} \) Stuart-Maxwell Marginal Homogeneity, \( ^{c} \) Wilcoxon Signed Rank test, \( ^{d} \) Median (IQR)

Table 3 presents the effects of Fitzpatrick skin phototype (FSP) on 25(OH)D levels following NBUVB therapy. The results reveal an increase in 25(OH)D levels in all the skin types following phototherapy with the most prominent increase seen in FSP V.

There was no correlation seen between psoriasis severity (week 12 BSA) with week 12 serum 25(OH)D, cumulative NBUVB dose and percentage of 25(OH)D increment. The above data is presented in Table 4.

### Table 4. Correlations between psoriasis severity (week 12 BSA) with serum 25(OH)D and cumulative NBUVB dose and percentage of 25(OH)D increment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>( r \text{ value} )</th>
<th>( p \text{ value} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 12 serum 25(OH)D</td>
<td>0.221</td>
<td>0.241</td>
</tr>
<tr>
<td>Cumulative NBUVB dose</td>
<td>0.176</td>
<td>0.353</td>
</tr>
<tr>
<td>Percentage of 25(OH)D increment</td>
<td>0.290</td>
<td>0.120</td>
</tr>
</tbody>
</table>

Data analysed with Spearman’s Rho Correlation test

There was also no correlation between cumulative NBUVB dose with serum 25(OH)D and percentage of 25(OH)D increment. (Table 5)

### Table 5. Correlations between cumulative NBUVB dose with serum 25(OH)D and percentage of 25(OH)D increment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>( r \text{ value} )</th>
<th>( p \text{ value} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 12 serum 25(OH)D</td>
<td>0.069</td>
<td>0.717</td>
</tr>
<tr>
<td>Percentage of 25(OH)D increment</td>
<td>-0.102</td>
<td>0.593</td>
</tr>
</tbody>
</table>

Data analysed with Spearman’s rho test

Spearman’s Rho Correlation test was also used to assess the correlation between percentage BSA improvement with percentage of 25(OH)D increment. We found no correlation with \( p = 0.585 \) and \( r = -0.104 \).

Adverse events such as dry skin 14(46.7%) and folliculitis 1(3.0%) were reported. These were mild however, and did not require NBUVB dose adjustment or cessation of therapy.

### Discussion

**Vitamin D status of patients with psoriasis**

Vitamin D insufficiency is common in patients with psoriasis and there is a correlation between psoriasis severity with vitamin D deficiency.\(^{15}\) A meta-analysis demonstrated that circulating 25(OH)D levels are lower in patients with psoriasis, and a small but significant negative correlation exists between 25(OH)D levels and psoriasis severity.\(^{16}\) Pitukweeraekule et al also found a significant relationship between low 25(OH)D levels and psoriasis.\(^{17}\) In agreement to this, the majority (75.8%) of our patients in our
study also had insufficient levels of 25(OH)D. We observed that serum 25(OH)D level in our cohort was lower than that from the northern latitudes.9 This is likely related to darker skin tones that function as natural sun protection and require at least three to five times longer exposure to make the same amount of vitamin D as a person with fairer skin tone.18 Another contributing factor could be inadequate sun exposure as the majority of our patients reported less than 1 hour of sun exposure per week.

The effect of NBUVB phototherapy on serum 25(OH)D in psoriasis patients

NBUVB phototherapy is a well-recognized standard treatment for psoriasis. The skin produces around 85% of total vitamin D. The rest is obtained from dietary sources such as fortified foods, eggs and oily fish. Our study confirms the results of several studies showing that NBUVB significantly increases serum 25(OH)D in patients with psoriasis.9,10,11 NB-UVB and UVA/UVB phototherapy significantly increased 25(OH)D serum level in patients with psoriasis and atopic dermatitis in Western Australia.19

Twelve NBUVB exposures within 4 weeks increased serum 25(OH)D concentration significantly more than 20μg of oral cholecalciferol daily.20 Significantly greater increase in serum 25(OH)D was seen among NBUVB treated individuals compared to those treated with the oral vitamin D3.21 Our study demonstrated improvement in serum 25(OH)D following NBUVB therapy in psoriasis patients with FSP III, IV or V living in a tropical country.

The effect of skin phototypes on phototherapy induced increment of serum 25(OH)D

There is limited and conflicting information relating to the effect of NBUVB therapy on vitamin D levels in psoriasis patients with darker skin tones, in particular FSP III, IV and V. UV transmission is obstructed by melanin, thus dark skinned individuals are thought to be less capable of vitamin D synthesis compared to fair-skinned subjects. Vitamin D status is also known to differ between geographical latitudes. In our study, the majority of patients with darker skin had vitamin D deficiency. Armas et al reported similarly low levels of 25-OH-D with darker skin.11 We found an increment in serum 25(OH)D among all FSP (III, IV and V) after 12 weeks of NBUVB therapy, the difference in serum 25(OH)D increment between all FSP was not significant. The mean value of serum 25(OH)D at baseline and after 12 weeks was significant for FSP IV. This could be due to a larger sample size as FSP IV had 21 patients, compared to FSP III (4) and FSP V (5) respectively.

FSP is most likely not a significant predictor of change in vitamin D level as reported by Ryan et al in a cohort where the majority of patients were of FSP III.9 This was in contrast to Libon et al in study comparing serum 25(OH)D levels after a single UVB exposure in fair (FSP II–III) and black skinned (FSP VI) volunteers.22 The study found that on day 6 post single UVB exposure, serum 25(OH)D levels of fair skinned volunteers increased significantly, but not in black-skinned people suggesting that skin pigmentation negatively influences vitamin D synthesis.

Relationship between cumulative NBUVB dose with improvement in serum 25(OH)D

Ryan et al. found the number of NBUVB exposures was the sole predictor of increase in serum 25(OH)D level.9 Those with greater number of exposures had a significantly higher serum 25(OH)D level, most likely produced by more prolonged exposure to NBUVB. We found no correlation between cumulative NBUVB dose with improvement in serum 25(OH)D at week 12. The number of phototherapy sessions/ NBUVB exposures rather than the cumulative NBUVB dose may be associated with improvement of serum 25(OH)D. Further research is required to confirm this association.

Relationship between improvement in serum 25(OH)D with reduction in psoriasis severity (body surface area affected by psoriasis)

NBUVB increases serum 25(OH)D levels in inflammatory skin conditions.8,9,10,17 There is little data on the effect of NBUVB on 25(OH)
D serum levels alongside severity of psoriasis. Our results support previous observations that NBUVB increases 25(OH)D levels in psoriasis patients and decreases the severity of psoriasis. Gupta et al showed significant improvement in Psoriasis Area and Severity Index (PASI) as well as serum 25(OH)D ($p < 0.05$). Ryan et al. also found serum 25(OH)D increased significantly with significant improvement in PASI at the end of NBUVB treatment. As minimal as 2 weeks of NBUVB treatment resulted in significant increase of 25(OH)D3 serum concentration.

We found significant improvement of BSA and increase in serum 25(OH)D levels after the completion of treatment. There was however, no correlation between psoriasis severity at week 12 with serum 25(OH)D or percentage of serum 25(OH)D increment. This is similar to a previous study, whereby the improvement in PASI as well as increase in serum 25(OH)D levels after 12 weeks of NBUVB were significant. However, correlation between PASI and 25(OH)D was weak and was statistically insignificant. Ryan et al also found no correlation between change in serum 25(OH)D levels and change in PASI but the change in the PASI correlated with cumulative dose of phototherapy.

Our study had several limitations. There was no control arm for comparison, however baseline and end of therapy were obtained to demonstrate improvement in vitamin D. A few factors influencing 25(OH)D levels such as dietary vitamin D intake and body mass index were not recorded or adjusted during the analysis. Body surface area affected (BSA) was used to represent psoriasis severity, BSA is routinely used in clinical practice however Psoriasis Area and Severity Index (PASI) is the validated gold standard.

**Conclusion**

NBUVB therapy resulted in a significant rise in 25(OH)D levels amongst psoriasis patients of FSP III, IV and V with significant improvement in psoriasis severity. There was no correlation between cumulative NBUVB dose and improvement in serum 25(OH)D. Vitamin D level is most likely not an important predictor in improvement of psoriasis after NBUVB treatment as there was no correlation between BSA improvement and increment of serum 25(OH)D level.

**Conflict of Interest Declaration**

The authors have no conflict of interest to declare.

**Acknowledgement**

We would like to thank the Director General of Health Malaysia for his permission to publish this article.

**References**


ORIGINAL ARTICLE

Rituximab as First-line Therapy for Severe Pemphigus: A Case Series and Review of Current Literature

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Summary
Pemphigus refers to a group of life-threatening, autoimmune blistering disease that presents as blisters and erosions involving the skin and mucosa. Systemic corticosteroids and rituximab have been recommended as mainstay therapy for pemphigus vulgaris and pemphigus foliaceus. Herein, we report three cases of pemphigus vulgaris and a case of pemphigus foliaceus treated with rituximab as first-line therapy.

Key words: Pemphigus, First-line, Rituximab

Introduction
Pemphigus is a group of life-threatening, autoimmune blistering disease that presents as blisters and erosions involving the skin and mucosa. Systemic corticosteroids and other immunosuppressive drugs have traditionally been considered the mainstay of therapy. High doses and long treatment period of systemic glucocorticoids to achieve adequate clinical response may lead to serious and life-threatening side effects. We hereby report three cases of pemphigus vulgaris and a case of pemphigus foliaceus treated with rituximab, we also included an updated review of the literature.

Case Series

Case 1
SH, a previously healthy 32-year-old indigenous woman, presented with progressively worsening blisters and erosions over her body and oral mucosa for the past 3 months. Physical examination revealed multiple crusted erosions over her face, lips, neck, trunk and limbs involving 30% of her body surface area (BSA) (Figure 1 a &b). Intraoral examination revealed irregular ulcers with erythematous bases. She also suffered from physical deconditioning and muscle weakness with grade 2 sacral pressure ulcer due to prolonged immobilization prior
to her hospital admission. Our differential diagnoses were pemphigus vulgaris, drug-induced bullous eruption, and bullous lupus erythematosus.

Laboratory values revealed leucocytosis, hypochromic microcytic anemia, hypoalbuminemia and hypokalaemia. Histopathological examination of a perilesional skin biopsy revealed suprabasal clefting and acantholysis resembling a tombstone appearance. Direct immunofluorescence showed intercellular IgG and C3 deposition in a fishnet-like pattern. A diagnosis of pemphigus vulgaris was thus made.

Figure 1. (a & b) Clinical presentation of the patient showing multiple crusted erosions over her face, neck, trunk and limbs and (c & d) after three months during follow-up

Treatment was initiated with methylprednisolone intravenously 500mg daily consecutively for 3 days, continued by hydrocortisone 100mg three times a day. However, her condition did not show significant improvement. Therefore, rituximab, a monoclonal antibody was given at 1gm intravenously for 2 infusions 15 days apart together with a lower oral prednisolone dose of 25mg daily (0.5mg/kg/day). She showed good and rapid clinical improvement and was subsequently discharged. We managed to taper her prednisolone dose fairly quickly over the next 3 months while azathioprine 50mg a day was added. After one year, her disease remained in remission without any oral or systemic medication.

Case 2

MR, a 59-year-old gentleman, diagnosed via skin biopsy with pemphigus vulgaris three years ago but who unfortunately with a history of poor treatment compliance, presented with generalized painful blisters and erosions over his skin and oral mucosa. Examination revealed multiple raw erosions with areas of peripheral crusting over his trunk and limbs, involving 20% BSA (Figure 2: a & b). There were also multiple erosive, desquamative lesions over lips, buccal mucosa and palate. Blood investigations were unremarkable apart from hypoalbuminemia. A repeat skin biopsy was not performed.

He too was treated with IV methylprednisolone 500 mg daily for three consecutive days. Subsequently, rituximab was given, due to poor clinical response, in addition to 0.5mg/kg/day oral prednisolone. He showed marked and rapid improvement over the following three days and was discharged well. He was still having mild disease activity on follow-up at 3 months and mycophenolate mofetil was added while prednisolone was quickly tapered off.
Figure 2. (a & b) Clinical presentation of the patient showing multiple crusted erosions over his trunk and limbs and (c & d) upon discharge at day 15

Case 3
MN, an otherwise healthy 20-year-old gentleman, presented with progressively worsening blisters and erosions all over his body for the past 3 months. Examination revealed thick-crusted erosions over his face, neck, trunk, and limbs. There was also bilateral non-cicatrizng conjunctivitis with mucopurulent discharge. Blood investigations revealed leucocytosis, normocytic normochromic anemia, hypokalaemia and hypoalbuminemia. Other laboratory values were unremarkable. Our differential diagnoses included pemphigus vulgaris, pemphigus foliaceus, subcorneal pustular dermatosis and generalized pustular psoriasis. Skin biopsy revealed subcorneal clefting containing acantholytic epidermal cells and occasional neutrophils. Immunofluorescence study showed intercellular IgG and C3 deposited in a fishnet-like pattern. Thus, a diagnosis of pemphigus foliaceus was made.

Due to the severity of his disease, he was given rituximab as first-line therapy, at 1000mg intravenously given as 2 infusions 15 days apart. He too, was discharged fairly early with 0.5mg/kg/day prednisolone and low-dose azathioprine. We managed to wean off prednisolone within 6 months and azathioprine within a year. At 18 months follow up, he remains disease-free and without any oral or topical treatment.

Case 4
ZS, a 59-year-old woman with type II diabetes mellitus, hypertension, erythrodermic psoriasis with symptomatic palmoplantar pustulosis despite methotrexate since 2018, presented with generalized raw erosions and flaccid blisters without mucosal involvement. Our differential diagnoses were pemphigus vulgaris, pemphigus foliaceus, subcorneal pustular dermatosis and generalized pustular psoriasis. Skin biopsy revealed subcorneal cleavage containing acantholytic epidermal cells and occasional neutrophils. Immunofluorescence study showed intercellular IgG and C3 deposited in a fishnet-like pattern. Thus, a diagnosis of pemphigus foliaceus was made.

However, despite an initial treatment of intravenous methylprednisolone pulse of 500mg daily for three days followed by oral prednisolone 1mg/kg/day and azathioprine 150mg daily, she still suffered a severe relapse even with minimal tapering of prednisolone six months later. Rituximab was thus electively given, similar to the patients above. This time, prednisolone could be tapered off quickly within six months without azathioprine. At the time of writing 15 months later, she is in complete remission without any systemic or topical treatment whatsoever.

Discussion
Pemphigus is a heterogenous group of autoimmune, blistering, and potentially life-threatening cutaneous disorders. It is characterized by acantholysis, resulting in intraepithelial blisters in mucous membrane and the skin. Pemphigus vulgaris (PV) and pemphigus foliaceus (PF) are the two most common forms of pemphigus. PF is attributed to IgG autoantibodies directed desmoglein 1...
(Dsg1) while autoantibodies against desmoglein 3 (Dsg3) are characteristic for mucosal PV and autoantibodies against Dsg1 and Dsg3 have been linked to mucocutaneous PV.

Treatment of pemphigus has historically been a challenge. Systemic corticosteroid is recommended as first-line treatment options for pemphigus. Adjuvant steroid-sparing immunosuppressants such as azathioprine, mycophenolate mofetil (MMF) or cyclophosphamide among others are often added for disease control. However, long-term immunosuppressive therapy especially corticosteroid can lead to serious adverse reaction. Moreover, a number of patients are also resistant to conventional therapy.

Rituximab is a monoclonal antibody directed against the CD20 antigen on the surface of B-lymphocytes. Hitherto, rituximab was reserved for pemphigus refractory to conventional therapies or patients who develop severe adverse reactions to conventional immunosuppressants.\textsuperscript{1} Multiple literatures have shown that rituximab is a valuable treatment for refractory pemphigus.\textsuperscript{2-12} Following that, European Academy of Dermatology and Venereology guideline recommends rituximab as a third-line therapy from 2015.\textsuperscript{13} Literatures have also reported successful experience with rituximab and corticosteroids as first-line combination therapy for pemphigus, however most of the previous studies only included a limited number of patients.\textsuperscript{14-17} More recently, Pascal Joly \textit{et al}, through a prospective open-label randomized trial, with a high level of evidence, has shown the clinical efficacy of rituximab as first-line agent for pemphigus.\textsuperscript{18} Pemphigus patients were randomly assigned to receive oral prednisolone, 1.0 or 1.5mg/kg/day tapered over 12 to 18 months (prednisolone alone group) or intravenous rituximab combined with oral prednisolone, 0.5 to 1.0mg/kg/day tapered over 3 or 6 months (rituximab plus short-term prednisolone group). This is the most robust data regarding the use of rituximab as first-line agent as it shows the first-line use of rituximab plus short-term prednisolone for patients with pemphigus is more effective than using prednisolone alone, with fewer adverse events. Moreover, it shows that rituximab can be regarded as the most important advance after the arrival of corticosteroid in the treatment of pemphigus. All these had led to the recommendation of rituximab as first-line treatment in new onset moderate-to-severe pemphigus by an international panel of experts in the management of pemphigus.\textsuperscript{19} Rituximab was also shown to be superior to MMF in producing sustained complete remission in patients with PV.\textsuperscript{20} The common dosing of rituximab for pemphigus were based on the lymphoma or the rheumatoid arthritis (RA) protocol. The RA protocol consists of 2 infusions of 1000mg, 2 weeks apart while the lymphoma protocol consists of 4 weekly infusions of 375mg/m\textsuperscript{2}. There are also different regimen with low-dose rituximab given as 2 infusions of 500mg, 2 weeks apart with or without concomitant use of immunoadsorption or intravenous immunoglobulin.\textsuperscript{21} However, there is still no universally accepted dosing protocol for pemphigus. The recommended course of rituximab by the international panel of experts consists of either the RA protocol or the lymphoma protocol.\textsuperscript{19} Although some studies suggest a potential benefit of the lymphoma protocol for pemphigus, uncertainties remain regarding specific dosing modalities. In a retrospective cohort study published in 2019, lymphoma protocol was shown to be associated with higher odds of achieving complete remission off therapy (CROT) as compared to the RA protocol.\textsuperscript{22} Another meta-analysis showed no superiority of lymphoma protocol over the RA protocol in all outcomes.\textsuperscript{21} While other study showed superiority of the RA protocol in achieving a higher response rate.\textsuperscript{23} Modified regimen with half the dose of conventional RA protocol has also been shown to be effective for pemphigus.\textsuperscript{24} The RA protocol however has the advantage of lower cost compared to the lymphoma protocol.\textsuperscript{1} The RA protocol was used in our patients with pemphigus as it was the regimen used by Pascal
Joly et al in their study (the study with the most robust data), however we did not proceed with the maintenance infusion at month 12 and 18 due to financial limitation.

Before initiating rituximab, special attention needs to be paid for possible contraindication in all patients. Rituximab is contraindicated in patients with hypersensitivity to rituximab or other murine proteins, active severe infections and severe heart failure (New York Heart Association class IV). Infusion related reactions (IRR) are adverse events associated with the use of rituximab, occurring within 24 hours after drug infusion. Mild to moderate IRR may include fever, skin rash, pruritus and nausea among others while more severe reactions include hypotension, angioedema, bronchospasm, hypoxia and cardiac related disorders. Our patients were all given prophylaxis comprising paracetamol, chlorpheniramine and corticosteroid to prevent the occurrence of IRR. Other adverse reactions related to rituximab may include infections, hematological abnormalities and mucocutaneous reaction among others. Fortunately, all of our patients did not suffer from any adverse reactions except for MN who suffered from bacteraemia during his complicated hospital stay.

In regards to the need of maintenance rituximab therapy, patients with high Pemphigus Disease Area Index [PDAI] score and low changes in anti-desmoglein antibody values have higher risks of relapse and may benefit from maintenance rituximab infusion at 6 months. Dosing of maintenance rituximab therapy varied among different literature. An infusion of 500mg-1000mg can be repeated at 6 months or only at 12 months. Besides rituximab as maintenance therapy, the use of azathioprine as maintenance therapy was shown to be beneficial in prolonging the duration of remission in patients who received rituximab as initial therapy. Two of our patients with newly diagnosed PV are in remission after being put on azathioprine as maintenance therapy following rituximab as initial therapy.

Finally, concerns have been raised regarding the prolonged immunosuppressive effect of rituximab, which could last at least 6 months, especially during the ongoing novel coronavirus disease (COVID-19) pandemic. Literatures have shown that rituximab therapy is associated with more severe COVID-19. Therefore, the attending physician has to offer individualised care and take into account the severity of the disease and potential benefits or risks of prescribing rituximab therapy to patients with pemphigus. In proven cases of COVID-19, glucocorticoids, rituximab and other steroid-sparing immunosuppressive agents should be discontinued. In this setting, the administration of intravenous immunoglobulin has been proposed as a potential option for pemphigus patients with COVID-19 and flare of disease. Dealing with vaccination for COVID-19, the American College of Rheumatology recommends vaccination 4 weeks prior to next scheduled rituximab cycle, and to delay rituximab 2-4 weeks after final vaccination dose if disease activity allows.

Conclusion
Our local experience has shown that rituximab is an effective and safe therapy for both newly diagnosed and refractory severe pemphigus, and should be considered as a first-line treatment option.

Conflicts of Interest Declaration
The authors have no conflict of interest.

Acknowledgement
We thank the staff of departments of Dermatology of Hospital Tengku Ampuan Afzan, Kuantan, Pahang, Malaysia for their support in this article. We would also like to thank the Director General of Health, Malaysia, for his permission to publish this article.
Table 1. Literature review of rituximab as first-line therapy for pemphigus

<table>
<thead>
<tr>
<th>Author, year, country</th>
<th>Methodology</th>
<th>n</th>
<th>Study period</th>
<th>RTX dosing regimen</th>
<th>Glucocorticoid</th>
<th>CAT</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agarwal A, et al, 2018, USA</td>
<td>Retrospective case control study</td>
<td>40</td>
<td>1999-2015</td>
<td>1000mg day 0, 14, May repeat cycle after 12 months.</td>
<td>RTX group Total prednisolone - 177.2 mg/mo</td>
<td>+</td>
<td>Rituximab significantly reduces the monthly prednisolone requirement among CAT-resistant PV patients similar with CAT-responsive patients.</td>
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<tr>
<td>Ingen-Housz-Oro S, et al, 2015, France</td>
<td>Case reports</td>
<td>5</td>
<td>-</td>
<td>1000mg day 0, 14 or 375mg/m2.</td>
<td>Topical high-potency corticosteroids</td>
<td>-</td>
<td>Concomitant use of rituximab and high-potency topical corticosteroids could be considered as treatment for PV in some patients with contraindications to use of high doses of systemic corticosteroids.</td>
</tr>
<tr>
<td>Vinay K, et al, 2017, Switzerland</td>
<td>Retrospective study</td>
<td>31</td>
<td>2008-2016</td>
<td>1000mg day 0, 14.</td>
<td>Prednisolone 0.5-1.0 mg/kg/day</td>
<td>+</td>
<td>Complete remission off therapy was more likely to be achieved by patients receiving rituximab earlier in the disease course (&lt;6 months) and as first-line steroid-sparing adjuvant.</td>
</tr>
<tr>
<td>Chen DM, et al, 2020, France</td>
<td>Open-label, randomized controlled trial</td>
<td>36</td>
<td>2010-2012</td>
<td>1000mg day 0, 14.</td>
<td>Prednisolone group -1.0 to 1.5 mg/kg/day, RTX plus short term prednisolone group -0.5 to 1.0 mg/kg/day</td>
<td>-</td>
<td>In patients with moderate-to-severe PV, rituximab plus short-term prednisolone was more effective than prednisolone alone with less corticosteroid exposure.</td>
</tr>
<tr>
<td>Joly P et al, 2017, France</td>
<td>Prospective, multicentre, parallel-group, open-label, randomised trial</td>
<td>90</td>
<td>2010-2012</td>
<td>1000mg day 0, 14 and 500mg at months 12 and 18.</td>
<td>Prednisolone group -1.0 to 1.5 mg/kg/day, RTX plus short term prednisolone group -0.5 to 1.0 mg/kg/day</td>
<td>-</td>
<td>First-line use of rituximab plus short-term prednisolone for patients with pemphigus is more effective than using prednisolone alone, with fewer adverse events.</td>
</tr>
</tbody>
</table>

RTX, rituximab; CAT, conventional adjuvant therapy; mo, months.

References

17. Chen DM, Oduguembo A, Cisnady E, Gearhart L, Lehane P, Cheu M et al. Rituximab is an effective treatment in patients with pemphigus vulgaris and demonstrates a
CASE REPORT

Iatrogenic Phaeohyphomycosis: A Rare and Underrecognized Disease

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Summary
Phaeohyphomycosis refers to a heterogenous group of mycotic infections caused by dematiaceous fungi where unintentional traumatic inoculation accounts for majority of the cases. Herein, we are reporting a rare case of iatrogenic subcutaneous phaeohyphomycosis which is secondary to intravenous cannula placement.

Key Words: Iatrogenic; Phaeohyphomycosis; Dematiaceous fungi

Introduction
Phaeohyphomycosis is a group of fungal infections caused by dematiaceous fungi in tissue. More than 150 species have been described as causal agents which includes Exophiala, Wangiella, Phialophora and Cladosporium among others. There is a large variety of clinical presentations which includes superficial cutaneous, subcutaneous disease, cerebral and disseminated disease. The subcutaneous infection typically occurs at exposed areas of the body from traumatic inoculation. We report this case of iatrogenic phaeohyphomycosis for its unusual mode of inoculation by intravenous cannula placement which is perceived to be a clean and sterile procedure.

Case Report
HS, a 70-year-old gentleman with type II diabetes mellitus, hypertension and end stage renal failure on haemodialysis, presented with slowly enlarging, asymptomatic nodules over the dorsum of both hands for the past one month. He reported that they started at previous sites of intravenous cannula insertion during his hospital stay one month ago. He did not notice any prior traumatic injury and was otherwise well.

Physical examination revealed an erythematous plaque with verrucous surface measuring 1 x
1cm, over the dorsum of his right hand. Another erythematous plaque with verrucous surface and minimal surface erosions, measuring 2.5cm x 1.5cm, was located over the dorsum of his left hand. There was no regional lymphadenopathy and examination of other systems was unremarkable.

We considered several differential diagnoses, including iatrogenic fixed cutaneous sporotrichosis, chromoblastomycosis, tuberculosis verrucosa cutis and non-tuberculous mycobacterial infection.

**Figure 1.** (a). Clinical presentation of the patient, showing erythematous nodule with verrucous surface on the bilateral aspect of both hand with minimal erosion; (b) After one month on itraconazole

Blood investigations were unremarkable apart from mild hypochromic microcytic anaemia and high urea and creatinine, in keeping with his underlying renal disease. Histopathological examination of the plaques revealed pseudoepitheliomatous epidermal hyperplasia with moderate lymphoplasmacytic infiltration with foci of neutrophilic microabscesses. No granulomas were appreciated. While Ziehl Neelsen and periodic acid Schiff (PAS) stains did not demonstrate any fungus, tissue culture, however, isolated *Exophiala* species.

Hence, a diagnosis of iatrogenic subcutaneous phaeohyphomycosis caused by *Exophiala* species was made and he was promptly treated with oral itraconazole. His lesions improved dramatically after one month of treatment and subsequently successfully cleared after 4 months of treatment.

**Discussion**

The infections caused by dematiaceous fungi, are classified into three groups which include phaeohyphomycosis, chromoblastomycosis and eumycotic mycetoma.¹⁻³ This variety of dematiaceous fungi develops in infected tissue as darkly pigmented yeast-like cells, pseudohyphae-like elements, hyphae, or in any combination of these forms.³⁻⁴ Phaeohyphomycosis should be distinguished from other infectious syndrome also caused by dematiaceous fungi which include chromoblastomycosis and eumycetoma.

There are many different clinical syndromes for phaeohyphomycosis.¹⁻⁴ One of the more extensive clinical syndrome classifications divides it into nine groups, which includes: (1) superficial (including black piedra & tinea nigra); (2) onychomycosis; (3) subcutaneous; (4) corneal or mycotic keratitis; (5) allergic fungal sinusitis; (6) allergic fungal bronchopulmonary mycosis; (7) pneumonia; (8) brain abscess; and (9) disseminated disease.⁴ Phaeohyphomycosis is caused by more than 150 species of fungi, which includes *Exophiala*, *Phialophora*, *Alternaria*, *Cladosporium*, *Scytalidium*, *Drechslera*, *Curvularia* and *Wangiella* species. The most common species are *E. jeanselmi* and *E. dermatitidis*.¹⁻³

Subcutaneous phaeohyphomycosis lesions most commonly occur on exposed area of body such as hands, arms, feet and legs.¹ Traumatic inoculation accounts for majority of the cause of subcutaneous phaeohyphomycosis, however cases are being reported which has no prior recollection of traumatic injury.³ There are also reports on iatrogenic phaeohyphomycosis.
This includes report of subcutaneous phaeohyphomycosis in association with intravenous cannula insertion and report demonstrating osteoarticular infection secondary to contaminated methylprednisolone injections.\textsuperscript{2,6}

The immune status of the host plays a major role in the clinical presentation of the patient. Typically, majority of cases of phaeohyphomycosis has been associated with an immunocompromised state, this includes human immunodeficiency virus patients, malignancies, transplant recipients, systemic lupus, vasculitis, primary immunodeficiency syndromes, debilitating chronic diseases and diabetes among others.\textsuperscript{1,3}

In addition to that, immunocompromised states are also at risk of cerebral and systemic phaeohyphomycosis. Despite that, cases in immunocompetent patients are on the rise.\textsuperscript{3} As for subcutaneous phaeohyphomycosis, this typically presents as papulonodules, verrucous, hyperkeratotic or ulcerated plaques, cysts, abscesses, pyogranuloma, non-healing ulcers or sinuses.\textsuperscript{1,7}

For the diagnosis of phaeohyphomycosis, histopathologically, the lesions show brown-walled septate hyphae or yeast-like cells, or both in tissue. In order to help differentiate it from eumycetoma and chromoblastomycosis which are also caused by dematiaceous fungi, eumycetoma is characterized by the presence of mycotic granules in draining sinus tract while chromoblastomycosis is a typically verrucous hyperplastic cutaneous infection characterized by the presence of medlar bodies (sclerotic bodies).\textsuperscript{2,3} All dematiaceous fungi are similar in morphology and cannot be differentiated in tissue. Hence, it can only be differentiated by cultures.

There is no uniform treatment approach for the treatment of these infections. The length of therapy and choice of treatment are primarily based on clinical presentation, underlying immune status of the host and the initial response to treatment.\textsuperscript{8} Literature shows surgical excision of the lesion has been successfully applied in some cases.\textsuperscript{9-13} Adding on antifungal monotherapy or combination therapy is also preferred to avoid local spread and to treat subclinical lesions.\textsuperscript{3} Broad-spectrum azoles are currently the mainstay of therapy, with itraconazole historically the most commonly used agent that demonstrates good activity against the vast majority of melanized fungi. Voriconazole is becoming more popular with preferable side effect profile and is available in intravenous formulation.\textsuperscript{3} However, it is not available in our local setting for this patient. Other systemic agents used successfully include amphotericin B, flucytosine & posaconazole.\textsuperscript{3} Fluconazole and ketoconazole have essentially no role in invasive disease cause by dematiaceous fungi. Terbinafine was also reported to be less effective, especially in serious systemic infection.\textsuperscript{2}

**Conclusion**

To the best of our limited knowledge, this is the second reported case of iatrogenic subcutaneous phaeohyphomycosis secondary to intravenous cannula insertion. While it is uncommon for a clean procedure as a source of inoculation to cause subcutaneous phaeohyphomycosis, clinicians should have a high index of suspicion and be aware of this infection. This is to avoid any delay in treatment so as to avoid further complications.

**Conflict of Interest Declaration**

The authors have no conflict of interest.

**Acknowledgement**

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**References**

CASE REPORT

Cutaneous Tuberculosis in HIV Patient: A Case Report

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Summary
Tuberculosis (TB) is a serious communicable disease of major concern in endemic regions. Cutaneous tuberculosis (CTB), which accounts for less than 1% of all cases, can cause severe infection in susceptible patients.¹ The diagnosis of CTB is challenging as it can present with a multitude of clinical presentations. The diagnosis must be supported by highly sensitive and specific investigations. This paper highlights the susceptibility of immunocompromised patients to the development of CTB and the challenges in making a diagnosis.

Key words: Cutaneous tuberculosis, CTB, HIV, Tuberculosis-HIV, CTB-HIV, Co-infection

Introduction
Mycobacterium tuberculosis (MTB) is the causative agent for TB. TB essentially affects the lungs and can involve extrapulmonary sites including the skin.² The occurrence of CTB is driven by the human immunodeficiency virus (HIV) epidemic as well as in specific settings such as healthcare facilities, prisons and homeless shelters. Increased incidence is also noted among intravenous drug users, and in those with diabetes mellitus and on immunosuppressive therapy.³ It is estimated that one-third to one-half of people with HIV infection are also co-infected with MTB worldwide.⁴

Case report
A 46-year-old gentleman with underlying hepatitis C and HIV presented with worsening oral thrush and dysphagia. He had multiple pinhead-sized nodulo-pustular lesions initially over face (Figure 1-d), which then progressed to the ears and then the upper limbs and lower limbs over one week. Some of nodules appeared to have central necrosis. He was an intravenous heroin abuser and diagnosed with HIV in October 2009 when he presented with a prolonged headache and left sided weakness. He was treated for cerebral toxoplasmosis. His baseline viral load was more than 50,000 copies/ml, CD4/CD8 ratio was 0.01 (0.83-6.1)
and CD4 count was 64 (355-1213). He was on Stavudine/Lamivudine/Nevirapine since June 2010. He managed to achieve a non-detectable viral load when he was compliant. This was until October 2016, after which he defaulted treatment.

General examination revealed extensive oral candidiasis. He had a residual left sided hemiparesis from previous cerebral toxoplasmosis. Sensory examination and lung findings were normal. There was no lymphadenopathy found. Clinically the differential diagnosis were atypical mycobacterial cutaneous infection and subcutaneous or deep fungal infection. Initial blood investigations showed normochromic normocytic anemia with thrombocytosis but no leucocytosis. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were significantly raised. Chest X-ray was normal initially. Tuberculin skin test reading was 0mm after 48 hours.

This patient underwent echocardiography which showed a 0.6cm to 1.5cm posterior inferior wall pericardial effusion and computed tomography of thorax, abdomen and pelvis showed a pericardial effusion on the posterior inferior wall with enhancement of the pericardial lining, multiple nodular opacities over the right lung, left lower lobe collapsed consolidation with minimal pleural effusion, necrotic mediastinal lymph nodes, hepatomegaly with minimal ascites but no evidence of focal liver lesion.

A punch biopsy of skin was done over the forehead. There was a localised ulceration with collection of neutrophils and histiocytes in the dermis forming microabscesses. However, no well-formed granuloma, obvious dysplasia or malignancy were seen. Abundant acid-fast bacilli (AFB) were demonstrated with Ziehl Neelson stain and Wide Fite stains.

Split skin smear (SSS) was positive with bacterial index 3.3 and morphological index 1.5. MTB and fungal tissue culture and sensitivity were negative. However MTB PCR (polymerase chain reaction) was positive and negative for Mycobacterium leprae. Based on clinical, radiological and PCR findings, the patient was treated for acute cutaneous military tuberculosis (ACTMB). He was started on intensive regimen of anti-TB drugs consisting of Rifampicin, Isoniazid, Pyrazinamide, Ethambutol and Pyridoxine. After 2 weeks, this patient had significant improvement of the skin lesions (Figure e-h).

**Figure 1.** (a) Localised ulceration with collection of neutrophils and histiocytes in the dermis, involving pilosebaceous units (Haematoxylin & Eosin stain (H&E), 4x); (b) The edge of the lesion is composed of histiocytes and some scattered within were epithelioid looking. No well-formed granuloma is seen (H&E, 10x); (c) Acid fast bacilli were demonstrated (Ziehl Neelson stain, 60x)
Discussion

The estimated incidence for TB-HIV cases was 193,000 in 2013. In general, Asian countries demonstrated a lower estimated prevalence of TB-HIV co-infection at 17.2% as compared to other regions such as Africa (31.2%), Europe (20.1%), Latin America (25.1%) and USA (14.8%). This low number may be unreliable due to poor screening as not many countries in the Asia-Pacific region tested more than two-third of patients who had TB for HIV. Many countries in Asia only demonstrated a prevalence of TB-HIV coinfection rate of less than 10% except for Thailand (15%) and Papua New Guinea (14%). This was in contrast to the African regions where the majority exceeded 50% and had the highest number of reported HIV co-infection cases. Overall, the incidence of CTB was only 0.7% with 9.1% HIV concurrence from 2007 to 2009 in India. Male patients demonstrated a higher prevalence of TB and TB-HIV co-infection in Malaysia (91.1%).

The lifetime risk to develop active TB in HIV individuals is 5-15% annually as compared to immunocompetent adults which is at 5-10%. Co-infection with HIV increases the risk of reactivation of latent TB by 20. On the other hand, TB exacerbates HIV infection. The depletion of CD4 T-cells due to HIV infection causes impairment of the intracellular clearance of MTB and disrupts the integrity and architecture of the granuloma which leads to TB reactivation. It has been proposed that TB-HIV co-infection as a ‘danger-couple’ model in which dysfunctional HIV-infected T cells lead to loss of intracellular killing abilities of macrophages harbouring MTB, while MTB-infected macrophages containing lipoarabinomannan (LAM) produce increased levels of TNF-α, IL-1 and IL-6 leading to enhanced viral replication and persistence in the macrophages.

Clinical variants of CTB mainly depends on cell-mediated immunity as the primary response to mycobacterial infection. It can be concluded that it is a direct reflection of the host’s cellular response.
immune status. This is totally different from leprosy where the predominant response is immunological.\textsuperscript{4} It is also important to note that the presentation of CTB depends on the bacillary load.\textsuperscript{4}

The clinical morphology of CTB can be differentiated by the mode of infection, i.e. either through exogenous or endogenous sources. The former is significantly less common. An exogenous source infection is by primary inoculation on the traumatic skin or mucous membranes which can lead to tuberculosis verrucosa cutis (TVC) and tuberculosis chancre.\textsuperscript{1,7} Endogenous routes may also be via hematogenous, lymphatic or contiguous spread to the skin which may lead to scrofuloderma, lupus vulgaris (LV), tuberculous gumma, orificial tuberculosis or ACTMB as clinical presentations.\textsuperscript{1,7} As MTB can be found at the lesional sites via PCR in this case, it is defined as true CTB instead of tuberculids.\textsuperscript{7} Tuberculids are delayed-type hypersensitivity reaction to bacterial antigens and can be manifested as papulonecrotic tuberculid, lichen scrofulosorum or erythema induratum of Bazin.\textsuperscript{1,7}

Scrofuloderma (80\%) is the most common presentation of TB-HIV cases in Brazil followed by tuberculous gumma (20\%) from samples collected from 2000 to 2016.\textsuperscript{10} In India, where there is a high incidence of TB and HIV, one study showed that 10.4\% of patient with scrofuloderma, 7.5\% of patient with LV, 11.7\% with TVC were HIV positive. Scrofuloderma represented the most commonly seen variant in the study.\textsuperscript{8}

ACMTB or tuberculosis cutis miliaris cuta generalisata usually occurs in immunocompromised patient such as Acquired Immunodeficiency Syndrome (AIDS) via hematogenous spread. The lesion can present with scattered erythematous macules and papules with central vesicles or pustules, characteristically from a pinhead size to 6 mm in diameter, that may rupture, and then form a crust. Ultimately, it heals with a hypopigmented scar and brownish halo.\textsuperscript{4,14,15} Pulmonary basal involvement, hilar or mediastinal lymphadenopathy and military TB are most commonly observed.\textsuperscript{13} Microscopic examination may demonstrate ill-formed or no granulomas, focal or extensive necrosis, microabscesses, abundant AFB and scattered non inflammatory cells.\textsuperscript{14,15} The absence of a cell mediated response in ACMTB results in non-specific necrosis with high bacillary load and negative tuberculin test.\textsuperscript{9} In this case, the patient demonstrated a few characteristics of ACMTB.

SSS was taken from the most representative lesion and stained by modified Ziehl Neelson (ZN) stain to demonstrate AFB.\textsuperscript{16} ZN stain was developed to show mycobacterial genus fastness which has become the cornerstone in TB diagnosis.\textsuperscript{17} Differentiation of MTB and Mycobacterium leprae by SSS alone is impossible. It was proven that PCR had higher sensitivity and specificity compared to SSS in diagnostic challenges.\textsuperscript{18} The lack of a positive tuberculin test, granulomatous reaction and high bacillary load would make ACMTB analogous to lepromatous leprosy.\textsuperscript{4} Even though co-infection between tuberculosis and leprosy has occurred since the thirteenth century, the probability is estimated at 0.0006 cases per 100000 population in Malaysia.\textsuperscript{19}

Routine sputum microscopy is inadequate to rule out TB and is not an optimal screening tool since 24-61\% of TB-HIV patients presents with sputum-negative disease.\textsuperscript{5} WHO has endorsed the Xpert MTB/RIF assay (PCR) as the primary TB diagnostic test for symptomatic people living with HIV as it is associated with 35-45\% improvement in the diagnostic sensitivity. Urine LAM assay can be added to rule out active TB in severely immunocompromised patients (CD4 count less than 100) to achieve diagnostic certainty.\textsuperscript{5}

One in four deaths among HIV patients is attributed to TB even though significant reduction of TB-related deaths among HIV patients was seen in Asia Pacific region.\textsuperscript{5,6} The outcome for ACMTB is grave. Seventy five
percent of cases had multidrug resistance to at least Rifampicin and Isoniazid and these cases eventually succumbed.\textsuperscript{4}

Female patients showed a higher tendency for treatment success according to Jalal et al. This study also significantly supports that a positive tuberculin test leads to a higher chance of treatment success and was assumed to be due to development of immune response to the MTB.\textsuperscript{9} However, this patient demonstrates a good response to treatment despite being a male and showing no reaction on tuberculin test.

\textbf{Conclusion}

CTB is a rare entity and the outcome is rarely reported. This case posed its own diagnostic challenges and high level of suspicion is needed due to the variable clinical manifestations. Early and specific diagnostic screening may improve patient’s prognosis.

\textbf{Conflict of Interest Declaration}

The authors have no conflict of interest to declare.

\textbf{Acknowledgement}

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\textbf{References}

CASE REPORT

Case Series of Akurit-4 Associated DRESS

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Summary
We describe nine cases of anti-tuberculosis DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome, a potentially serious complication of treatment that led to interruption of treatment, systemic corticosteroid usage and the resumption of treatment with different regimens. All patients had skin rash, six out of nine patients with hepatitis, two out of nine patients had acute kidney injury, five out of nine patients died. All-cause mortality is high in our cohort.

Key words: Akurit-4; Tuberculosis; DRESS

Introduction
Saltzstein and Ackerman in 1959 described a cutaneous adverse reaction to anticonvulsant drugs that included fever, eosinophilia, lymphadenopathy and sometimes hepatosplenomegaly.1 It was subsequently defined by Bocquet et al as drug rash with eosinophilia and systemic symptoms (DRESS).2 Currently, the Registry of Severe Cutaneous Adverse Reaction (RegiSCAR) scoring system is the diagnostic criteria that is widely used for drug reaction with eosinophilia and systemic symptoms (DRESS).3 DRESS is considered one of the severe cutaneous adverse drug reaction(SCAR) with a case fatality rate of 10–20%.4

DRESS occurs generally between 2 weeks and 3 months after drug initiation and is characterized by fever, rash and visceral involvement. Its not uncommon that antituberculosis drugs are implicated with DRESS.5

In 2012, the Ministry of Health, Malaysia, has launched the third edition of tuberculosis clinical practice guideline to make a Grade A recommendation that prefers fixed-dose combination (FDC) anti tuberculosis drug as the first-line regime for intensive phase treatment for newly diagnosed pulmonary tuberculosis (TB) patient.6 One of the fixed dose combination (FDC) brands that are currently used in Malaysia...
is Akurit-4, that are proven to be bioequivalent to separate-drug regime which consist of EHRZ [ethambutol (E), isoniazid (H), rifampicin (R), and pyrazinamide (Z)] at the same dose level. We describe the experience as a dermatology department in a tertiary referral hospital in the management of DRESS syndrome associated with Akurit-4. A retrospective observational study of nine patients with DRESS syndrome related to drugs used in the treatment of TB was conducted at the Hospital Tengku Ampuan Afzan, Kuantan Pahang, Malaysia between 2017 and 2020. The diagnosis of TB was based on clinical findings and/or smear positivity. The causal relationship between antituberculosis treatment and DRESS was based on history of prior treatment, absence of other medications, the disappearance or improvement of symptoms when treatment was stopped and, in some cases, the recurrence of DRESS when re-administered an anti-tuberculosis drug.

**Case Series**

There were nine patients with predominantly male (seven patients).

Patient number 1 is a 24-year-old lady G2P1 at 22th week period of gestation. She presented with fever associated with maculopapular rash after 35 days treatment with Akurit-4. She was treated with intravenous hydrocortisone, topical corticosteroid and a total course of 14 weeks of tapering prednisolone. Skin biopsy was performed in this case. She had an initial rechallenged with isoniazid after 8th week of SCAR however was withheld due to increment of her ALT. Subsequently at 6th week post-partum (after 14th week post SCAR) she had uneventful desensitization of full regime EHRZ.

Patient number 2 is a 28-year-old Malay gentleman was diagnosed with pulmonary tuberculosis by district clinic and was started Akurit-4 that develop DRESS at Day 10. After the course of systemic corticosteroid, revision of clinical diagnosis was made by respiratory team as bacterial pneumonia and no reintroduction of anti-tuberculosis drug was made.

Patient number 3 has underlying retroviral disease with pulmonary TB and tuberculous lymphadenitis. She developed DRESS 15 days after starting Akurit-4. After her course of prednisolone, she was lost to follow up. Subsequent tracing from a different healthcare centre was found that she had died from pulmonary related complication.

Patient number 4 has underlying Type 2 Diabetes Mellitus (DM) on oral hypoglycaemic agent (OHA). He had first admission at day 15 for DRESS after starting on Akurit-4. He was discharged well with tapering dose of prednisolone. Subsequently was readmitted for recurrent DRESS after introduction of EHRZ. He had six weeks of eventful and prolong hospitalization, that was complicated with line related methicillin-sensitive *Staphylococcus aureus* bacteraemia with infective endocarditis, uncontrolled diabetes that was complicated by erythroderma secondary to DPP4-inhibitors, and an extended spectrum beta-lactamase (ESBL) line related sepsis. He was eventually succumbed due to multi-organ failure.

Patient number 5 had underlying DM presented with severe transaminitis (with peak ALT 2200 U/L and AST 1600 U/L) presented on day 35 after Akurit-4. He succumbed to death due to fulminant hepatic failure. However no documentation in regard to prior level of liver enzymes after the initial course of anti-tuberculosis treatment.

Patient number 6 was a 46-year-old gentleman with underlying retroviral disease and co-infection Hepatitis C. He was admitted for smear positive PTB which complicated with line related enterococcus bacteraemia. He presented with generalized maculopapular rash at day 16 of Akurit-4. He was given initial course of intravenous hydrocortison 100 mg three times daily for five days and subsequently 6 weeks of tapering course of oral prednisolone.

Patient number 7 has multiple comorbidities i.e.: DM, Hypertension, Ischemic heart disease (IHD). His onset of DRESS was Day 14 after

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Case was expanded by the author for the purpose of this case report.
Table 1. Clinical features, biochemical abnormalities, treatment and outcome of nine cases with Akurit-4 drug-related DRESS syndrome

<table>
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<th>Platelet (10^9/L)</th>
<th>Eosinophil (10^9/L)</th>
<th>ALT/AST (μmol/L)</th>
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<th>Initial Treatment Given</th>
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It was difficult to establish a causal relationship between which one or more anti-tuberculosis drugs and DRESS syndrome in these nine cases. As all of these data were collected retrospectively by manual method, some of which had incomplete information. None of the patients undergone laboratory testing of cardiovascular marker (such as creatine kinase (CK) or troponin) or pancreatic enzyme marker (such as amylase or lipase). The clinical information and outcomes are summarised in Table 1.
Discussion

All antituberculosis drugs pose a risk of DRESS syndrome. In general, rifampicin was the most commonly suspected drug because of its larger indications, but in the case of tuberculosis infections, isoniazid was the most commonly suspected drug.8 In our case series, the characteristics of antituberculosis drug-associated DRESS syndrome are consistent with literature data9 with a mean time to onset of 19.4 days. Liver and kidneys were the most frequently involved organs. Skin biopsy were performed in two cases.

A reintroduction of culprit drugs is generally considered contraindicated after a diagnosis of DRESS syndrome. Because of the severity of the tuberculosis infection, the lack of therapeutic options and the risk/benefit balance, a reintroduction could be justified.10

Treatment of DRESS syndrome generally includes withdrawal of the offending drugs, correction of electrolyte imbalance, and administration of corticosteroid. In our clinical practice, systemic corticosteroids have become a mainstay of therapy in the form of intravenous hydrocortisone and prednisolone. The prednisolone dose will be tapered down slowly over course of 8 to 12 weeks as rapid tapering may increase the risk of relapse.9

Other options include intravenous immunoglobulin or plasmapheresis have been reported to show a promising treatment effectiveness.11 As none of our patients received this treatment, further studies are required to establish the benefits of these immunosuppressants.

Based on the larger cohort from Taiwan which include a total of 60 cases, DRESS syndrome has mortality rate of around 10%.4 Among those describe, only two patients on anti-tuberculosis drug and none of them died. In our cohort, five out of nine patients had died due to various reasons (55% mortality rate). This include two patients (22.2%) which attributed directly to fulminant hepatic failure due to DRESS, while the others due do various complication of prolonged hospitalization and comorbidities.

Despite DRESS is a life-threatening syndrome, difficulty in identifying predictive factors for death remain a challenge. It is worth mentioning that five out of six patients with transaminitis died, however whether its usefulness as a marker remain questionable.11 Apart from that, differences of other clinical variables were not found between cases resulting in death and those that survived.

Blood eosinophilia could be a useful marker of disease progression and treatment response and recurrence in patients with DRESS.3 However, more experience and clinical evidence is needed.

Existing human leucocyte antigen (HLA) data is minimal in relation to anti-TB drugs. There has been an association reported in Korean patients with DRESS for the class I allele HLA-C*04:01,12 which extends to the haplotype HLA-A* 11:01-B*15:01-C*04:01. However, these alleles are not reported in the cases presented by Ye et al.13

Our study has several limitations. The retrospective review is subject to publication bias. The conclusions we were able to draw are limited by data gaps in these cases. Some details on clinical and outcome parameters or on therapy were often not described. No HHV-6 serology was done due to unavailability of the test in our centre.

Conclusion

Our case series highlights the diagnosis and challenges in clinical management of Akurit-4 associated DRESS and its high all-cause mortality.

Conflict of Interest Declaration

All authors have no financial/conflict of interest to disclosed.

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References


CASE REPORT

Pyoderma Gangrenosum Arising De Novo Over an Unusual Site: A Case Report

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Summary
Pyoderma gangrenosum (PG) of the breast is a rare rapidly progressive neutrophilic dermatosis, which usually co-exists with severe underlying systemic conditions. A woman presented with a non-healing ulcer over her right breast with characteristic sparing of nipple-areola complex (Bork-Baykal phenomenon). It was diagnosed as pyoderma gangrenosum on the basis of clinico-pathological correlation and managed successfully with systemic corticosteroids and anti-inflammatory drugs along with wound care. The diagnosis and treatment of PG is challenging particularly at unusual sites given the paucity of robust clinical evidence and lack of consensus opinion regarding specific management guidelines. It is imperative that PG is considered as a clinical diagnosis in any patient with enlarging, sterile, necrotic lesions unresponsive to appropriate antibiotics. Early recognition of PG at rare locations can prevent devastating sequelae such as over-zealous surgical debridement and deep tissue infections associated with a chronic open wound leading to severe cosmetic morbidity.

Key words: Pyoderma gangrenosum, Neutrophilic dermatosis, Bork-Baykal phenomenon

Introduction
Pyoderma gangrenosum (PG), a rare inflammatory skin condition of unknown etiology.¹ Annually, three to ten in a million are reported as newly diagnosed cases with 50–70% suffering from underlying systemic diseases like autoimmune (inflammatory bowel disease and rheumatoid arthritis) or hematologic disorders (leukemia and lymphoma).² PG generally presents as an initial papule, pustule or nodule after minor trauma, progressing to painful deep necrotic ulcers that wax and wane over time and may mimic an infection. Common sites are lower extremities (pretibial area) followed by trunk, head, neck, hands, peristomal skin and extracutaneous tissues (lungs, liver, bones) infrequently.³

Breast PG is seldom encountered, with only 43 cases reported worldwide, 70% of which emerged after breast surgical intervention.⁴ PG is often erroneously diagnosed as a necrotizing
infection where surgical intervention initiates pathergic phenomenon and accelerates necrotic process. Herein, we report mammary PG in the absence of systemic association or antecedent surgical manipulation.

Case report
A 52-year-old female presented with a progressively enlarging painful raw area over the right breast since one month. It had started few months ago as a small pus-filled reddish lesion which increased in size and ulcerated. She denied trauma, surgical procedures, fever, weight loss, abdominal or joint pain, diarrhea or similar lesions elsewhere in the past. She had received multiple antibiotic courses without improvement. General and systemic examination were within normal limits except pallor. Local examination showed a single, tender, well-defined eight by seven cm ulcer over the right breast with violaceous margins, undermined edges and healthy pink granulation tissue with sparing of areola and nipple (Figure 1a).

Differential diagnoses kept were pyoderma gangrenosum, Paget’s disease, pemphigus vegetans and atypical mycobacterial ulcer. Laboratory investigations (complete hemogram, liver and renal function tests, C reactive protein, erythrocyte sedimentation rate), chest X ray, ultrasonography of abdomen and pelvis, electrocardiography, 2D Echocardiography and gastroenterology evaluation were normal except anemia of chronic disease and iron deficiency (Hemoglobin-7.8mg/dL, peripheral blood smear showed microcytosis and anisocytosis). Pus culture and Ziehl Neelsen stain were negative. Histopathology (hematoxylin and eosin stain) showed unremarkable epidermis, perivascular mononuclear and dermal neutrophilic infiltration with micro-abscess in subcutaneous tissue in scanner view; (d) Histopathology (hematoxylin and eosin stain) showing neutrophilic infiltration in subcutaneous tissue in 40x.

A final diagnosis of pyoderma gangrenosum was made. Patient was started on tablet prednisolone one mg/kg (tapered off gradually over four months) along with antibiotics (ciprofloxacin, metronidazole, piperacillin-tazobactam and meropenem). Two monthly pulses of injection methylprednisolone (1000 mg for three consecutive days per month) were administered with tablet colchicine 0.5mg twice daily and capsule doxycycline 100mg once daily with wound care. After the first pulse, the ulcer showed marked improvement with shrinking margins. Complete resolution with post-inflammatory pigmentary changes and cribriform scarring was seen after ten months (Figure 1b).

Discussion
French dermatologist Brocq termed pyoderma gangrenosum as “geometric phagedenism”, considering it a bacterial infectious disease.5 Today, it is classified as a neutrophilic...
dermatosis, as histological examination exhibits predominantly neutrophilic infiltrates, without evidence of infection. Although the underlying pathogenesis remains unclear, autoimmune mechanisms of dysregulated inflammation, neutrophilic dysfunction, and genetic factors have been implicated.

Previously, no criteria consistently or reliably distinguished PG from necrotizing soft tissue infections, particularly in the absence of systemic diseases. Recently, a validated set of criteria have been published [1 major criterion: biopsy of ulcer edge demonstrating neutrophilic infiltrate- and 8 minor criteria: (1) exclusion of infection; (2) pathergy; (3) history of inflammatory bowel disease or inflammatory arthritis; (4) history of papule, pustule, or vesicle ulcerating within 4 days of appearing; (5) peripheral erythema, undermining border, and tenderness at ulceration site; (6) multiple ulcerations, at least 1 on an anterior lower leg; (7) cribiform or “wrinkled paper” scar(s) at healed ulcer sites; and (8) decreased ulcer size within 1 month of initiating immunosuppressive medication(s)], wherein one major criterion (skin biopsy demonstrating neutrophilic infiltration) and four out of eight minor criteria (exclusion of infection, history of papule ulcerating within four days, undermined borders and tenderness and decreased size of ulcer within one month of initiating immunosuppressive medication) are mandatory for diagnosis and were fulfilled in our case.

Another subtle clinical clue that helped us confirm the diagnosis of PG was the typical sparing of nipple-areola complex (Bork-Baykal phenomenon). This quaint appearance has been also been reported with capillary malformations and large melanocytic nevi. It is probably attributable to the immunologic privilege imparted by increased quantum of melanocytes in this area. Pathergy (development of skin lesions that resist healing after tissue injury) is an important feature.

Previous cases of PG have been documented after breast surgery and silicon augmentation mastopexy. However, the development of de novo ulcers in the absence of any systemic associations is extremely rare. The clinical course of PG is unpredictable. Skin biopsies for histology and microbiology are critical to narrow the differential diagnosis. Infections that can mimic PG include atypical mycobacterial ulcers, cutaneous tuberculosis, cutaneous leishmaniasis, sporotrichosis, and other deep fungal infections. The non-infectious differential comprises vasculitis, thrombophilia, cutaneous malignancies and drug-induced conditions.

Initial wound cultures yielding skin flora such as *S. aureus* are often erroneously considered the culprit. In true PG, targeted antimicrobial therapy eventually fails, and lesions can progressively enlarge with debridement.

Treatment of PG remains challenging as no single effective therapeutic regimen or consensus guideline exists. Initial investigation for associated underlying systemic disease is crucial as treating this can hasten resolution. For mild disease such as single or superficial lesions, conventional evidence-based first-line treatments involve topical medications such as high-potency corticosteroids or calcineurin inhibitors. There is a paucity of data to inform clinical decision-making when considering second-line systemic therapies (methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide, dapsone, thalidomide, and intravenous immunoglobulins) which are mainly used as steroid-sparing agents for maintenance or in combination with first-line agents for refractory disease. Our case responded remarkably to two pulses of methylprednisolone with daily colchicine and doxycycline (used as anti-inflammatory agents) for ten months.

**Conclusion**

Pyoderma gangrenosum of the breast is a rare entity, to be considered when rapidly progressing ulcerative lesions are observed. Though often correlated to previous surgical treatment or systemic inflammatory and hematologic disorders, our patient developed it de novo. A vigilant clinical examination (particularly for characteristic clues like the
Bork-Baykal phenomenon), histopathological evaluation and systemic assessment is paramount, while treatment with topical or systemic glucocorticosteroids along with adjuvant drugs and wound care is the optimum first-line therapeutic approach.

Conflict of Interest Declaration
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References
CASE REPORT

Subcutaneous Sarcoidosis (Darier Roussy Sarcoid): A Rare Entity of Cutaneous Sarcoidosis

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Summary
Sarcoidosis is a multisystem disease characterised by granulomatous inflammation possibly due to hyperactivation of the immune system; with unknown etiology. Subcutaneous sarcoidosis (also known as Darier Roussy sarcoid) is a rare type of specific cutaneous lesion of sarcoidosis characterised by multiple firm, asymptomatic to mildly tender, mobile, round to oval, and skin coloured nodules. Herein we report a rare case of subcutaneous sarcoidosis.

Key words: Subcutaneous sarcoidosis, Darier Roussy sarcoid, Non-caseating granulomas

Introduction
Sarcoidosis is a multisystem disease characterised by granulomatous inflammation possibly due to hyperactivation of the immune system; with unknown etiology.¹ The clinical features of sarcoidosis can be cutaneous and non-cutaneous. For cutaneous findings, it can be classified into specific and non-specific findings. Subcutaneous nodules (Darier-Roussy sarcoid) is a form of specific cutaneous lesion of sarcoidosis.¹ Subcutaneous sarcoidosis accounts for < 6% of sarcoidosis;² with fewer than 100 cases reported so far.³ Herein we report a rare case of subcutaneous sarcoidosis on both forearms associated with acute polyarthritis in an elderly gentleman.

Case Report
A 69-year-old Indian gentleman with underlying hypertension and type 2 diabetes mellitus for more than 10 years, presented with multiple asymptomatic skin coloured nodules over bilateral forearms for 2 months. Prior to the onset of the nodules, he had an episode of multiple joint pain involving both ankle joints and shoulder girdle of which he was diagnosed with polymyalgia rheumatic (PMR) by a rheumatologist. However, he had no temporal headache or ophthalmic symptoms. This acute episode of polyarthritis was relieved...
drastically with corticosteroid over 24 hours. Subsequently, he noticed multiple soft to firm and painless subcutaneous nodules over both his forearms which gradually increased in size over 2 months. There were no similar nodules on his legs or other parts of his body.

Otherwise he did not experience any cough, shortness of breath, eye symptoms or neurological symptoms. There was no uveitis or peripheral neuropathy. He was diagnosed with gouty arthritis for more than 10 years with history of obstructive uropathy which had resolved. He had been taking allopurinol only when eating seafood which he claimed would precipitate the pain. He had no cardiorespiratory symptoms. Neither had he contact with tuberculosis patient nor contributory family history. He never smoked but drank alcohol on social event. On physical examination, there were multiple non-tender, soft to firm subcutaneous nodules measuring approximately 3cm x 4cm on both forearms with normal overlying and surrounding skin (Figure 1a). It was not attached to the underlying structure.

Respiratory examination was normal and there were no peripheral lymph nodes palpable. There was no organomegaly and examination of other systems were unremarkable. The clinical differential diagnosis included erythema nodosum, nodular vasculitis, rheumatoid nodules, subcutaneous sarcoidosis and subcutaneous granuloma annulare.

**Figure 1** (a) Multiple subcutaneous nodules on left forearm (arrows show the outline of the nodules); (b) low power magnification (4x10) of non-caseating granulomas; (c) Non-caseating granulomatous infiltrate in the dermis extends into subcutaneous fat; (d) Non-caseating granuloma composed of epithelioid histiocytes, multinucleated giant cells and sparse lymphocytes at the periphery. Asteroid body is seen here (arrow); (d) Non-caseating granuloma composed of epithelioid histiocytes, multinucleated giant cells and sparse lymphocytes at the periphery. Schaumann body is seen here (arrow).
Laboratory investigations revealed raised ESR 63 mm/hour, C-reactive protein (CRP) 23, negative rheumatoid factor (RF) and anti-citrullinated cyclic peptide (CCP), serum calcium 2.47 mmol/L, normal complete blood count, renal and liver profiles. Skin biopsy was performed which showed multiple noncaseating granulomatous inflammation in the deep dermis and subcutis (Figure 1b&c). The naked granulomas were composed of epithelioid histiocytes with abundant eosinophilic cytoplasm and oval nuclei containing a small central nucleolus, with variable amount of multinucleated giant cells and only sparse lymphocytes at the periphery. Asteroid body and Schaumann body were seen (Figure 1d&e). Ziehl Neelsen stain for acid fast bacilli and Periodic acid-Schiff stain for fungal body were all negative. Tissue culture for tuberculosis was negative.

Further investigation revealed raised serum Angiotensin Converting Enzyme (ACE) levels (123 U/L) (Normal level: 16-85 U/L) or 2.09 mcKat/L (0.27 – 1.45 mcKat/L). His biochemical profiles, serum calcium and phosphate as well as tumour markers were normal.

The quantiferon gold test for tuberculosis was negative. Other blood investigations revealed Anti-nuclear Antibody (ANA) 1:160 (speckled), Erythrocyte Sedimentation Rate (ESR):40 and Rheumatoid Factor:<20. Plain chest radiography was reported as normal. Computed tomography (CT) scan of the thorax revealed multiple hilar, mediastinal and paraaortic lymph node enlargement consistent with stage I sarcoidosis.

He was diagnosed as subcutaneous sarcoidosis with sarcoid arthritis. He was eventually started on topical clobetasol propionate cream with oral prednisolone 30mg od and tapered off within 1 month. It was combined with oral hydroxychloroquine 200mg od. His skin lesion resolved completely after 1 month of therapy.

Discussion
Cutaneous involvement in sarcoidosis occurs in 20% to 35% of patients and can present as a variety of different morphologies. Cutaneous sarcoidosis can be divided into specific and nonspecific lesions depending on the presence of noncaseating granulomas on histologic studies. Specific sarcoidosis lesions have granulomas on histologic examination and often show the apple-jelly coloration characteristic of granulomatous skin lesions on diascopy. The other differential diagnosis of apple-jelly diascopy include lupus vulgaris, pseudolymphoma and lupoid rosacea. Specific lesions include maculopapules, plaques, subcutaneous nodules, lupus pernio, scar infiltration, annular, verrucous, lichenoid, psoriasiform angiolupoid and ulcerative lesions. Nonspecific skin lesions are lack of granulomas and caused by inflammatory reactions to sarcoidosis. The most common nonspecific lesions are erythema nodosum, erythema multiforme, calcifications, prurigo, nail clubbing, and Sweet syndrome.

Subcutaneous sarcoidosis (also known as Darier-Roussy sarcoidosis) is a rare form of cutaneous sarcoidosis. Clinically it is characterized by multiple firm, asymptomatic to mildly tender, mobile, round to oval, and skin coloured nodules. It commonly involves the extremities, but the trunk and face can also be affected. It is more prevalent in middle aged women, who commonly presents with lymphadenopathy or pulmonary infiltrates on chest imaging; as well as elevated levels of serum ACE.

Systemic involvement was noted in 64% and 60% of patients with specific and nonspecific skin lesions respectively in a review of 120 patients with cutaneous sarcoidosis. Pulmonary sarcoidosis is the most common manifestation of systemic involvement with up to 90% of patients having abnormal chest radiographs. Bilateral hilar adenopathy (stage I disease) is seen in about half of patients with intrathoracic sarcoidosis. Ocular sarcoidosis is seen in one-third of patient with sarcoidosis with at least two-thirds of cases have anterior uveitis while posterior uveitis occurs in up to 28% of sarcoidosis cases.
Other important systemic involvement include cardiac, hepatic and neurological sarcoidosis. Hypercalcemia and hypercalciuria can be seen in patients with sarcoidosis due to activated macrophages in sarcoidal granulomas which promote conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D leading to increased intestinal absorption of calcium, bone resorption, and urinary calcium excretion.\textsuperscript{6}

Being a great imitator, diagnosis of cutaneous sarcoidosis requires a high index of clinical suspicion. Cutaneous sarcoidosis is usually an early manifestation of the disease in up to one third of cases.\textsuperscript{10} This should prompt the clinician to evaluate for systemic involvement. Moreover, the skin is a convenient source for tissue biopsy and therefore the diagnosis of cutaneous sarcoidosis can be made more rapid than other forms of sarcoidosis. A reasonable diagnosis of cutaneous sarcoidosis can be made in most cases from the appearance of skin lesions supported by confirmatory histology after excluding other noncaseating granulomatous diseases.\textsuperscript{6}

The characteristic histologic finding of sarcoidosis is presence of noncaseating epithelioid granulomas, with minimal or absence of lymphocytes or plasma cells (naked granuloma).\textsuperscript{11} In subcutaneous sarcoidosis, the non-caseating granulomas is present in the subcutaneous tissue.\textsuperscript{12} Within the giant cells, Schaumann bodies and Asteroid bodies may be found but are not specific for sarcoidosis.\textsuperscript{6} Schaumann bodies are rounded, laminated basophilic inclusions that represent degenerating lysosomes and observed in 48%-88% of cases in sarcoidosis.\textsuperscript{13} Schaumann bodies can also be seen in other inflammatory granulomatous conditions such as tuberculosis, chronic beryllium disease, hypersensitivity pneumonitis and Crohn’s disease.\textsuperscript{14} Asteroid bodies are star-shaped spiculated structures that represent engulfed collagen seen as eosinophilic stellate inclusions and it is observed in 2%-9% of sarcoidal granulomas.\textsuperscript{15} Asteroid bodies are most commonly seen in sarcoidosis, histoplasmosis and foreign body granulomas, but can be seen in any multinucleated giant cells formation.\textsuperscript{16}

Angiotensin-converting enzyme (ACE) levels can be increased in up to 60\% of cases with sarcoidosis but the value as a diagnostic test and prognostic marker remains limited.\textsuperscript{6} It is because serum ACE levels may also be raised in other granulomatous diseases and can be influenced by genetic polymorphisms.\textsuperscript{16} In view of lack of a specific diagnostic test, sarcoidosis is a diagnosis of exclusion and diagnosis requires the following 3 criteria: clinicoradiographic findings compatible with the diagnosis, histologic confirmation of noncaseating granuloma and exclusion of other known causes of granulomatous disease.\textsuperscript{17}

Differential diagnosis of subcutaneous sarcoidosis include erythema nodosum, subcutaneous granuloma annulare, tuberculosis, rheumatoid nodules, epidermal cyst, lipoma, and deep mycosis.\textsuperscript{5} Based on the clinical and histopathological findings in our patient, diagnosis of subcutaneous sarcoidosis was made after excluding all the above differential diagnosis.

Corticosteroid is the mainstay treatment for sarcoidosis as it suppresses inflammation and halt the progress of granuloma formation.\textsuperscript{18} Ultrapotent corticosteroid (e.g. Clobetasol) is the drug of choice for limited mild cutaneous lesions.\textsuperscript{18} Intralesional corticosteroids are used for small sarcoid plaques and papules, with dose of 3-20mg/ml repeated 4 weekly until the lesions have flattened.\textsuperscript{18} Systemic corticosteroid is indicated for severe disfiguring or destructive lesions, widespread involvement, and lesions refractory to localized treatment.\textsuperscript{18} Prednisolone dose ranges form 0.3-0.5mg/kg/day; with responses noted within 4-8 weeks after initiation of treatment.\textsuperscript{3}

Second line therapy are reserved for steroid-resistant sarcoidosis and for patients who are unable to tolerate steroids.\textsuperscript{18} Examples of second-line therapy include antimalarial therapy, cytotoxic agents such as methotrexate, azathioprine, leflunomide, and mycophenolate.\textsuperscript{5} Antimalarial agents (e.g. chloroquine and hydroxychloroquine) have anti-inflammatory
properties, but relapse of sarcoidosis following discontinuation of therapy is very common.\textsuperscript{18} The recommended dose of hydroxychloroquine is 200-400mg/day for at least 12 weeks to induce clinical improvement. Methotrexate is given at 10-25mg/week for at least 6 months to be effective.\textsuperscript{19}

Biologics are reserved as third-line therapy, of which infliximab can be a good choice.\textsuperscript{18} Alternative treatment modalities for sarcoidosis include pentoxyfylline, tetracyclines, thalidomide, isotretinoin, allopurinol, cyclosporin and laser therapy.\textsuperscript{4,18} Newer treatment that have been proven effective include repository corticotropin injections and rituximab.\textsuperscript{4} For our patient he was started on oral prednisolone 30mg od (at 0.5mg/kg/day), hydroxychloroquine 200mg od and topical corticosteroids with complete resolution of lesion following 1 month of therapy.

**Conclusion**

Subcutaneous sarcoidosis is rare, which requires clinicopathology correlation for diagnosis. It remains a diagnosis of exclusion. Cutaneous sarcoidosis remains one of the great imitators due to its varied clinical presentation. The hallmark of histopathology examination is a naked or sarcoidal non-caseating granuloma. The mainstay of treatment for sarcoidosis include corticosteroid, antimalarials and methotrexate.

**Conflict of Interest Declaration**

The authors have no conflict of interest to declare.

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**References**

CASE REPORT

A Case of Isolated Trichorrhexis Nodosa and Trichoscopic Images

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Summary
Trichorrhexis nodosa (TN) is a hair shaft disorder characterized by fragile hair with nodes on the hair shaft. Here we report a case of acquired localized trichorrhexis nodosa and describe the importance of noninvasive tools like trichoscopy and light microscopy in the diagnosis of an isolated TN.

Key words: Trichorrhexis nodosa, Hair shaft, Nodes, Trichoscopy

Introduction
TN is a hair shaft disorder characterized by fragile hair with nodes on the hair shaft. It may be congenital, acquired or occur secondary to physical and chemical trauma. Careful history taking and simple examination can avoid unnecessary tests and can diagnose this condition. Here we report a case of acquired localized trichorrhexis nodosa and describe the importance of noninvasive tools like trichoscopy and light microscopy in the diagnosis of an isolated TN.

Case Report
A 28-year-old man presented with a lock of hair on the frontotemporal hairline that was different from the rest (Figure 1a). The patient had no systemic medical illnesses and there was no family history of similar illness. He denied history of trauma, itching, use of hair cosmetics, hair bleaching, hair dyes, hair perming or straightening.

On examination the hair was dry, brittle and of varying lengths, there were multiple white spots along the hair shafts in the affected area and the hair over the rest of the scalp was normal. Differential diagnosis considered was pediculosis capitis, peripilar keratin casts, trichorrhexis nodosa and white piedra.

Trichoscopy demonstrated broken hair shafts and white nodes along hair shafts (Figure 1b). Light microscopy (40x) showed fraying of cortical fibers giving the appearance of two paint brushes thrust together (Figure 1c). Based on Trichoscopy and light microscopy, diagnosis of trichorrhexis nodosa was confirmed. As
there was no evident cause for trichorrhexis nodosa in this patient we suspected physical or chemical trauma as an incriminating factor. We also advised him to use straight combs with elongated bristles. Patient was also given multivitamins (B-complex forte) and asked to look out for any habit tics that may be causing cuticle damage.

Discussion
Trichorrhexis nodosa was first described by Samuel Wilks in 1856 and it was named by M. Kaposi in 1876. It may be congenital, acquired or associated with some disorders like hypothyroidism, Menke’s kinky hair syndrome, argininosuccinicaciduria and iron deficiency. Acquired TN, however, is much more frequent and is classified into 3 major groups: proximal (predominantly among blacks) or distal (the most common in Spain) according to the area of the hair shaft in which the nodules appear, and localized.

Very few cases of localized TN have been reported in the literature. Its main clinical characteristic is that it is limited to well defined hairy areas generally the scalp, but also the beard, moustache, pubic hair, etc. Several factors including physical traumas that may cause sufficient damage to the hair shaft include excessive brushing, back combing, stressed hairstyles, the application of heat, and prolonged exposure to ultraviolet light. Chemical traumas include excessive exposure to salt water, shampooing, setting, perming, bleaching, and dyeing of hair.

Macroscopically, hair shafts affected by Trichorrhexis nodosa contain small white nodes at irregular intervals throughout the length of the shaft. The number of nodes may vary from one to several, depending on the length of the hair. These nodes represent areas of cuticular cell disruption, which allows the underlying cortical fibers to separate and fray. The cortical fibers display outwards and fracture, giving the node the microscopic appearance of two brooms or paintbrushes thrust together end to end by their bristles. Complete breakage often occurs at these nodes. There is no specific treatment...
for TN. The only possible effective measure is to identify the predisposing factors and to avoid repeated traumas. Certain coadjuvant treatments (such as hair repairers or vitamin complexes) can also be helpful. 7,8

Trichoscopy is a non-invasive diagnostic tool. It allows detailed visualisation of hair and provides clues for inherited and aquired causes of hair loss. Hair examination using trichoscopy and light microscope in routine clinical practice may provide useful information for the correct diagnosis, ranging from common head and pubic lice infestations to rarer shaft abnormalities.9,10

**Conclusion**
Trichorrhexis nodosa is a hair shaft disorder that can be easily diagnosed with a careful history and simple examination using dermatoscopy and light microscope which can thereby avoid unnecessary tests.

**Conflict of Interest Declaration**
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