

Common Viral Skin Diseases in Clinical Practice: **Treatment of Cutaneous Warts: An Updated Inventory of Therapeutic Options**

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Slide 1: Treatment of Cutaneous Warts: An Updated Inventory of Therapeutic Options

Hi, I'm Bob Skinner. I am here today to talk about the treatment of cutaneous warts. This will be an updated inventory of current therapeutic options.

Slide 2: Disclosure

This is my disclosure, consultant and speaker's bureau. You can see listed 3M Pharmaceuticals, Stiefel, Novartis, Amgen, and Connetics.

Every wart treatment available today is unapproved, so every mode of treatment I will be speaking about will be off-label.

Slide 3: Quality-of-Life Assessment

This first slide is a quality of life assessment of patients with warts. As you can see, warts are quite a bit of problem for people. Eighty-two % are mildly to extremely embarrassed. About 70% are mildly to extremely concerned about negative appraisals by others. About 25% have moderate to extreme difficulty in playing sports. About half the patients said they had moderate to severe discomfort, and almost a third had moderate to severe pain with their warts.

Slide 4: Warts: Not Merely Skin Blemishes

This is a study looking at 85 people aged 2 to 76 who ended up having 250 common and plantar warts and they were followed for 9 months. About 80% sought treatment for these warts. Almost 50% to 60% had unsuccessful treatment in the past. About half experienced pain during treatment, a third had inconvenient treatments, and 22% had multiple treatments, with 20% of these producing scarring. Interestingly enough, during their 9-month study period, about a third of the patients had at least one wart regress spontaneously. This was about 20% of the 250 warts had spontaneously regressed over this 9-month time period.

Slide 5: Warts in Children Seen At a Tertiary Referral Center

This paper is "Viral warts in children seen at a tertiary referral center." This was reported from a center in Singapore, where they had 302 cases of warts. Sixty-two % were boys, 38% were girls. Eighty-eight % of these were treated with liquid nitrogen, at least in this clinic, at this referral center. Their clearance rate with this was 48.3%. The other patients were treated with electrocautery, with a 73% clearance. But as you can see in this large referral center, most of the patient were treated with liquid nitrogen.

Slide 6: What's New in HPV Infection?

I think this really sums up the problem with wart treatments today. This is from a paper by Allen, and I just will read this quickly, "Warts continue to be a therapeutic challenge, especially widespread warts in children. A single, most effective treatment has not been defined. Conventional methods attempt to non-specifically destroy infected tissue. Most of these procedures are painful, poorly tolerated by children, and often requiring multiple treatments. The efficacy of destructive techniques is impossible to verify in controlled, clinical trials. And uncontrolled success rates are sub-optimal, and often no better than that seen with placebo." I think this really is, in a nutshell, the problem with wart treatment today.

Slide 7: Local Treatments for Cutaneous Warts

Local treatments for cutaneous warts—this is actually a paper by Gibbs. Every 2 or 3 years they routinely look at all the various treatments for warts and present what they think are still the current best treatments. In this case, they looked at 52 randomized controlled trials and found that in these trials the average cure rate of placebo was approximately 30%. But as they have suggested before in their papers, the best available evidence for topical treatments still is salicylic acid. In their review of papers, salicylic acid's cure rate was 75%, as opposed to the control in these studies of 48%.

Interestingly, the cryotherapy, which is our main treatment for office-based wart therapy, they compared different regimens rather than methods of wart treatment or placebo. So they really could not say much about the cryotherapy as opposed to other treatments because the studies have not been done. In two studies cryotherapy was no better than placebo. They found no consistent evidence for any effectiveness of intralesional bleomycin.

Slide 8: Evidence-Based Review of Wart Treatment

Another look with this study of evidence-based review of wart treatment they just found that there were not many evidence-based studies available. Again, topical treatment with salicylic acid seemed the most safe and effective, and there was really no evidence of other therapies for common warts that were superior to salicylic acid for either cure rates or side-effects. There just were not many evidence-based studies for other treatments that they could look at.

Slide 9: Efficacy and Cost-Effectiveness of Salicylic Acid and Cryotherapy

In looking at the effectiveness and cost-effectiveness of salicylic acid and cryotherapy for cutaneous warts, this paper found that the most effective method was salicylic acid. Interestingly enough, the most cost-effective cryotherapy mode of delivery was nurse-led cryotherapy clinics. Their second most cost-effective therapy was GP-prescribed salicylic acid, and overall, OTC therapies were the most cost-effective. So, again, this matches up with the Gibbs' summaries of current state of treatment for warts.

Slide 10: Natural History of Common Warts

The natural history of common warts, about 20% to 40% of these warts resolve over 1 to 2 years without treatment. In a study of healthy children, 93% of the children who had warts at age 11 resolved by age 16.

Slide 11: Efficacy Rates of Various Treatments for Warts

This is a review of the efficacy rates of various treatments for warts. And you can see that these really range all over the board. Again, the placebo rate was approximately 30%, which we saw in the Gibbs review. Topical salicylic acid was 75%. Cryotherapy ranged from 30% to 70%. One study with DNCB had an 80% clearance rate. Cimetidine was listed as 46% to 75%, and we will see later that this probably was not the case. When you add cimetidine with levamisole, they reported an 86% clearance. Candida or mumps injections had 74%. Imiquimod had a 56%, but this was done without adjuvant therapy, so it is somewhat less accurate; and duct tape, the one study that has been done had an 85% efficacy rate.

Slide 12: Common Warts

Common warts. The diagnosis, of course, is usually made clinically. The rough papules or nodules, the subungual ones are under the nail, periunguals around the nail; plantar and palmar warts are thick, endophytic, hyperkeratotic nodules. The trouble with these are, at least the plantar warts, you walk on them every day, so you kind of smash them into the skin, and they are just harder to get at.

Paring down a wart reveals the characteristic black dots that patients call seeds or seed warts, but we all know these are thrombosed capillaries as the blood vessels approach the surface. But it is a way that you can diagnose a wart; if you are unsure if you pare it down and see these black dots, you feel good about that diagnosis. The biopsy reveals characteristic koilocytotic cells that the pathologist can tell us that this is indeed a wart.

Slide 13: Common Warts

Of course, a picture of common warts, the verrucous plaques that are very characteristic and are diagnosed clinically.

Slide 14: Human Papillomaviruses

Warts are caused by the human papillomavirus. They cause benign epidermal proliferations, which are produced by this double-stranded DNA virus. There are now 100 types that have been characterized by DNA hybridization, some of the common ones: HPV 1 for plantar warts, 2 for common warts, and 3 for flat warts.

Slide 15: Clinical Considerations

Warts make up about 70% of cutaneous warts, the common kind. Most are on the hands, dorsum, on the fingers and feet. But they can occur anywhere on the skin, including the palms and soles. Again, the subungual and periungual and plantar warts are the most difficult to treat, at least in my experience.

Slide 16: Salicylic Acid

I'll start taking about the various therapies now. First of all will be the two over-the-counter therapies, the first being salicylic acid. In this study, it was considered first line therapy. It is commercially available in 17% and 40% solutions, creams, gels and plasters. This is really all that is available over-the-counter. Several years ago the FDA mandated all the prescription wart medications be available only over-the-counter, and only containing salicylic acid.

There are six randomized clinical trials that have been done, and again the cure rate is 75% as opposed to the control rate, which was 48%, and is actually quite high. You need to continue the treatment for at least three months. It is very slow, and we just tell patients not to give up and keep going at it. And they may need to pare the warts down with an emery board or metal file to get better penetration of the salicylic acid.

Slide 17: OTC Cryosurgery

The OTC cryosurgery has been available for several years now. It is available without prescription and it is patient applied. In my own personal history, in my family history, it hasn't worked very well. The residents have bought some of these and we have tried it on them and some of the patients and again, have not had very good results. There are no published success rates that I can find, and therefore I am not really sure how effective these are. But there are several brands made now and it is certainly an option for patients to treat the warts, once these have been diagnosed as warts.

Slide 18: Pediatric patient with failed salicylic acid treatment and OTC cryotherapy

This is a pediatric patient who came in and he had failed the salicylic acid treatment and also OTC cryotherapy, and therefore what are the options available to treat him?

Slide 19: Cryosurgery

Cryosurgery, I think, again, is probably the gold standard, or at least with office-based treatments. It is thought that you have to repeat the treatments at approximately 2- to 3-week intervals for best results. The paper mentioned here by Micalli considers it a second-line therapy, with a first-line therapy being salicylic acid.

Some other papers are interesting. They found no significant difference between cryosurgery and placebo cream, or no treatment, with wart clearance in 2 to 4 months. There is no difference between salicylic acid and cryosurgery in this other study at 3 to 6 months.

Slide 20: Cryosurgery

Some other papers have reported, though, aggressive cryosurgery has better clearance at 1 to 3 months in what they call gentle cryosurgery. But there is no difference at cryosurgery at 2-, 3-, or 4-week intervals, and I think everybody thinks that 2- to 3- week intervals are best. But in this study there was really no difference when you froze a wart. They also found in this study that there is no difference between no further treatment of warts, freezing them once and prolonging treatment for 3 months. The studies on cryosurgery really are across the board, and there are really no good studies that show it is more effective than any other kinds of treatment.

Slide 21: Cryosurgery

There is data suggesting that the freeze/thaw/freeze increases clearance at a better rate, and recent papers show that a 10-second freeze was more effective than a traditional freeze. The disadvantages of cryosurgery, of course, are pain, and you can have postinflammatory hypo- and hyper pigmentation, particularly in dark-skinned patients. And it is possible to scar if you really freeze hard.

Slide 22: Cryotherapy

Cryotherapy in this paper was summed up on what the best method is. The thought is applying the liquid nitrogen for 5 to 25 seconds, and including a 1- to 2-millimeter area surrounding the wart to ensure adequate depth of freezing. This is from some papers in the past where they biopsied warts and found that there was still viable wart virus a few millimeters around the wart.

For thick warts, again, it is probably beneficial to pare it down so you can get better penetration of the cryosurgery. In some other studies the cure rates have been reported to be 60% to 70 %clearance, although, as I have said, there are several studies that show no effect of cryotherapy when comparing it to salicylic acid.

Slide 23: Duct Tape

Duct tape has become very popular over the last three years. I know when this was reported in all the papers and on TV; patients would come in and say, “Well, I’m sorry I didn’t wait longer because I realize I can treat myself now.” It is, again, available over-the-counter, obviously. It is inexpensive and it is safe. In the one study that has been done on 51 patients, they compared duct tape. In this case the patients left it on for 6 days, removed it, soaked in water, debrided the area and then repeated. As opposed to cryosurgery, which was 10 seconds every 2 or 3 weeks. They found a complete resolution was duct tape 85%, cryosurgery 60%. So it seems that there is a fairly inexpensive and safe treatment that patients can undertake themselves, and had better clearance rates rather than cryosurgery. Again, this is one study so it has not been replicated in other studies.

Slide 24: Cimetidine

Cimetidine is interesting. It is an oral medication and therefore there is no need for topical treatment. I think that is very appealing to patients and parents of patients, that you do not have to put something on that stings or burns. You do not have to freeze them and you can just give somebody a pill. The thought is that it stimulates cell-mediated immunity. The question is, does it work? In very fairly extensive uncontrolled trials, it seems to be fairly effective. But in two randomized, controlled trials recently, it showed no difference in treatment of common warts with cimetidine over placebo. In this paper, the conclusion was cimetidine is an expensive placebo that should not be used in treatment of verrucae.

Slide 25: Cimetidine

But other studies have shown, this was on warts on the feet, retrospective questionnaire of 8 years produced an 84% success rate, and cimetidine plus levamisole had a 65% clearance versus cimetidine alone, which is only about a third of the patients. Again, if you really look at the placebo-controlled, randomized studies, there was no effect on cimetidine over control.

Slide 26: Intralesional Immunotherapy

Intralesional immunotherapy I think is very interesting. This has become popular probably in the last 10 years. One paper has shown injection of a combination of *Candida albicans*, mumps, and trichophyton skin test was more effective and safe than a single antigen. Usually that antigen is *Candida* alone. One study showed a 42 % clearance rate of resistant warts with mumps or *Candida* intralesionally. Their average number of treatments was about four.

Slide 27: Intralesional Immunotherapy

This is very interesting and it is hard to know exactly how it works. It may be that it does work similarly to Aldara in terms of using the toll-like receptors. It is just that in this case you are injecting it and you may actually be able to activate those receptors by injection, rather than by applying a

product. It is, though, difficult in children. We have had problems using it because children do not like to have needles stuck in them, so you may need topical anesthetic prior to injection to use. And the most common side effects have been reported as itching, and an influenza-like illness, which is brief, and also a report of a painful, purple digit after injecting. I think this was Candida in a wart.

Slide 28: Contact Immunotherapy

Contact immunotherapy also has been used for years, and what this is, of course, is developing a type IV allergic reaction, generated by sensitizing the patient to some topical, and then applying dilute concentrations. Dinitrochlorobenzene is currently probably the most common used, DNCB. In one study, which was placebo-controlled there was an 80% clearance rate versus 43% for the placebo. However, it is considered mutagenic and so it is not used much these days. Diphenylcyclopropene, DCPC, probably is most commonly used now. In this case, six patients with chronic and resistant facial warts cleared, and the combination of DCPC and 15% salicylic acid had an 88% clearance.

Another study with 135 patients had about an 88% complete clearance over 6 months. So, there is some good data with contact immunotherapy. Not a whole lot of studies, but it is a method to use. I usually reserve it for when nothing else has worked and you are kind of pushed to the wall and you need something to try.

Slide 29: Contact Immunotherapy

Disadvantages have been reports of urticaria, painful local blistering, and a generalized eczematous eruption. Also, it is fairly hard to use. You have to buy the chemicals, you have to sensitize the patient, and then of course the patient is rubbing on something that they are very allergic to, and wherever they get it, they break out with contact dermatitis. So, it is, I think, one of the most difficult ways to treat warts, but there certainly is some good data for clearance rates.

Slide 30: Bleomycin Injections

Bleomycin injections are used by some dermatologists, and I think they feel that this may be one of the better therapies. It is a chemotherapy drug which inhibits DNA synthesis when injected into the wart. It does cause quite a bit of necrosis in the area and it may be that it is not the effect of the drug on the virus, but the actual removal of viral infected skin that is the method of treatment. There are though few randomized, placebo-controlled studies. In one review there were 14% to 99 % clearance rates, which, averaged, is a very broad span of clearance rates.

One recent study, though, had 87% clearance with bleomycin injections. Dr Shelly, years ago, reported the inoculation of warts with bleomycin and he had 90% clearance rates with using a needle and kind of slamming the bleomycin into the wart over and over and over. I do not know if many people are still using this method. I think most treatment with bleomycin is now injected straight into the wart.

However, if you look at the data, one study showed an increased number of warts were cured with placebo after 6 weeks. But in another study, there is no significant difference versus placebo in 30 days. And in one study, actually, the bleomycin cleared fewer warts than placebo. So, again, like all the other treatments, there is a mixed message here, with some studies showing effect. Again, most of those studies are uncontrolled case reports, as opposed to double-blind, placebo-controlled, randomized studies.

Slide 31: Bleomycin Injections

This was just a paper by Horn, and what he did was describe his method of treatment. If anybody is

interested in using this, he goes step-by-step how much he uses, how much you draw up, and how long it lasts, and that type of thing. His experience over 22 years was with 3,000 treatments. His summary was it is excellent for periungual and very good for recalcitrant warts, reasonable for plantar, and fair for subungual.

The disadvantage, of course, again, is you are injecting something into the skin. Most people do not like needles stuck into their skin, and it may be extremely painful, and actually, as it is developing its response, it may also continue being painful with necrosis in the area.

Slide 32: Imiquimod 5% Cream

Imiquimod 5% cream is a topical immune response modifier. It induces interferon, leading to a TH1 response and cell-mediated immunity. It actually is the only antiviral treatment available. All the other treatments are nonspecific removal of wart-infested tissue, as far as the data looks anyway. It is, though, noneffective monotherapy, and in the studies that have been done—two of them—the clearance rates are low because it really does need an adjuvant treatment for penetration of thick warts to initiate this immune cascade. So therefore, just putting it on the warts by itself really is not going to be good enough. Therefore, there are no placebo-controlled trials with imiquimod and adjuvant treatment.

Slide 33: Imiquimod 5% Cream

I will just go through some of the studies that have been done and these are all again either case reports or open studies. There are no placebo-controlled studies.

This was imiquimod cream with a 40 % salicylic acid pad cleared a large plantar wart. A patient with extensive recalcitrant common warts with the great toe cleared with imiquimod. Three patients with recalcitrant warts with a combination of salicylic acid, 50% to 100 % effective in 6 to 9 weeks. Long-lasting; in this case, 6-year therapy resistant warts cleared with an application applied twice daily to 37 patients. Ten out of 37, 20% complete clearance, 18 out of 37 had 50% reduction. All these papers are very resistant warts, resistant to all kinds of treatments, and clearing with imiquimod cream.

Slide 34: Imiquimod 5% Cream

Another report of 10 cases with recurrent warts applied once a day under occlusion and 90% clearance. No recurrence at 3 months. Children with therapy-resistant warts, in this case up to 2 to 7 years, the imiquimod was applied twice a day, 16 out of 18 cleared. A minimum of treatments was about 6 months. A mosaic plantar wart resistant to all modalities after 15 years cleared with imiquimod. Resistant plantar and periungual warts cleared in another study. And finally, in this study 12 out of 15 patients with periungual and subungual, the most difficult kind of warts to treat, cleared. These are all reports, again, of very resistant, long-lasting treatment-resistant warts that cleared with imiquimod.

Slide 35: Imiquimod 5% Cream

The local effects are mostly what you will see, redness, itching, burning, and pain. No systemic effects seen. Of course this is not injected, so you do not have to worry about people being afraid of needles.

Slide 36: Imiquimod 5% Cream

My favorite method, really, is using imiquimod cream for subungual and periungual, plantar, and those patients that are referred to me with multiple, unsuccessful treatments, and warts present for years and years. I like to use liquid nitrogen every 2 to 3 weeks, and have the patient apply 40%

urea gel in the morning under occlusion, and the imiquimod 5% cream applied at night under occlusion.

Slide 37: Imiquimod 5% Cream

If I am unable to freeze a wart at any regular time, I like the patients to use a 40% salicylic acid plaster occlusion of the imiquimod 5% cream. Somebody actually told me about this, this was his favorite treatment. I think it has been fairly successful. I have used this on myself to clear a plantar wart when nothing else seemed to work, including freezing it myself every 2 days for 6 weeks.

We have a large skin-care clinic here in Memphis. We have about 120 patients that are scheduled a day for a half day and we see many, many patients with warts. It is an all referral clinic, mostly children who sometimes cannot return for regular trial therapy, as they live 3 and 4 hours away. Over the years, the residents have developed their favorite treatment, which is a 5% imiquimod cream with duct tape occlusion. They use that a lot and get very good results from it. It is certainly easy to use and has very little side effects.

Slide 38: Hypnosis

Interestingly enough, hypnosis has popped up over the years as a therapy for warts, and there aren't really any double-blind studies done, but at least the open studies seem fairly effective. How the hypnosis works, it seems that you actually have the ability to get rid of the wart, you just do not know how to do that. I tell people with the imiquimod that you have the ability to turn your immune system against the wart; you just do not know how to do that. And that is what the imiquimod is going to do. It is going to tell your immune system to go after this wart.

In this one study, it was more effective at 6 weeks than salicylic acid and this guy is also placebo, or no treatment. They did a simulated x-ray treatment, which was a suggestion therapy, and it cleared warts in five children.

An individual hypnoanalytic technique cured 33 out of 41, 80% consecutive patients with warts. There was a recent report of a female patient successfully treated with hypnosis for warts on two occasions, separated by 7 years. So, when nothing else works, hypnosis might be a positive treatment.

We used to practice next to a pain clinic. There was a psychologist there who actually did hypnosis. I used to every once in a while send him patients and he would successfully treat their warts after nothing else worked. I think it is a very interesting thing that patients are able to rid themselves of warts; they just really do not know how to do that.

Slide 39: Flat Warts

Flat warts are a different type of wart, very commonly seen. They are flat-topped, smooth, skin-colored papules and are easily found in the face, the dorsum of hands, and the arms. I think the Köbner phenomenon really is the key to diagnosing these warts. You get this linear arrangement of lesions where you scratch, and that at least always makes me feel good that I have the right diagnosis.

Slide 40: Flat Wart Treatment

The treatments are varied: curettage, cryotherapy. There is a report clearing warts imiquimod 5% cream and tretinoin cream. Cimetidine has been reported to be effective, 5-fluorouracil cream. One report of contact immunotherapy and one report of intralesional Candida antigen. All these are single reports of effective therapies on flat wart treatments.

Slide 41:
**Personal Experience With
Treatment of Flat Warts**

I have had several patients who have failed all treatments for flat warts prior to the introduction of imiquimod cream. My first patient was a young woman who had lesions on her legs, and I tried everything; absolutely nothing worked. When imiquimod was released I gave her a prescription for it and said, "I want you to try this. I'm not sure if it will work." I did not see her back until about 2 years later when she came back to see me for acne, and I said, "What happened with the flat warts?" And she said, "Oh, that cream worked fine." I said, "I wish you would have told me after all this struggle. I would have liked to know something worked that well." Since then I have had several other treatments. The same thing with patients, I have tried a lot of things and they failed, and the imiquimod cream worked. I probably had 20 patients over the time since it has been released that have cleared their flat warts with daily application of imiquimod cream for one month. And that is the type of response I expect.