CHAPTER 1

General introduction

DAILY PRACTICE

A 10-year-old girl consults general practice with a plantar wart that has persisted on her left foot for over one year. Her medical history is unremarkable. She is accompanied by her mother who always makes sure her children use flip-flop sandals in swimming pool changing areas and shoes in primary school gymnasiums. *'I don't know how she got the wart, but I don't want her to get any more and I don't want her to give warts to other people'*. When the natural course and several over-the-counter (OTC) treatments failed to help, she encouraged her daughter to visit her general practitioner (GP). Although the girl is worried about the treatment, she agreed to get rid of the wart because it is painful when running and it looks unpleasant. *'My brother had 13 warts and was bullied by his friends and I don't want that!'*

GPs welcome patients with cutaneous warts every day. Like the girl, patients usually have two important questions:

1. *How did I get the warts?*
2. *How do I get rid of the warts?*

At first sight, these questions about this common ailment seem easy to answer. Especially because warts are known to be caused by the human papillomavirus (HPV) and several treatment options are available. However, the work presented in this thesis reveals that providing patients with evidence-based answers to these questions is not that easy. Specifically, knowledge on the *transmission* of warts to answer *How did I get the warts?*, and knowledge on the effectiveness of *treatment* for warts to answer *How do I get rid of the warts?* is still largely lacking. This general introduction provides background information about cutaneous warts, addresses the most apparent gaps in knowledge about the *transmission* and *treatment* of warts, and presents the study aims to fill these gaps.

TRANSMISSION

Definition of warts

Cutaneous warts are benign hyperkeratotic papillomas of the skin.[1] Their size ranges from a few millimetres to confluent conglomerates of several centimetres. The normal skin lines are interrupted by skin coloured to brownish-grey tumours. Small black dots may be visible, which represent capillary thrombosis. The diagnosis is established clinically; no supplementary histologic or virologic investigations are needed. Warts are classified according to localization and morphology.[2] Common warts (verruca vulgaris) are preferentially located on the dorsa of the hands, but may also be palmar, periungual, on the face, or on other

parts of the skin. The appearance is usually cauliflower-like, but may also be smooth (verruca plana) or filliform (verruca filiformis). Plantar warts (verruca plantaris) may be single endophytic lesions located on the pressure points of the foot (myrmecia warts) or multiple confluent more superficial lesions (mosaic warts).[3] In some cases, cutaneous warts may be confused with other lesions such as epithelial cysts, corns or other benign tumours of the skin.[4] Genital warts (condylomata accuminata), mollusca contagiosa, and senile warts (sebborreic keratosis) are different types of lesions which are not dealt with in this thesis.

Pathophysiology

Warts are caused by the human papillomavirus (HPV). The full complexity of the relationship between warts, HPV and patient immunity is not yet fully elucidated.[2;5;6] Skin tissue normally protects itself from viral invasion by several interrelated defence mechanisms, such as an intact stratum corneum, complement phagocytosis, and both cellular and humoral immunity. Small defects of the skin are sufficient for HPV to infect the basal epithelial layer of the skin. In contrast to an acute viral infection such as influenza (which is short-lived and induces a strong immune response with anti-viral immunity) HPV infections are more persistent. HPV evades immunologic defences through antigenic variation, genomic integration, and resides in sites not accessible to immune defences. Infection may be asymptomatic or may cause an irregular hyperplasia of the epidermis and hyperkeratosis, clinically visible as a wart.[7] In immunocompetent patients warts do not show malignant proliferation.

Human papillomavirus types

It was long assumed that a single virus was responsible for all types of warts.[8] Only since the mid-1970s were multiple HPV types characterised.[9;10] At present, we know that papillomaviruses (PV) are a family of viruses infecting cutaneous and mucosal epithelia of vertebrates.[11] They may persist asymptomatically or cause benign as well as malignant proliferative lesions. Commonly used nomenclature in the taxonomy of PVs has a genome-based approach, because PVs are not suitable for culture techniques or robust antibody responses.[5] PVs have circular double-stranded genomes with 8 genes. The L1 gene encodes for the principal capsid protein of the virus. Classification of PV is based on the L1 nucleotide sequence similarity: different *genera* share less than 60% nucleotide sequence identity, *species* within a genus share between 60-70%, and dissimilarity between *types* is at least 10%.[12] At present, more than 150 human PV types have been fully sequenced.[11]
Types belonging to the alpha genus infecting the genital mucosa are best understood: HPV 16 and 18 are the most prevalent types in the pathogenesis of cervical cancer, and HPV 6 and 11 cause genital warts and laryngeal papillomas. In this same phylogenetic

tree of PVs, at least 15 types belonging to the alpha [13-19], gamma [14;20], and mu [21] genera have been found associated to cutaneous warts. Studies on cutaneous wart-associated HPV types are scarce compared to studies on cervical dysplasia-associated HPV types.[22;23] Moreover, the few epidemiological studies including more than 100 lesions were carried out in dermatologic populations and used time-consuming HPV typing methods. Specific types of infecting HPV are correlated with histological characteristics of the wart. However, correlations with clinical characteristics of patients are less obvious, [2;21;24;25] and little is known about correlations with cure or response to treatment.[19;26]

Human papillomavirus transmission

Amplification of viral DNA in the HPV infected cells of the skin results in the production of high numbers of HPV copies that potentially may infect other individuals. HPV is transmitted through direct contact with contaminated skin or via objects carrying the virus.[3;11] Floors of swimming pools and public showers are most frequently hypothesised to be HPV reservoirs and routes for transmission of warts.[27] However, there is no direct evidence that these places are HPV reservoirs and few studies have actually examined risk factors for HPV transmission. Moreover, existing studies have methodological weaknesses and their results are contradictory.[27-34]

Prevention

Based on consensus regarding this weak evidence on the transmission of warts, several recommendations to prevent warts have been issued through official organizations of dermatology, general practice, and public health.[35-40] Recommendations to prevent getting plantar warts focus on public places, and recommendations to prevent spreading warts once you have them primarily aim at limiting the spread of warts within one individual (Table 1.1). Studies explicitly examining risk factors for developing warts could provide direction for more evidence-based recommendations.

TREATMENT

Burden of warts

The prevalence of warts in the general population is reported to range from 1-13%,[41-43] peaking between 5-14 years up to 24%.[44;45] Patients experience pain, irritation or cosmetic inconvenience.[46] Social interaction may even be affected in patients with widespread warts.[47] Entries in Dutch registries from general practice show that about 2% of the gen-

Table 1.1. Overview of recommendations for the prevention of cutaneous warts.

To prevent getting warts:
Do not go barefoot in public places [a,b,e]
Wear flip-flops in communal showers [d,f]
Keep feet dry [c-f]
Avoid sharing shoes, socks, or towels [d,e]
Change socks daily [e]
Do not touch someone's wart [f]
To prevent spreading warts:
Avoid scratching warts [a,c-f]
Avoid sucking fingers, or biting nails that have warts [c,d]
Do not try to cut away or burn warts yourself [e]
When paring down warts, take care not to damage surrounding skin, dispose of dead skin carefully and do not use the file for other purposes [e]
Cover the wart with a waterproof plaster when swimming [d,e]
Check children's feet periodically for warts [e]
Children with warts should not be excluded from activities such as sports and swimming, but should take measures to minimise transmission [d]

[a] Dutch College of General Practitioners (NHG)
[b] Dutch Association of Dermatologists (NVDV)
[c] Dutch Communal Health Service (GGD)
[d] National Health Service (NHS)
[e] British Association of Dermatologists (BAD)
[f] American Academy of Dermatology (AAD) [35-40]

eral population and 6% of primary school children present their warts to general practice for advice every year, ranking 11th in the list of the most common reasons for consulting general practice.[48] Only a small proportion of these patients are referred to dermatology clinics. In the UK, similar numbers are reported, resulting in almost 2 million people visiting general practice at a cost of about 40 million British pounds per year.[49] An additional yearly 17 million British pounds is spent on OTC preparations.[50] In the USA, the total yearly direct and indirect medical costs are estimated to be over 1 billion dollars.[51] In addition to the burden in the general immunocompetent population, warts are recognised as complication of long-term immunosuppression therapy with rates as high as 90% reported in patients 5 years after renal transplantation.[50]

Natural course

The duration of warts persisting without treatment ranges from a few months to over a decade. The most cited study on the natural course of cutaneous warts reported two thirds of patients free of warts after 2 years.[52] However, that study was conducted in 1963 among an institutionalised mentally disabled population. Another study conducted in

1959 with a complete resolution after one year of 57% only included hand warts in Dutch primary school children,[32] and a cohort of 11-year-old British children concluding follow-up in 1993 showed a 5-year resolution of 93%; however, this latter study did not provide data on short-term follow-up.[44] Because of the benign natural course of warts, some physicians and healthcare planners promote a wait-and-see policy.[53]

Treatment of warts

The first documented problems related to the treatment of warts were reported in the 1st century AD in the medical encyclopaedia *'De Medicina'* by Aulus Cornelius Celsus: "*The myrmecia are held by very broad roots, and so cannot be excised without causing a large wound*".[54] Nowadays, physicians still hesitate to perform surgical excision of a wart because of the complications of the procedure in combination with possible recurrence after treatment.[55] The fact that warts also resolve spontaneously over time has fuelled beliefs in all kinds of folklore to get rid of warts (Figure 1.1).

Even today, a variety of OTC medications, GP treatments and specialist therapies are available (Table 1.2).[49;55] The number of different methods alone indicates that none of the treatments is considered generally effective. In 2006, the extensive Cochrane systematic review on topical treatments for cutaneous warts concludes: '*There is a considerable lack of evidence on which to base the rational use of topical treatments for cutaneous warts.*'[55] Although the evidence was scarce, topical treatment with salicylic acid showed the most

Figure 1.1. Fragment from The adventures of Tom Sawyer by Mark Twain, 1876.

"Say – what is dead cats good for, Huck ?"
"Good for ? Cure warts with."
"No ! Is that so ? I know something that's better."
"I bet you don't. What is it ?"
"Why, spunk-water. . . You got to go all by yourself, to the middle of the woods, where you know there's a spunk-water stump, and just as it's midnight you back up against the stump and jam your hand in and say :
'Barley-corn, barley-corn, injun-meal shorts,
Spunk-water, spunk-water, swaller these warts,'
and then walk away quick, eleven steps, with your eyes shut, and then turn around three times and walk home without speaking to anybody. Because if you speak the charm's busted… Sometimes I take 'em off with a bean."
"Yes, bean's good. I've done that."
"Have you ? What's your way ?"
(…)

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Table 1.2. Overview of reported treatments for cutaneous warts.[a]

	Over-the counter	Primary Care	Secondary Care[b]
Removal	Self-removal	Excision	
		Curetage	
		Cautery	
Destruction	Cryotherapy (-50ºC)[c]	Cryotherapy (-196 ºC)[d]	Photodynamic treatment
		Silver nitrate	Pulsed dye laser
Keratolysis	Low-dose salicylic acid[e]	High-dose salicylic acid[f]	Lactic acid
		Monochloroacetic Acid	
Immunostimulation	Thuia oil		Dinitrochlorobenzene
			Intralesional Interferons
Animitotic effects			5-Fluorouracil
			Intralesional Bleomycin
Occlusion	Duct tape		
Suggestion	Prayer	Hypnosis	

[a] This overview does not aim to be complete, but illustrates the variety of widely available treatments.
[b] In addition to treatments also used in primary care.
[c] Dimethylether/propane cryotherapy.
[d] Liquid nitrogen cryotherapy, applied by cotton bud, application pen, or sprayer.
[e] Low dose = 17% or lower concentration ointments.
[f] High dose = 30-50% concentration ointments

convincing results.[56-60] Pooled data from five trials showed a cure rate of 117/160 patients (73%) after salicylic acid treatment compared with 78/162 (48%) in controls, which translates to a risk ratio of 1.6 (95% CI 1.2-2.2).[55] Two low-quality trials directly comparing salicylic acid and cryotherapy did not reveal differences in effectiveness.[59;61] Therefore, the Cochrane review proposes: *'The most urgent need is for a trial to compare topical salicylic acid, cryotherapy and placebo in primary care'*. This recommendation was an important starting point for the research in this thesis.

In addition to the widely available cryotherapy and salicylic acid, several specialised treatments are available in a hospital setting (Table 1.2). Evidence for these treatments is limited and large-scale use in primary care is not feasible. However, an exception may be monochloroacetic acid (MCA) which is a powerful irritant used by dermatologists and podiatrists for several decades.[62;63] A trial from the UK and two small unpublished pilot studies from the Netherlands showed promising results of MCA in primary care with few side effects.[64-66]

Apart from treatment effectiveness, other arguments such as side effects, treatment burden, patient satisfaction, and costs also influence treatment choices in practice, especially because patients with warts are often children. Moreover, specific subgroups of patients could be identified, allowing to distinguish patients with high treatment response from patients who will not benefit from treatment. [49]

OUTLINE OF THIS THESIS

Aims

Fuelled by the most apparent gaps in knowledge on the *transmission* and *treatment* of warts, the aims of this thesis are:

1. To examine risk factors for the development of warts and gain a deeper understanding of the *transmission* of the wart-associated human papillomavirus in order to provide direction for evidence-based recommendations for wart prevention;
2. To investigate the effectiveness and side effects of commonly used treatments in general practice and identify subgroups of patients with a favourable treatment response in order to optimise *treatment* in general practice.

These two aims are the backbone of the thesis; in addition, several secondary aims were formulated. However, all aims share the view of a general practitioner and the intention to fill in the gaps of knowledge on the *transmission* and *treatment* of warts. To achieve these aims studies are conducted in different populations, which are briefly described below.

Part one: Transmission

In a prospective cohort of primary school children, hands and feet are examined at baseline and at follow-up to collect epidemiological data on their warts and evidence on wart transmission. In **Chapter 2**, the baseline data from this study cohort represent the prevalence of common and plantar warts in primary schoolchildren. Through parental questionnaires, parental awareness of their children's warts, as well as cross-sectional relations with environmental risk factors, is explored. Based on these findings and on the theoretical degree of HPV exposure, a model for risk factors for the development of warts is tested in **Chapter 3** to provide direction for evidence-based patient information on the prevention of warts. To study HPV types more directly than through risk factors for transmission, a newly developed HPV typing technique for genotyping all known wart-associated HPV types is introduced. The objective of **Chapter 4** is to investigate which specific HPV types cause warts in a primary care population. In addition, the relation between specific HPV type and patient characteristics is explored.

Part two: Treatment

For the study in **Chapter 5**, the cohort of primary school children with warts at baseline is used to acquire data on the resolution of warts after one year. This study investigated factors related to enhanced resolution of warts and aims to describe all OTC as well as GP-delivered treatments used by school children. In **Chapter 6**, a survey among Dutch GPs

shows which treatments are most frequently used for warts in practice. In addition, the study explores GPs' motivation for these choices and compares the choices with favoured treatments based on currently available evidence.
The following three chapters present results from two subsequent Warts Randomised Treatment Studies (WARTS). Both WARTS studies are pragmatic, multicenter, randomised trials in immunocompetent patients presenting new warts in general practice. The three-armed WARTS-1 compares the effectiveness of liquid nitrogen cryotherapy, salicylic acid self-application and a wait-and-see policy (**Chapter 7**). It also reports on side effects, treatment burden and patient satisfaction, and presents subgroup analysis for common and plantar warts, for children under the age of 12 years, and warts with a duration over 6 months. With the knowledge gained from WARTS-1, the WARTS-2 study compares the effectiveness and side effects of monochloroacetic acid with cryotherapy in common warts, and with cryotherapy combined with salicylic acid in plantar warts (**Chapter 8**). Using the newly developed HPV typing technique from Chapter 4 and the trial population from Chapter 7, the interaction between subgroups based on specific HPV type infecting the wart and treatment response is explored in **Chapter 9**.

Final chapters

The aim of the general discussion in **Chapter 10** is to bring the findings back to daily practice, to present explanations for the observed effects, and to provide recommendations for future research. **Chapter 11** summarises the contents of all chapters and **Chapter 12** contains a summary in Dutch.

REFERENCES

(1) Androphy EJ, Lowy DR. Warts. In: Fitzpatrick's Dermatology in General Medicine (Wolff,K, Goldsmith,LA, Katz,SI et al, eds), Seventh edn. USA: McGraw-Hill, 2008: 1914-23.

(2) Jablonska S, Orth G, Obalek S et al. Cutaneous warts. Clinical, histologic, and virologic correlations. Clin Dermatol 1985;3:71-82.

(3) Jablonska S, Majewski S, Obalek S et al. Cutaneous warts. Clin Dermatol 1997;15:309-19.

(4) Bruggink SC, Eekhof JAH. Wratten. In: Kleine kwalen bij kinderen (Eekhof,JAH, ed). 2009.

(5) Burkhart CG. The endogenous, exogenous, and latent infections with human papillomavirus. Int J Dermatol 2004;43:548-9.

(6) Malejczyk J, Majewski S, Jablonska S. Cellular immunity in cutaneous and genital HPV infections. Clin Dermatol 1997;15:261-74.

(7) Antonsson A, Forslund O, Ekberg H et al. The ubiquity and impressive genomic diversity of human skin papillomaviruses suggest a commensalic nature of these viruses. J Virol 2000;74: 11636-41.

(8) Rowson KE, Mahy BW. Human papova (wart) virus. Bacteriol Rev 1967;31:110-31.

(9) Gissmann L, Pfister H, zur HH. Human papilloma viruses (HPV): characterization of four different isolates. Virology 1977;76:569-80.

(10) Orth G, Favre M, Croissant O. Characterization of a new type of human papillomavirus that causes skin warts. J Virol 1977;24:108-20.

(11) Bernard HU, Burk RD, Chen Z et al. Classification of papillomaviruses (PVs) based on 189 PV types and proposal of taxonomic amendments. Virology 2010;401:70-9.

(12) de Villiers EM, Fauquet C, Broker TR et al. Classification of papillomaviruses. Virology 2004;324: 17-27.

(13) Chan SY, Chew SH, Egawa K et al. Phylogenetic analysis of the human papillomavirus type 2 (HPV-2), HPV-27, and HPV-57 group, which is associated with common warts. Virology 1997; 239:296-302.

(14) Hagiwara K, Uezato H, Arakaki H et al. A genotype distribution of human papillomaviruses detected by polymerase chain reaction and direct sequencing analysis in a large sample of common warts in Japan. J Med Virol 2005;77:107-12.

(15) Harwood CA, Spink PJ, Surentheran T et al. Degenerate and nested PCR: a highly sensitive and specific method for detection of human papillomavirus infection in cutaneous warts. J Clin Microbiol 1999;37:3545-55.

(16) Lai JY, Doyle RJ, Bluhm JM et al. Multiplexed PCR genotyping of HPVs from plantaris verrucae. J Clin Virol 2006;35:435-41.

(17) Porro AM, Alchorne MM, Mota GR et al. Detection and typing of human papillomavirus in cutaneous warts of patients infected with human immunodeficiency virus type 1. Br J Dermatol 2003;149:1192-9.

(18) Rubben A, Krones R, Schwetschenau B et al. Common warts from immunocompetent patients show the same distribution of human papillomavirus types as common warts from immunocompromised patients. Br J Dermatol 1993;128:264-70.

(19) Rubben A, Kalka K, Spelten B et al. Clinical features and age distribution of patients with HPV 2/27/57-induced common warts. Arch Dermatol Res 1997;289:337-40.

(20) Chen SL, Tsao YP, Lee JW et al. Characterization and analysis of human papillomaviruses of skin warts. Arch Dermatol Res 1993;285:460-5.

(21) Egawa K, Delius H, Matsukura T et al. Two novel types of human papillomavirus, HPV 63 and HPV 65: comparisons of their clinical and histological features and DNA sequences to other HPV types. Virology 1993;194:789-99.
(22) Munoz N, Bosch FX, de SS et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med 2003;348:518-27.
(23) de SS, Diaz M, Castellsague X et al. Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. Lancet Infect Dis 2007;7:453-9.
(24) Jablonska S, Obalek S, Golebiowska A et al. Epidemiology of butchers' warts. Arch Dermatol Res 1988;280 Suppl:S24-S28.
(25) Egawa K, Inaba Y, Yoshimura K et al. Varied clinical morphology of HPV-1-induced warts, depending on anatomical factors. Br J Dermatol 1993;128:271-6.
(26) Tomson N, Sterling J, Ahmed I et al. Human papillomavirus typing of warts and response to cryotherapy. J Eur Acad Dermatol Venereol 2011;25:1108-11.
(27) Johnson LW. Communal showers and the risk of plantar warts. J Fam Pract 1995;40:136-8.
(28) Gentles JC, Evans EG. Foot infections in swimming baths. Br Med J 1973;3:260-2.
(29) Vaile L, Finlay F, Sharma S. Should verrucas be covered while swimming? Arch Dis Child 2003; 88:236-7.
(30) Rigo MV, Martinez-Campillo F, Verdu M et al. [Risk factors linked to the transmission of papilloma virus in the school environment. Alicante, 1999]. Aten Primaria 2003;31:415-20.
(31) Kilkenny M, Marks R. The descriptive epidemiology of warts in the community. Australas J Dermatol 1996;37:80-6.
(32) van der Werf E. Een onderzoek naar het voorkomen en het verloop van wratten bij schoolkinderen [Studies on the incidence and course of warts in school children.]. Ned Tijdschr Geneeskd 1959;103:1204-8.
(33) Doeglas HM, Nater JP. [Epidemiological study of patients with warts]. Ned Tijdschr Geneeskd 1973;117:216-20.
(34) Benz U, Gilliet F. [Possible causative factors in epidemic incidence of plantar warts]. Schweiz Med Wochenschr 1976;106:666-71.
(35) British Association of Dermatologists (2012) Patient information leaflet on plantar warts. http://www.bad.org.uk/site/859/default.aspx
(36) American Association of Dermatology (2012) Tips for the management of warts. http://www.aad.org/skin-conditions/dermatology-a-to-z/warts/tips/warts-tips-for-managing
(37) Nederlandse Vereniging voor Dermatologie en Venerologie (2012) Wratten. http://www.huidarts.info/documents/?v=2&id=52
(38) Nederlands Huisarts Genootschap (2008) Patientenfolder Wratten. http://nhg.artsennet.nl/kenniscentrum/k_voorlichting/NHGPatientenfolders/NHGPatientenfolder/PF06.htm
(39) Clinical Knowlegde Summaries - NHS (2009) Warts and Verrucae. http://www.cks.nhs.uk/warts_and_verrucae/management/scenario_warts_and_verrucae#-378974
(40) Gemeenschappelijke Gezondhiedsdienst (GGD) (2012) Gezondheidsrisico's in basisschool en buitenschoolse opvang. www.rivm.nl/cib
(41) Johnson MT, Roberts J. Skin conditions and related need for medical care among persons 1-74 years. United States, 1971-1974. Vital Health Stat 11 1978;i-72.
(42) Rea JN, Newhouse ML, Halil T. Skin disease in Lambeth. A community study of prevalence and use of medical care. Br J Prev Soc Med 1976;30:107-14.
(43) Beliaeva TL. [The population incidence of warts]. Vestn Dermatol Venerol 1990;55-8.

(44) Williams HC, Pottier A, Strachan D. The descriptive epidemiology of warts in British schoolchildren. Br J Dermatol 1993;128:504-11.
(45) Kilkenny M, Merlin K, Young R et al. The prevalence of common skin conditions in Australian school students: 1. Common, plane and plantar viral warts. Br J Dermatol 1998;138:840-5.
(46) Dudley W. The psychological impact of warts on patients' lives. Prof Nurse 1995;11:99-100.
(47) Ciconte A, Campbell J, Tabrizi S et al. Warts are not merely blemishes on the skin: A study on the morbidity associated with having viral cutaneous warts. Australas J Dermatol 2003;44:169-73.
(48) van der Linden MW, Westert GP, de Bakker H et al. Tweede nationale studie naar ziekten en verrichtingen in de huisartpraktijk. Klachten en aandoeningen in de bevolking en in de huisartspraktijk. Utrecht/Bilthoven: NIVEL/RIVM 2004.
(49) Thomas KS, Keogh-Brown MR, Chalmers JR et al. Effectiveness and cost-effectiveness of salicylic acid and cryotherapy for cutaneous warts. An economic decision model. Health Technol Assess 2006;10:iii, ix-87.
(50) Schofield J, Grindlay D, Williams HC. Skin conditions in the UK: a health care needs assessment. Nottingham: Centre of Evidence Based Dermatology 2009.
(51) Bickers DR, Lim HW, Margolis D et al. The burden of skin diseases: 2004 a joint project of the American Academy of Dermatology Association and the Society for Investigative Dermatology. J Am Acad Dermatol 2006;55:490-500.
(52) Massing AM, Epstein WL. Natural history of warts. A two-year study. Arch Dermatol 1963;87: 306-10.
(53) Ordoukhanian E, Lane AT. Warts and molluscum contagiosum: beware of treatments worse than the disease. Postgrad Med 1997;101:223-32, 235.
(54) Celsus AC. De Medicina, book 5, chapter 28, section 14. Around 25AD.
(55) Gibbs S, Harvey I. Topical treatments for cutaneous warts. Cochrane Database Syst Rev 2006;3: CD001781.
(56) Bart BJ, Biglow J, Vance JC et al. Salicylic acid in karaya gum patch as a treatment for verruca vulgaris. J Am Acad Dermatol 1989;20:74-6.
(57) Spanos NP, Williams V, Gwynn MI. Effects of hypnotic, placebo, and salicylic acid treatments on wart regression. Psychosom Med 1990;52:109-14.
(58) Bunney MH, Hunter JA, Ogilvie MM et al. The treatment of plantar warts in the home. A critical appraisal of a new preparation. Practitioner 1971;207:197-204.
(59) Steele K, Irwin WG. Liquid nitrogen and salicylic/lactic acid paint in the treatment of cutaneous warts in general practice. J R Coll Gen Pract 1988;38:256-8.
(60) Felt BT, Hall H, Olness H et al. Wart regression in children: comparison of relaxation imagery to topical treatment and equal time interventions. American Journal of Clinical Hypnosis 1998;41: 130-7.
(61) Bunney MH, Nolan MW, Williams DA. An assessment of methods of treating viral warts by comparative treatment trials based on a standard design. Br J Dermatol 1976;94:667-79.
(62) Benton EC. Therapy of cutaneous warts. Clin Dermatol 1997;15:449-55.
(63) J.Colin Dagnall MS. Monochloroacetic Acid and Verrucae. British Journal of Chiropody 1976;41: 105-7.
(64) Steele K, Shirodaria P, O'Hare M et al. Monochloroacetic acid and 60% salicylic acid as a treatment for simple plantar warts: effectiveness and mode of action. Br J Dermatol 1988;118: 537-43.

(65) Altena G, Blomsma E, Grotenhuis A. Behandeling van wratten in de huisartspraktijk: Monochloorazijnzuur versus Salicylzuur. Disciplinegroephuisartsgeneeskunde, Afdeling Huisartsopleiding, Rijksuniversiteit Groningen 2004.
(66) Boot-ten Damme HW, van der Ploeg TJ, van Til RF. Behandeling van voetwratten in de eerste lijn: Cryotherapie versus Monochloorazijnzuur. Disciplinegroep Huisartsgeneeskunde, Rijksuniversiteit Groningen, Faculteit der Medische Wetenschappen 2004.