

The Epidemiology and Treatment of Anogenital Warts in Singapore: A Retrospective Evaluation

Y C Chan,*^{MBBS, MRCP (UK)}, K Y Ng,**^{SRN}, R K W Chan,***^{FAMS, MBBS, MRCP}

Abstract

Introduction: A retrospective study in the referral centre for sexually transmitted infections (STIs) in Singapore to describe the epidemiology and treatment outcome of patients with anogenital warts. **Subjects and Methods:** We reviewed the case records of 301 patients with anogenital warts who were seen over a 1-year period (1999). We also attempted to interview every patient by telephone to find out if they had any clinical recurrences for which treatment was sought elsewhere. **Results:** There were 255 males and 46 females with a mean age of 34 years. Two hundred and nineteen (72.8%) presented with symptoms lasting 12 weeks or less. In males, warts occurred most frequently in the preputial cavity (52.5%) and on the penile shaft (40.8%). In females, they occurred most frequently on the external genitalia (91.3%). Two hundred and thirty-five males were treated with cryotherapy and 69% (95% CI, 62.6% to 74.8%) achieved clinical resolution after a mean of 6 treatment cycles. Seven males were treated with podophyllin 0.25% in ethanol and 71% (95% CI, 29.0% to 96.3%) were clinically cured after a mean of 4 treatment cycles. Thirty-nine females were treated with cryotherapy and 67% (95% CI, 49.8% to 80.9%) achieved clinical cure after a mean of 4 treatment cycles. Of the 290 patients treated at the centre, 212 (73%; 95% CI, 67.3% to 77.8%) patients (184 males, 28 females) achieved clinical cure after a mean of 7 weeks (range, 1 to 34 weeks); 90% (95% CI, 86.0% to 93.2%) of them by 15 weeks. Seven-two patients defaulted follow-up and 6 responded partially to treatment. Of the 212 patients who achieved clinical cure, 195 were interviewed by telephone, on an average, 17.7 months after clinical resolution. Thirty-seven (19%; 95% CI, 13.7% to 25.2%), all males, relapsed clinically after a mean of 100 days (range, 5 to 329 days); 90% (95% CI, 84.6% to 93.6%) relapsed by 228 days. **Conclusions:** Podophyllin 0.25% in ethanol was the most cost-effective treatment for males. One in 5 patients had a recurrence of their warts and most had their recurrence within 8 months of initial resolution.

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Introduction

Anogenital warts are caused by specific subtypes of the human papillomavirus (HPV), of which serotypes HPV 6 and 11 are the most common. There are 3 types of HPV infection:¹

- 1) clinical—visible papules and plaques;
- 2) subclinical—unnoticed by the patient, but detectable by “acetowhitening” or histology. The phenomenon of “acetowhitening” refers to HPV-infected areas being whitened by the application of 3% to 5% acetic acid for 5 to 10 minutes;
- 3) latent—no acetowhitening or histological changes but the HPV DNA is present and may be subsequently reactivated.

To date, the transmission and infectivity of HPV is not fully elucidated.² Transmission of HPV is believed to be facilitated by the presence of clinically-apparent lesions.³ Treatment of clinically-apparent warts is performed for cosmesis as well as to reduce the viral burden in the hope

of decreasing transmission. The majority of treatment studies have follow-up periods of less than 6 months and the risk of recurrence following clinical resolution after 3 months is poorly documented.⁴ In addition, most studies do not analyse the response to treatment according to the site of occurrence of the warts.

We conducted a retrospective study in the Department of STD Control (DSC), which is the referral centre for sexually transmitted infections (STIs) in Singapore, to describe the epidemiology and treatment of patients with anogenital warts.

Subjects and Methods

All patients who attended the DSC, with previously untreated visible anogenital warts over a 12-month period (1 January 1999 to 31 December 1999), were entered into the study. The diagnosis of anogenital warts was based on clinical evaluation. The treatment modalities used and our definition of one treatment cycle for the purpose of this

* Registrar

** Staff Nurse

*** Senior Consultant

National Skin Centre

Address for Reprints: Dr Chan Yuin Chew, National Skin Centre, 1 Mandalay Road, Singapore 308205.

study are shown in Table I. Podophyllin 0.25% in ethanol is formulated in the DSC by dissolving 0.25 g of podophyllin resin powder in 100 mL of ethanol.

All the patients were routinely offered screening for syphilis and human immunodeficiency virus (HIV) infection. Relevant investigations for other STIs were done if the patients had symptoms or signs to suggest their presence. The appropriate treatment for these diseases was given according to the DSC guidelines.⁵ Patients were followed-up until their anogenital warts had clinically resolved and all other STIs had been appropriately treated. They were then instructed to return to the clinic if they had any recurrence.

During the period December 2000 to April 2001, we reviewed their case records. Health advisors at the DSC contacted patients by telephone to confirm the findings in the case records, to fill in missing details and, in particular, to find out whether the patients had any recurrence of anogenital warts for which he or she had not sought treatment at the DSC. A maximum of 3 telephone calls were made on 3 separate days at different times of the day to contact each patient; failing which, he or she would be classified as “uncontactable”.

The mean number of treatment cycles required for clinical resolution was analysed using Kruskal Wallis test. The number of patients who achieved clinical resolution and the percentage relapse in this group of patients were analysed using Fisher’s exact test. A *P* value of less than 0.05 was considered significant.

Results

The case records and telephone interviews were reviewed, on an average, 18 months from the date of first diagnosis.

Patient Characteristics

A total of 301 patients with previously untreated anogenital warts attended the DSC in the period 1 January 1999 to 31 December 1999. There were 255 males and 46 females, giving a male-to-female ratio of 5.5:1. The mean age at presentation was 34 years, with a range of 18 to 72 years. The mean age at presentation for males was 34 years (range, 20 to 72 years) and that for females was 31 years (range, 18 to 65 years). The majority of patients [238 (79%)] were aged 40 years or below. There were 247 Chinese (82%), 20 Indians (6.6%), 12 Malays (4%) and 22 patients (7.4%) of other races, mainly Thais, Bangladeshis and Caucasians.

The median duration of symptoms at presentation was 4 weeks, with a range of 1 to 250 weeks. The majority of patients [219 (73%; 95% CI, 67.4% to 77.8%)] had symptoms lasting 12 weeks or less. However, there was a small but substantial group of 37 patients (12.3%; 95% CI, 8.8% to 16.5%) who sought medical attention only after having symptoms for 2 years or more.

Distribution and Number of Warts

The distribution and number of lesions for males and females are presented in Tables II and III, respectively (some patients had warts on more than one site). In males,

TABLE I: TREATMENT MODALITIES FOR ANOGENITAL WARTS AND DEFINITION OF TREATMENT CYCLES

Treatment	1 treatment cycle defined as
Liquid nitrogen	1 session (done by a staff nurse in the clinic once a week)
Podophyllin 0.25% in ethanol Podophyllotoxin 0.5% solution	3 consecutive days of twice daily self application per week (done by the patient)
Podophyllin 25% in tincture benzoin	1 session a week (done by a staff nurse in the clinic)
Imiquimod 5% cream	3 alternate days of once daily self application per week (done by the patient)
Electrodestruction	1 session (done by a doctor in the clinic)

TABLE II: DISTRIBUTION AND NUMBER OF ANOGENITAL WARTS IN 255 MALES

Site	1 to 5 warts	6 to 10 warts	>10 warts	No. of warts unrecorded	Total (%)
Urethra	19	0	0	0	19 (7.5)
Preputial cavity	59	11	24	40	134 (52.5)
Penile shaft	50	8	17	29	104 (40.8)
Scrotum	9	2	1	5	17 (6.7)
Perianal	7	2	0	8	17 (6.7)
Anal canal	4	0	0	0	4 (1.6)

TABLE III: DISTRIBUTION AND NUMBER OF ANOGENITAL WARTS IN 46 FEMALES

Site	1 to 5 warts	6 to 10 warts	>10 warts	No. of warts unrecorded	Total (%)
External genitalia	15	6	9	12	42 (91.3)
Vagina	1	1	1	5	8 (17.4)
Cervix	6	0	0	0	6 (13.0)
Perianal	4	0	4	3	11 (23.9)
Anal canal	0	0	0	0	0 (0)

TABLE IV: RESPONSE OF PATIENTS TO THE INITIAL TREATMENT MODALITY

Treatment modality	No. of patients treated	Mean no. of treatment cycles required for resolution	Median no. of treatment cycles required for resolution	No. of patients who achieved clinical resolution (%)	% relapse in those who achieved clinical resolution (n)
Male					
Liquid nitrogen	233	6	5	160 (69%)	22% (36)
Podophyllin 0.25% in ethanol	7	4	3	5 (71%)	20% (1)
Podophyllin 25% in tincture benzoin	4	5	4	3 (75%)	0% (0)
Imiquimod	7	10	12	3 (43%)	0% (0)
Female					
Liquid nitrogen	39	4	3	26 (67%)	0% (0)

Note: too few male patients were treated with podophyllotoxin and electrodesiccation to give meaningful results

TABLE V: COMPARATIVE COSTS OF TREATMENT MODALITIES IN MALES

Therapy (no. of patients who were treated)	Cost to patient per week (\$\$)		Mean no. of weeks to achieve resolution	Total cost (\$\$) ^b	Effectiveness ^c	Cost index ^d
	Treatment fees	Possible loss of earnings ^a				
Liquid nitrogen (233)	4.88	26.92	6	190.80	54%	353
Podophyllin 0.25% in ethanol (7)	3.35	6.97	4	41.28	57%	73
Podophyllin 25% in tincture benzoin (4)	4.88	26.92	5	190.80	75%	254
Imiquimod 5% cream (7)	10.95	6.97	10	179.20	43%	417

^a due to time spent in attending the DSC clinic and on treatment in the clinic

^b cost per week x mean no. of weeks needed to achieve clinical resolution

^c calculated as clinical resolution rate x (1- relapse rate)

^d total cost/effectiveness

warts occurred most frequently in the preputial cavity and the penile shaft. In females, they occurred most frequently on the external genitalia, which included the labia majora, labia minora, fourchette and introitus. Of the 42 women with warts on the external genitalia, 8 (19%) also had warts in the vagina or cervix.

Four male patients had warts in the anal canal, 3 were homosexuals with a history of receptive anal intercourse and had concurrent perianal warts. One was a heterosexual with concurrent penile shaft warts; he had no history of receptive anal intercourse.

Response to Treatment

The response of patients to the initial treatment modality

is shown in Table IV. In males, the majority (233/251) were treated with liquid nitrogen, 69% (95% CI, 62.6% to 74.8%) of whom achieved clinical resolution after a mean of 6 treatment cycles. Seven males were treated with podophyllin 0.25% in ethanol, 71% (95% CI, 29.0% to 96.3%) of whom were clinically cured after a mean of 4 treatment cycles. However, neither the number of treatment cycles required for clinical resolution ($P = 0.051$) nor the number of patients who achieved clinical resolution ($P = 0.521$) were significantly different among the 4 treatment modalities. All the females were treated with liquid nitrogen and 67% (95% CI, 49.8% to 80.9%) achieved clinical resolution after a mean of 4 treatment cycles.

We also analysed the response to the initial treatment

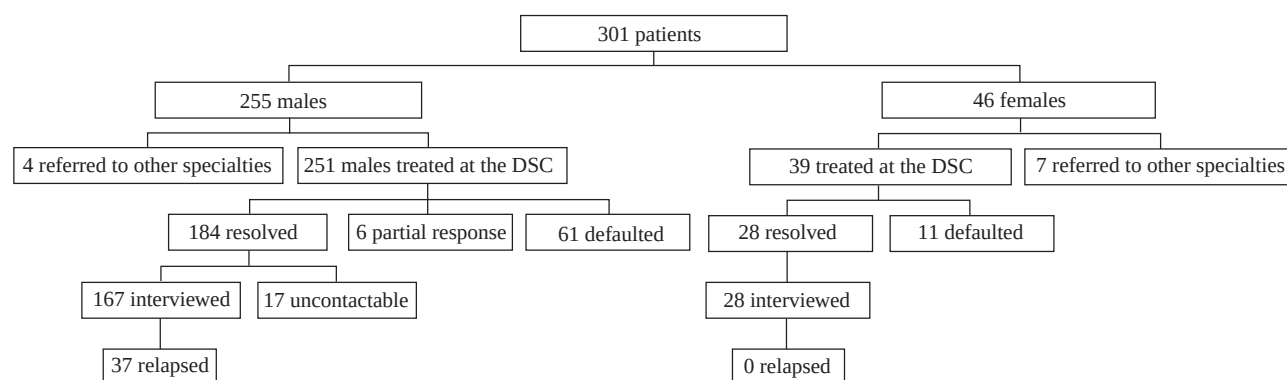


Fig. 1. Treatment outcome of 301 patients with anogenital warts.

modality according to the site of occurrence of the warts in both male and female patients (data not shown). For analysis according to the site of occurrence, we disregarded patients with warts in more than one site.

In males, anal warts were disregarded as they did not occur in isolation. We have the most experience with liquid nitrogen: clinical resolution of 62% to 91% was achieved after a mean of 5 to 8 treatment cycles. Scrotal warts were the most successfully treated (91%), and urethral warts were the least (62%). We referred 1 patient with urethral warts and another 3 with anal and perianal warts to urological and colorectal surgeons, respectively, for further treatment.

In females, vaginal warts were disregarded as they did not occur in isolation. We referred 6 patients with cervical warts to gynaecologists for further treatment. For external genital warts, 75% achieved clinical cure with liquid nitrogen therapy.

Treatment Outcome (Fig. 1)

Eleven patients were referred to other specialties (urology, gynaecology and colorectal surgery) for further management: 4 males (1 had anal, 2 had perianal and 1 had urethral warts) and 7 females (6 had cervical warts and 1 had concurrent pelvic inflammatory disease).

Of the remaining 290 patients, 212 (73%; 95% CI, 67.3% to 77.8%) patients (184 males, 28 females) achieved clinical resolution. The diagnosis of clinical resolution was made on physical examination of 199 patients and based on telephone interview in 13 patients, who were all males. The mean duration to clinical resolution was 7 weeks (range, 1 to 34 weeks), regardless of treatment modality used; 90% (95% CI, 86.0% to 93.2%) of them achieved clinical resolution by 15 weeks. One hundred and eighty-four males (73% of male patients treated at the DSC) achieved clinical resolution after a mean of 6 weeks; 90% (84.3% to 93.7%) of them by 13 weeks. Twelve of the 184 male patients required a second treatment modality. Twenty-

eight females (72% of female patients treated at the DSC) achieved clinical resolution after a mean of 9 weeks; 90% (95% CI, 71.8% to 97.7%) by 18 weeks. Seventy-two patients (61 males, 11 females) defaulted follow-up and could not be contacted by phone, and 6 patients (all males) had partial response to treatment and declined further treatment.

Relapse after Clinical Resolution (Fig. 1)

Of the 212 patients who achieved clinical resolution, we were able to interview 195 (92%) by telephone after a mean period of 17.7 months after clinical resolution. Thirty-seven (19%) patients, all males, reported a clinical relapse after a mean of 100 days (range, 5 to 329 days). Of these 37 male patients, 50% (95% CI, 31.9% to 65.6%) relapsed by 79 days and 90% (95% CI, 74.6% to 97.0%) relapsed by 228 days.

The relapse rates for each of the main modes of treatment over a mean period of 17.7 months are shown in Table IV. In those who achieved clinical resolution with podophyllin 25% in tincture benzoin and imiquimod as the initial therapy, none relapsed. The relapse rates for liquid nitrogen and podophyllin 0.25% in ethanol were 22% (95% CI, 16.3% to 29.8%) and 20% (95% CI, 0.51% to 71.6%), respectively. However, this difference in relapse rate among the 4 treatment modalities did not reach statistical significance ($P = 0.577$).

Association with HIV Infection

Two hundred and seventy-eight patients (235 males, 43 females) (92.3%) were screened for HIV infection. Eight patients (2.9%; 95% CI, 1.3% to 5.6%), 6 males and 2 females, tested positive (confirmed by the Western Blot). Twenty-three patients declined HIV screening.

In the HIV positive group of patients, 2 men were treated with liquid nitrogen for preputial warts: one had 1 to 5 warts and achieved clinical resolution after 3 treatment cycles;

the other had 10 to 15 warts and needed 34 treatment cycles. One man had 1 to 5 urethral warts with partial response despite 10 cycles of liquid nitrogen followed by 8 cycles of podophyllin 25% in tincture benzoin. One woman with cervical warts was referred to the gynaecologist for further treatment. The remaining 4 patients (50%) defaulted treatment at the DSC and were uncontactable.

Association with Syphilis

Two hundred and eighty-four patients (241 males, 43 females) (94.4%) were screened for syphilis using the VDRL test. Three patients (1.1%; 95% CI, 0.22% to 3.1%), all males, tested positive (confirmed by the TPPA test). Seventeen patients declined screening for syphilis.

Association with Other STIs

Twenty-six other patients had a concurrent STI; 2 patients had more than one other STI. Five had non-gonococcal urethritis, 13 had herpes genitalis, 5 had gonorrhoea, 1 had chlamydia urethritis, 2 had mucopurulent cervicitis, 1 had trichomonas vaginitis and 1 had hepatitis B infection.

Cost-effectiveness of Treatment at the DSC

The comparative costs of some treatment modalities in our male patients are shown in Table V. Too few male patients were treated with podophyllotoxin and electro-dessication to give meaningful results; these 2 treatment modalities were excluded in the analysis. We also excluded patients who needed more than 1 treatment modality. We did not do a similar comparison for female patients as none were treated with modalities other than liquid nitrogen.

Calculations were thus made⁶—we first calculated the weekly cost of treatment to the patient according to the treatment regimens given in Table I, with the assumption that the patient consulted the doctor on an average of every 4 weeks. For example, if he had been treated with liquid nitrogen, in a month he would spend \$12 on medical consultation and \$7.50 on treatment, giving an average of \$4.88 per week. We estimated that he would have spent about 106 minutes per week on transport, waiting, consultation and treatment. This would translate to a loss of earnings amounting to \$26.92. This is based on the average Singapore monthly wages of \$3063 and the average number of hours worked per week of 47.1, giving the average worker a salary of \$15.20 per hour.⁷ The mean number of weeks to achieve clinical resolution was 6, and from this we were able to calculate the total cost required for a successful outcome. The effectiveness was calculated as clinical resolution rate (this was 69% in Table IV) x (1 relapse rate); the relapse rate following liquid nitrogen in this study was 22%. Finally, the cost index was calculated as total cost/effectiveness and this (\$353) was an estimate of the average cost to completely clear a patient of lesions using liquid nitrogen treatment.

Discussion

The Centres for Disease Control and Prevention recommend the following regimens for first-line treatment of anogenital warts:⁸

- 1) patient applied therapies e.g., podophyllotoxin and imiquimod;
- 2) provider administered therapies e.g., liquid nitrogen, trichloroacetic acid and surgical removal.

The treatment of choice is determined by several factors, including number, size, morphology and anatomic site of the warts, treatment cost, patient preference, provider experience and possible adverse effects. The actual cost of treating warts is a complex function of the costs of medication, services of health care workers and time spent in attending the clinic as well as the effectiveness of therapy, which in turn determines the average number of visits needed to completely clear the lesion. In our study, podophyllin 0.25% in ethanol was the most cost effective treatment. The next most cost effective treatment modality was podophyllin 25% in tincture benzoin, followed by liquid nitrogen and imiquimod cream. The cost index for provider administered therapies would be even greater (and hence less cost effective) for patients with higher salaries and if we had included clinic maintenance and manpower costs. Podophyllotoxin was found to be the most cost effective in a review paper.⁹ We did not have enough patients treated with podophyllotoxin or electrosurgery in this study for comparison.

Podophyllin is a plant compound that causes cells to arrest in mitosis, leading to tissue necrosis. It is not a standardised compound, so the efficacy varies among batches. It should be applied sparingly to each wart and allowed to air dry. To minimise irritation, it should be washed off in 4 hours. In excess amounts, it can be systemically absorbed and is associated with a risk of complications, including hypokalaemia, peripheral neuropathy, bone marrow suppression and coma.¹⁰ Goh et al¹¹ found that podophyllin 0.5% or 0.25% in ethanol was as efficacious as the conventional podophyllin 25% in tincture benzoin which required regular clinic visits for application by a trained staff nurse. Podophyllin 0.5% or 0.25% in ethanol can be used by patients for self treatment at home and was more cost effective than the conventional therapy. Patients who used podophyllin 0.25% showed a similar clearance rate as podophyllin 0.5% but with no side effects. It should be noted that podophyllin in ethanol is compounded in house by our pharmacy and not commercially available. Podophyllotoxin is a pure standardised compound that is the major biologically active lignan of podophyllin resin. It is more efficacious and has a lower potential for systemic toxicity. It is, however, much more costly. This class of drugs is contraindicated in

pregnancy.

Cryotherapy with liquid nitrogen eradicates warts by thermal cytolysis. It is a safe and comparably effective method that can be used for eradication of warts in any location. Patients will likely experience pain and blistering; the former often prevents thorough treatment of the lesions. Topical anaesthesia with EMLA (lignocaine/prilocaine) cream may help.

A review of 40 studies showed that no one treatment was consistently superior to the others in efficacy.⁹ All therapies demonstrated highly variable success and recurrence rates. Our experience in treatment of male patients was similar. However, the small cohort of male patients treated with modalities other than liquid nitrogen may also have contributed to the lack of a significant difference between the treatment modalities. In our study, 73% of the male and female patients achieved clinical resolution after a mean of 7 weeks, regardless of the treatment modality used. We feel that this may be an underestimation as some of those who defaulted may have done so because they had achieved clinical resolution of their anogenital warts. The majority (90%) of male and female patients had achieved clinical resolution after 13 and 18 weeks, respectively.

The majority of treatment studies in the literature have follow-up periods of less than 6 months and the risk of recurrence of genital warts after 3 months of clinical clearance is poorly evaluated.⁴ Regardless of the treatment used, the majority of studies showed recurrence rates of 15% to 60% within 3 months.^{2,12} This is likely to be related to subclinical infection of surrounding skin and mucosa.¹³ We were able to interview, by telephone, 92% of our patients who had achieved clinical resolution. This was done, on an average, 17.7 months post clinical resolution. Nineteen per cent of those interviewed had a clinical relapse after a mean of 100 days. It has been noted that treatment appeared to be more effective with warts that are present for less than 1 year.¹⁴ Most of our patients presented early, with 73% having had symptoms for less than 12 weeks. This may allow for more effective treatment and explain the relatively low rate of recurrence in our study. Another possibility is the underreporting of clinical relapses due to warts recurring in areas which are not easily visualised. None of the 28 female patients who were successfully treated noticed any clinical relapse; this could be an underrepresentation as the patient may not notice warts that had recurred in the vagina or the cervix.

The use of condoms should be advised until all the genital warts have cleared clinically. As the majority of recurrences occurred within 8 months (more than 90% of those who eventually relapsed had done so by this time), it may be prudent to advise condom use for at least 8 months following clinical resolution. However, couples in long-term

relationships may choose not to use condoms once the genital warts have cleared clinically as it is highly likely that the regular partner of someone with genital warts would already have been infected with HPV.^{15,16} Although the use of condoms to prevent transmission of subclinical HPV infection is not established, patients who engage in high-risk sexual behaviour should be advised to use condoms to prevent transmission of other sexually transmitted diseases.

The most frequent locations of anogenital warts i.e., the preputial cavity in men and external genitalia in women are considered to be more susceptible to infection because of the epithelial damage that generally incur during sexual intercourse.¹⁷ In our study, 19% of women with warts on the external genitalia also had vaginal or cervical warts; this justifies routine thorough gynaecologic examination in all female patients.

Some patients, as in one of our male patients, had anal warts but had never practised anal intercourse. These patients may be embarrassed as having warts at this site may suggest otherwise. They can be reassured that anal warts are widely known to occur in the absence of reported anal intercourse.^{18,19}

In conclusion, anogenital warts are a common sexually transmitted infection. Treatment of visible warts is justifiable, both for cosmesis as well as to reduce the possible viral burden which may enhance transmission of infection. In our study, the majority of patients were clinically cured within 4 months. We found podophyllin 0.25% in ethanol to be the most cost effective treatment for males. One in 5 patients had a recurrence of their warts and most had their recurrence within 8 months of initial resolution.

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