

GUIDELINE

Clinical guideline for the diagnosis and treatment of cutaneous warts (2022)

Peiyao Zhu^{1,2,3,4} | Rui-Qun Qi^{1,2,3,4} | Yang Yang^{1,2,3,4} | Wei Huo^{1,2,3,4} |
 Yuqing Zhang⁵ | Li He⁶ | Gang Wang⁷ | Jinhua Xu⁸ | Furen Zhang⁹ |
 Rongya Yang¹⁰ | Ping Tu¹¹ | Lin Ma¹² | Quanzhong Liu¹³ | Yuzhen Li¹⁴ |
 Heng Gu¹⁵ | Bo Cheng¹⁶ | Xiang Chen¹⁷ | Aijun Chen¹⁸ | Shengxiang Xiao¹⁹ |
 Hongzhong Jin²⁰ | Junling Zhang²¹ | Shanshan Li²² | Zhirong Yao²³ | Weihua Pan²⁴ |
 Huilan Yang²⁵ | Zhu Shen²⁶ | Hao Cheng²⁷ | Ping Song²⁸ | Lingyu Fu²⁹ |
 Hongxiang Chen³⁰ | Songmei Geng³¹ | Kang Zeng³² | Jianjian Wang³³ | Juan Tao³⁰ |
 Yaolong Chen^{33,34,35}  | Xiuli Wang³⁶ | Xing-Hua Gao^{1,2,3,4} 

¹Department of Dermatology, The First Hospital of China Medical University, Heping District, Shenyang, P.R. China

²NHC Key Laboratory of Immunodermatology, China Medical University, Heping District, Shenyang, P.R. China

³Key Laboratory of Immunodermatology, China Medical University, Ministry of Education, Heping District, Shenyang, P.R. China

⁴National and Local Joint Engineering Research Center of Immunodermatological Theranostics, Heping District, Shenyang, P.R. China

⁵Department of Clinical Epidemiology and Evidence-Based Medicine, The First Hospital of China Medical University, Heping District, Shenyang, P.R. China

⁶Department of Dermatology, First Affiliated Hospital of Kunming Medical University, Kunming, P.R. China

⁷Department of Dermatology, Xijing Hospital, Fourth Military Medical University, Xi'an, Shaanxi, P. R. China

⁸Department of Dermatology, Huashan Hospital, Fudan University, Shanghai, P.R. China

⁹Shandong Provincial Hospital for Skin Diseases & Shandong Provincial Institute of Dermatology and Venereology, Shandong First Medical University & Shandong Academy of Medical Sciences, Jinan, P.R. China

¹⁰Department of Dermatology, General Hospital of Beijing Military Command of PLA, Dongcheng District, Beijing, P.R. China

¹¹Department of Dermatology and Venerology, Peking University First Hospital, Beijing, P.R. China

¹²Department of Dermatology, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, P.R. China

¹³Department of Dermatology, Tianjin Medical University General Hospital, Tianjin, P.R. China

¹⁴Department of Dermatology, Second Affiliated Hospital of Harbin Medical University, Harbin, P.R. China

¹⁵Institute of Dermatology, Chinese Academy of Medical Sciences and Peking Union Medical College, Nanjing, P.R. China

¹⁶Department of Dermatology, The First Affiliated Hospital of Fujian Medical University, Fuzhou, P.R. China

¹⁷Department of Dermatology, Xiangya Hospital, Central South University, Changsha, P.R. China

¹⁸Department of Dermatology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, P.R. China

¹⁹Department of Dermatology, The Second Affiliated Hospital, School of Medicine, Xi'an Jiaotong University, Xi'an, P.R. China

²⁰Department of Dermatology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Dongcheng District, Beijing, P.R. China

²¹Department of Dermatology, Tianjin Academy of Traditional Chinese Medicine Affiliated Hospital, Tianjin, P.R. China

²²Department of Dermatology, The First Hospital of Jilin University, Changchun, Jilin Province, P.R. China

²³Department of Dermatology, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, P.R. China

Peiyao Zhu, RuiQun Qi, and Yang Yang contributed equally.

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2022 The Authors. *Journal of Evidence-Based Medicine* published by Chinese Cochrane Center, West China Hospital of Sichuan University and John Wiley & Sons Australia, Ltd.

²⁴Department of Dermatology, Shanghai Key Laboratory of Molecular Medical Mycology, Second Affiliated Hospital of Naval Medical University, Shanghai, P.R. China

²⁵Department of Dermatology, General Hospital of Southern Theatre Command of PLA, Guangzhou, P.R. China

²⁶Department of Dermatology, Institute of Dermatology and Venereology, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital, Chengdu, P.R. China

²⁷Department of Dermatology and Venereology, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, P.R. China

²⁸Department of Dermatology, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, P.R. China

²⁹Department of Clinical Epidemiology and Evidence-Based Medicine, The First Hospital of China Medical University, Heping District, Shenyang, P.R. China

³⁰Department of Dermatology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, P.R. China

³¹Department of Dermatology, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, P.R. China

³²Department of Dermatology, Nanfang Hospital, Southern Medical University, Guangzhou, P.R. China

³³Evidence-Based Medicine Center, School of Basic Medical Sciences, Lanzhou University, Lanzhou, P.R. China

³⁴World Health Organization Collaborating Center for Guideline Implementation and Knowledge Translation, Lanzhou, P.R. China

³⁵GIN Asia, Lanzhou, P.R. China

³⁶Institute of Photomedicine, Shanghai Skin Disease Hospital, School of Medicine, Tongji University, Shanghai, P.R. China

Correspondence

Xinghua Gao, Department of Dermatology, The First Hospital of China Medical University, 155 Nanjing Bei Street, Shenyang 110001, P.R. China.

Email: gaobarry@hotmail.com

Xiuli Wang, Institute of Photomedicine, Shanghai Skin Disease Hospital, School of Medicine, Tongji University, Shanghai 200050, China.

Email: wangxiuli_1400023@tongji.edu.cn

Yaolong Chen, Evidence-Based Medicine Center, School of Basic Medical Sciences, Lanzhou University, Lanzhou 730000, China.

Email: chenyaolong@lzu.edu.cn

Abstract

Aim: Cutaneous warts caused by human papillomavirus are benign proliferative lesions that occur at any ages in human lives. Updated, comprehensive and systematic evidence-based guidelines to guide clinical practice are urgently needed.

Methods: We collaborated with multidisciplinary experts to formulate this guideline based on evidences of already published literature, focusing on 13 clinical questions elected by a panel of experts. We adopted Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to form classification of recommendations as well as the improved Delphi method to retain respective recommendations with a consensus degree of over 80%.

Results: Our guideline covered aspects of the diagnosis and treatment of cutaneous warts such as diagnostic gold standard, transmission routes, laboratory tests, treatment principle, clinical cure criterion, definitions, and treatments of common warts, flat warts, plantar warts, condyloma acuminatum, and epidermodysplasia verruciformis. Recommendations about special population such as children and pregnant women are also listed. In total, 49 recommendations have been obtained.

Conclusions: It is a comprehensive and systematic evidence-based guideline and we hope this guideline could systematically and effectively guide the clinical practice of cutaneous warts and improve the overall levels of medical services.

KEYWORDS

common wart, condyloma acuminatum, epidermodysplasia verruciformis, flat wart, plantar wart

1 | INTRODUCTION

Cutaneous warts are proliferative diseases caused by human papillomavirus (HPV) infection of keratinocytes. Viral warts are common with a prevalence rate of 7–12%.^{1,2} HPV is a double-stranded DNA virus with more than 200 types being identified. HPVs can be grossly divided into high-risk types and low-risk types for their carcinogenic potentials. The life cycle of HPV is closely associated with the proliferation and differentiation of epithelium. Cutaneous HPV infection commonly

manifests as warts including flat warts (*verruca plana*, on hands and face), common warts (*verruca vulgaris*), planta warts (*verruca plantaris*, on soles of feet), and condyloma acuminatum (anogenital warts, on genitalia, anus or perianal area).³ Most cutaneous HPV infection leads to benign proliferative lesions, while rarely develops into cutaneous cancers such as squamous cell carcinoma.⁴ Appropriate measures for prevention, diagnosis, treatment, and long-time management of cutaneous HPV infection are mandatory for dermatologists, pediatricians, urologists, gynecologists, and general practitioners.

Albeit there are several major guidelines or consensus for cutaneous warts,⁵⁻¹³ a comprehensive and systematically produced guidance for management of cutaneous HPV infection including flat warts, common warts, plantar warts, and anogenital warts is missing. We summarized the recent clinical progress and incorporated recommendations based on evidence and expert consensus, dedicated to provide a general guideline for the prevention, diagnosis, treatment, and long-term management of cutaneous warts.

2 | METHODS

2.1 | Scope and registration of the guideline

The target population of this guideline are patients with cutaneous warts including common warts, flat warts, plantar warts, condyloma acuminatum (CA), and epidermodysplasia verruciformis (EV), caused by HPV infection. The content covers aspects such as screening, diagnosis, treatment, and prevention. Special populations such as children and pregnant women are also taken into account. The guidelines are applicable to medical institutions at all levels. Target implementing agencies are medical institutions and health management departments that provide health care services to the target population. The main users of the guidelines are medical workers in the departments of Dermatology and Venereology, Obstetrics and Gynecology, and Preventive Health Care. Proctologists and infectiologists are practitioners of this guideline as well.

This guideline has been bilingually registered on the International Practice Guidelines Registry Platform (<http://www.guidelines-registry.cn>) with registration number IPGRP-2020CN078 on June 9, 2020.

2.2 | Guideline working group

This guideline was launched and formulated by the Chinese Society of Dermatology on June 1, 2020. Methodological support was provided by the WHO Collaborating Centre for Guideline Implementation and Knowledge Translation, GRADE China Center, and Evidence-Based Medicine Center of Lanzhou University. The guideline working group consisted of five groups: (I) a guideline steering committee, consisted of 9 senior clinical experts and methodologists; (II) a consensus expert group, consisted of 32 panelists from professional field of dermatology; (III) a secretarial group, who was fully responsible for the coordination and management of the guide, the collection and sorting of evidence and data, the arrangement and recording of various tasks, the contact and communication of relevant experts, and all issues not covered by other working groups; (IV) an evidence evaluation group consisted of 33 members, which was responsible for finding, collecting, evaluating and synthesizing relevant evidence, and applying GRADE grading system,¹⁴ making decision tables, and preparing for expert consensus; and (V) an external review group consisted of 10 members, which was mainly responsible for reviewing the first draft of the guideline, putting forward comments and suggestions, and its work was intended to be completed before the guideline was officially released.

2.3 | Collection and determination of clinical questions

We used predesigned questionnaires to collect clinical questions. The responders of the survey were clinical doctors in dermatology. Meanwhile, by referring to the relevant guidelines and systematic reviews of HPV-related skin diseases, we collected potential clinical questions. We distributed original questionnaires to 20 dermatologists in the first round and modified questionnaires to 50 dermatologists in the second round of the survey with both 100% response ratios. Through two rounds of questionnaire surveys, based on the scoring results by order of importance of the clinical issues, 13 clinical questions were finally included in this guideline.

2.4 | Evidence collection

This guideline collected evidence from systematic reviews, meta-analysis, and network meta-analysis. The search terms included "Warts" or "Condylomata Acuminata" or "Epidermodysplasia Verruciformis" or "verruca vulgaris" or "verruca plantaris" in both Chinese and English respectively from 2010 to 2020, in the order of title or abstract. Search databases included Medline, Embase, Cochrane Library, Epistemonikos, China Biology Medicine (CBM), Wanfang, and China National Knowledge Infrastructure (CNKI). In cases where no systematic reviews or meta-analysis were available, we systematically searched the database, generating a systematic review according to the original research data or incorporating it into the original research to construct an evidence body. A flow chart of literature screening was shown in Figure 1. Among the 49 recommendations of the 13 clinical questions, 43 recommendations were based on existing reviews while 6 recommendations were based on newly generated reviews or evidence bodies of original research. A total of 29 new reviews were generated for this guideline. The information from the included research papers was extracted according to the predesigned data extraction table. The screening and information extraction of each document was done independently by two groups of members. A third party was consulted if there were discrepancies.

2.5 | Evidence assessment and grading

We used the systematic review bias risk assessment tool, A MeaSurement Tool to Assess systematic Reviews (AMSTAR) scale, to evaluate the bias risk of the included systematic reviews, meta-analysis, and network meta-analysis.¹⁵ We also used the Cochrane risk of bias (ROB) assessment tool (for randomized controlled trials), diagnostic accuracy research quality assessment tool (Quality Assessment of Diagnostic Accuracy Studies, QUADAS-2, for diagnostic tests), and Newcastle-Ottawa Scale (NOS, for cohort studies and case-control studies) for methodological quality evaluation of respective types of original research.¹⁶⁻¹⁸ The evaluation process was completed by two members independently and if there was a disagreement, they would discuss it together or consult a third party to resolve it. The GRADE

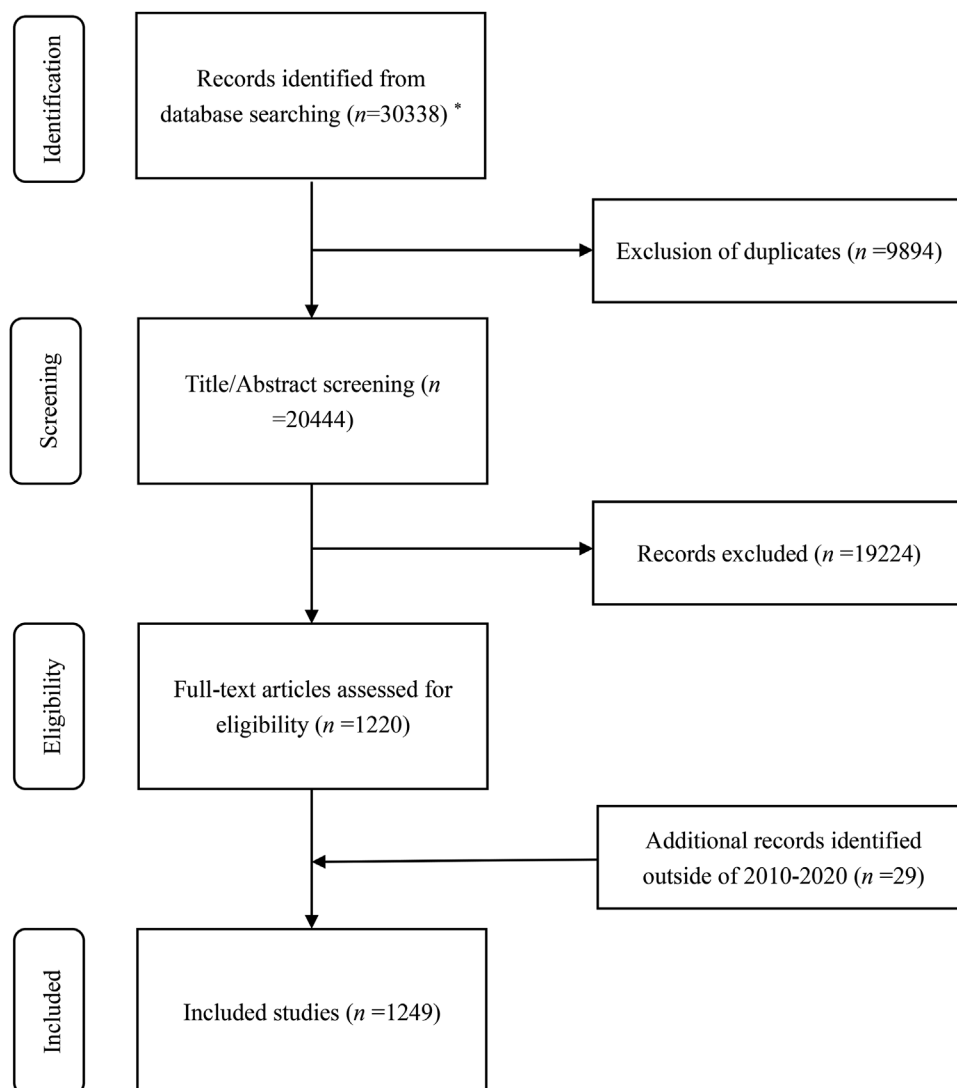


FIGURE 1 Flow chart of literature screening

*Results of searching: Medline ($n = 4687$), Embase ($n = 3312$), Cochrane Library ($n = 1313$), Epistemonikos ($n = 215$), CBM ($n = 8334$), Wanfang ($n = 8768$), and CNKI ($n = 3709$)

method (Table 1) was used to evaluate the quality of the evidence, and the quality of the evidence was divided into four levels: high, moderate, low, and very low.^{14,19,20} They had been presented in an evidence summary table.

2.6 | Formulation of recommendations

After four to five rounds of revisions, 60 relevant recommendations and the supporting materials for recommendations were initially determined. The secretary group made the GRADE decision-making table and reached a consensus on recommendations through 2–3 rounds of surveys using the improved Delphi method.²¹ Upon evaluation by 27 expert panels and after considering the patient's preferences and values, and the costs, benefits, and harms of the interventions, 49 recommendations were finally formed with a consensus degree of

over 80% and the corresponding recommendation basis was included. We referenced Reporting Items for Practice Guidelines in Healthcare (RIGHT) to write this guideline. The expert panel approved a diagram of management of patients with cutaneous warts (Figure 2). Plan for updates on recommendations of this guideline will be initiated around 2025 according to the requirement by the international guide.^{22,23}

3 | RESULTS

Question 1: What is the gold standard for the diagnosis of skin/mucosal HPV infection?

Recommendation:

1. Typical viral warts can be diagnosed by clinical visual examination. Pathological examination and HPV genotyping are recommended in

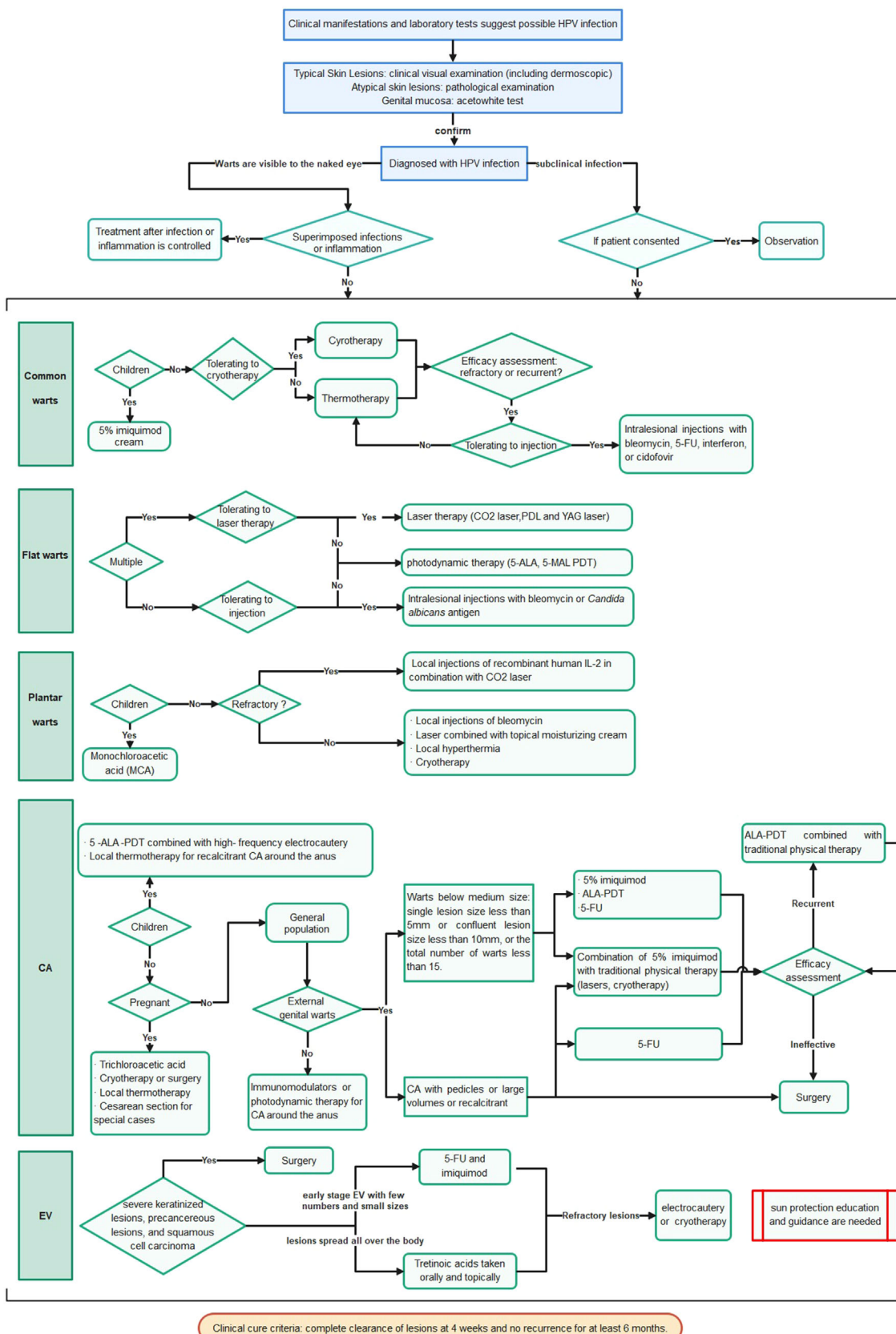


FIGURE 2 A diagram of the diagnosis and treatment of cutaneous warts

TABLE 1 Strength of recommendations and levels of evidences

Item	Definition
Strength of recommendations	
Strong (1)	It clearly shows that the intervention does more harm than good or does more good than harm.
Weak (2)	The benefits and harms are uncertain or the quality of the evidence shows comparable benefits and harms.
Levels of evidences	
High (A)	We are very confident that the observed value is close to the true value.
Moderate (B)	We have moderate confidence in the observed value: the observed value is likely to be close to the true value, but it might be substantially different.
Low (C)	We have limited confidence in the observed value: the observed value may be substantially different from the true value.
Very low (D)	We have little confidence in the observed value: the observed value can be substantially different from the true value.

cases of atypical lesions (suspected precancerous lesions or cancer) and in cases where the diagnosis is uncertain. (1C)

2. A 3–5% acetowhite test is suggested in the diagnosis of HPV infection in the genital mucosa. (2C)

Summary of the evidence:

Viral warts are generally diagnosed by visual recognition. However, the identification of atypical skin lesions should be evaluated by pathological examination and HPV genotype testing. For early genital mucosa viral warts, the application of 3–5% acetic acid can help in the detection of subclinical skin lesions.^{5–8,24}

A case series study²⁵ which examined 51 suspected men with CA by pathological examination and colposcopy showed that the accuracy of histopathological examination in the diagnosis of CA was higher than that of colposcopy (95.60% vs. 88.20%). A case series described that infection by different HPV types contributed to varied histological patterns in association with clinical types.²⁶ A diagnostic accuracy test²⁷ showed that the HPV-positive rate of the histopathologically diagnosed CA was 95.00%. The sensitivity and specificity for the prediction of HPV 6/11 by pathological examination were 43.60–46.60% and 64.70–71.70%, respectively. A case-series study²⁸ showed that all 116 hyperplastic warts were positive, and 57.70% of flat warts in the moist area were positive, while those in the dry area were practically negative when 5% acetic acid was applied. Two clinical studies revealed that in patients with CA, the accuracy of 5% acetic acid white test was 55.30% while in patients with subclinical HPV infection, the sensitivity and specificity of the acetowhite test were 92.30% and 58.20%, respectively.^{29,30}

Question 2: What are the transmission routes of HPV infection of skin or mucosa?

Recommendation:

1. Sexual and mother-to-fetus vertical transmissions are the main transmissions route of HPV to cause CA. (1C)
2. Virus transmission by skin contact, hand spreading, and contact with underwear or inanimate objects are responsible for common warts, plane warts, and plantar warts. (2D)
3. High-temperature evaporation treatment, i.e., CO₂ lasers, produces smog from the destructed HPV containing lesions that could transmit HPVs. (2B)

Summary of the evidence:

HPV has more than 200 types and causes multiple diseases including cutaneous and anogenital warts, cervical cancer, and anal cancer in men and women. Understanding the transmission routes of HPV can lead to better prevention for it.³¹

A cross-sectional study³² found that 64.29% (169/263) couples, of whom at least one person was infected and 42.01% of partners harbored the same HPV type (95% CI [36, 47]). The high degree of concordance suggests a high probability of sexual transmission. A cohort study³³ showed that the mother-to-fetus vertical transmission rate of HPV was 27.66%. There was no significant difference in infants' HPV infection rate between vaginal delivery and cesarean delivery (25.71% vs. 28.81%).

A systematic review in 2020³⁴ showed that mucosa of the upper respiratory tract (nose, mouth, pharynx) is a more common site with warts in CO₂ laser users compared to the normal population, as well as to those who don't use LEEP (Loop Electrosurgical Excision Procedure) or CO₂ lasers (0.60–3.40% vs. 5.10–12.90%) (OR = 5.75, 95% CI [1.55, 21.38], $p < 0.001$). Therefore, local exhaust ventilation such as smoke evacuators was recommended when performing laser or electrosurgical treatments for patients with warts.³⁵

Question 3: What are the laboratory tests for cutaneous warts?

Recommendation:

1. Acetowhite test is recommended for the diagnosis of subclinical CA. (1C)
2. In cases where identification of HPV types is required, noninvasive sampling by skin swabbing is recommended for HPV testing, resection or clamping of the warty tissue may be necessary in the case.(1C)
3. Dermoscopy may aid in the diagnosis of viral warts. (2D)
4. For vulvar CA harboring high-risk HPVs, cervical HPV test is suggested. (2B)

Summary of the evidence:

Albeit controversial for the recommendation of acetowhite test for the diagnosis of CA, it is still clinically used as an economical and convenient inspection method. Several studies^{28–30,36} have shown

the efficacy of acetowhite test to detect CA, including those with inconspicuous clinical appearance.

A case-series study³⁷ reported that PCR detection from samples of the resected wart and the wart swab yielded HPV-positive rates of 92.00% and 88.00%, respectively ($p > 0.05$). Another case-series study³⁸ showed that 25 swabbed samples possess identical HPV types to the biopsy counterpart with 96.00% sensitivity, a result validating that wart swabs can be reliably used for HPV typing sampling. A self-controlled experiment³⁹ showed that both two sampling methods, swabbing the surface of the lesion and taking a shave biopsy, reached a high agreement for detection of HPV DNA in CA (87.80% agreement) and penile intraepithelial neoplasia (100% agreement). However, the agreement in these two methods was low to moderate for detecting most individual HPV types, thus a combination of biopsy with swabbing may provide additional information for HPV genotyping.

A case-series study⁴⁰ including 132 patients with a total of 220 suspected CA lesions showed that the positive rate of dermatoscopic diagnosis was higher than that of a physician's visual diagnosis. A study⁴¹ reported that dermoscopy provided a higher positive rate and superiority in observing tiny warts than visual observation ($p < 0.01$). This method possessed the advantages of high sensitivity, quick and accurate diagnosis, and noninvasiveness. However, it has limitations for its inaccessibility in deep urethral orifice and skin wrinkles.

Two cohort studies^{42,43} showed a higher risk of cervical cancer, CIN (Cervical Intraepithelial Neoplasia), and cervical cancer in situ in female patients with CA. In 2012, a study⁴⁴ reported that the rate of cervical high-risk HPV infection was significantly higher in women with CA than in the general population.

Question 4: What is the treatment principle for cutaneous warts?

Recommendation:

1. Remove the wart as early as possible and eliminate the subclinical infection around the wart as much as possible to reduce or prevent recurrence. (1C)
2. Superimposed infections and inflammation should be controlled before treating CA lesions. (1C)
3. Decision on the treatment of genital warts in pregnant women should be based on the size of warts and the impact on the fetus. (2D)
4. Precaution to avoid contact with flowing particles should be taken during the evaporating surgical treatment of warts. (2C)

Summary of the evidence:

The primary goal of treatment is to remove warts and improve the presenting symptoms. According to the published guidelines,^{5,13,45} most patients' warts disappear after treatment while the recurrences are frequent. Genital warts may heal, remain unchanged, or increase in number and size in untreated patients. Treatment may weaken the infectivity of HPV, but may not necessarily eradicate HPV. A guideline of the Chinese Society of Dermatology in 2021⁹ suggested that visible genital warts should be treated. For subclinical infections, laser, cryotherapy, topical imiquimod, photodynamic therapy (extending to

1 cm around warts) should be appropriately implemented to reduce the rate of recurrence.

So far, there is no effective anti-HPV drug to clear HPV infection. Surgery and physical therapy can remove visible warts. An expert consensus in 2017 in China⁴⁶ indicated that cytological examination should be performed before the treatment of vaginal and cervical CA. And if necessary, colposcopic biopsy should be performed to exclude the precancerous and cancerous lesions of the vagina and cervix.

A guideline from the Chinese Society of Dermatology in 2015⁴⁷ stated that patients with CA may be complicated with other sexually transmitted diseases. In such cases, the inflammation or other superimposed infections should be controlled first, to avoid spreading skin lesions after treatment.

The numbers and sizes of genital warts may increase with the progress of the pregnancy. The safety profile of topical podophylotoxin and imiquimod during pregnancy has not been established and thus prohibited. Cryotherapy, surgery, and trichloroacetic acid for genital warts are applicable to pregnant women. Pregnant women should be treated appropriately to ensure the safety of the fetus. China's 2014 Guidelines for Diagnosis and Treatment of CA¹⁰ and an expert consensus in 2017¹¹ both recommended that pregnant women infected with CA should be treated as early as possible. Genital warts rarely affect delivery, and their spontaneous resolution was common during the puerperium. In 2019, a guideline from the Infection and Sexual Health Clinical Research Center of the Institute of Global Health, University of London, UK⁶ stated that for small, slow-growing warts which did not affect pregnancy and delivery, the treatment of genital warts could be postponed until after childbirth. If there are warts that might block the birth canal, pelvic outlet obstruction, or vaginal delivery, a joint consultation with specialists in obstetrics and gynecology, neonatology, and venerology is necessary.⁹ The spouse or partner who had sexual contact with the patient should be examined and they need to be treated if with lesions. Avoidance of intercourse is recommended during treatment. Choices of treatment methods should be based on considerations of the size, location, age, and other factors of the skin lesions. Toxic drugs or methods prone to scarring were not recommended.

During the surgical treatment of HPV-related lesions, especially when using smoke-producing surgical treatment methods (laser or electrosurgery), it was recommended to comply with laser safety regulations and hygiene guidelines to protect patients and physicians from contacting infectious particles.⁵

Question 5: What is the clinical criterion for the cure of warts?

Recommendation:

1. The clinical criteria for cure of warts are complete clearance of lesions at 4 weeks and no recurrence for at least 6 months. (1B)

Summary of the evidence:

According to the current literature, there has been no uniform definition of clinical criteria for the cure of HPV infection. A systematic review published in 2017⁴⁸ referred that short-term complete

clearance referred to complete clearance of lesions at 4 weeks (± 4 weeks) at the end of treatment (EOT), intermediate-term complete clearance referred to complete clearance of lesions at 16 weeks (± 8 weeks) at the EOT, and long-term clearance referred to complete clearance of lesions at 12 months (± 6 months) at the EOT. Intermediate-term recurrence referred to recurrence of lesions at 16 weeks (± 8 weeks) at EOT in patients who had a complete clearance at 4 weeks (± 4 weeks) at EOT. Long-term recurrence referred to recurrence of lesions at 12 months (± 6 months) at EOT in patients who had a complete clearance at 4 weeks (± 4 weeks) at EOT. Another systematic review in 2017⁴⁹ reported that, in HIV-positive patients with genital warts, short-term complete clearance referred to complete clearance of lesions at 4 weeks (after EOT), intermediate-term complete clearance referred to complete clearance of lesions at 24 weeks (± 16 weeks) at EOT, and long-term clearance referred to complete clearance of lesions at 12 months (± 2 months) at EOT. Intermediate-term and long-term recurrence respectively referred to recurrence of lesions at 24 weeks (± 16 weeks) and 12 months (± 2 months) after EOT in patients who had a complete clearance at EOT. For other warts, an RCT⁵⁰ in 2020 including recalcitrant common warts and a study protocol for a single-center randomized controlled trial⁵¹ in 2020 including common warts, plantar warts, flat warts, and filiform warts both stated that the recurrence rate was assessed at 6 months after enrolment.

Question 6: How to define multiple, recurrent, and refractory cutaneous warts?

Recommendation:

1. Multiple warts are defined as a patient with two or more than two warts. (2D)
2. Recurrent warts are defined as warts that appear near the original site of warts, which have been completely cleared. The intermediate-term recurrence of warts is 4 months (± 2 months) by the end of treatment, and the long-term recurrence is 12 months (± 6 months) by the end of treatment. (2B)
3. Refractory warts are defined as warts that last for at least 2 years with poor response to more than two traditional treatment options. (2B)

Summary of the evidence:

There has been no uniform definition of multiple/generalized, recurrent, and refractory warts thus far. Clinicians mostly classify them according to their understanding.

In a cohort study,⁵² albeit the authors didn't explicitly define multiple warts, the presumptive were those patients with more than one warty lesion. In a 2016 case report,⁵³ the generalized wart was defined as diffuse cutaneous warts over 20 in number that is distributed in more than one area of the body.

In 1989, a nonrandomized controlled study⁵⁴ indicated that recurrent warts were those that appeared near the original sites with warts that had been cleared completely. Two systematic reviews in 2017^{48,49} showed that intermediate-term recurrence of genital warts was 4 months (± 2 months) after the EOT, and long-term recurrence was

12 months (± 6 months) after the EOT (the skin lesions were completely cleared at the EOT). Two Chinese expert consensuses in 2015 and 2017^{11,12} stated that the recurrence of CA mostly occurred in 3–6 months after treatment, and most often occurred in the first 3 months. If there were no recurrence 6 months after treatment, the chance of recurrence was low.

In a nonrandomized controlled study,⁵⁵ refractory warts were defined as those who failed to respond to two traditional treatments or warts that lasted for over 2 years. A cohort study⁵⁶ showed warts were more persistent and refractory to treatment in organ transplant recipients. In an RCT in 2018,⁵⁷ the included refractory warts were those that lasted for more than 2 years and failed response to more than two treatment methods (laser surgery, electrosurgery, curettage, liquid nitrogen freezing therapy, and topical salicylic acid treatment). In an observational study,⁵⁸ refractory warts were those resistant to conventional treatments and there was no improvement after trying different methods.

Question 7: What are the recommended clinical treatment methods for common warts?

Recommendation:

1. Local injections with bleomycin, 5-Fluorouracil (5-FU), and cidofovir are suggested for refractory and recurrent common warts. Local adverse reactions of intralesional injection therapy include pain, burning, itching, erythema during the procedures, and postinflammatory pigmentation. (2B)
2. Cryotherapy is recommended for common warts. However, patients receiving cryotherapy need to tolerate treatment-related pain and, may experience other side effects, such as posttreatment scarring and hyper/hypopigmentation. (1B)
3. Thermotherapy is suggested for patients with common warts, especially multiple warts, who cannot tolerate local injection and cryotherapy. The recommended treatment temperature is on average at 44°C over the lesion, and the treatment time lasts for 30 min. Repeated treatments are required. Common adverse reactions include burning sensation, occasional heat-induced blisters, and postinflammatory pigmentation. (2C)

Summary of the evidence:

Common warts are mostly caused by HPV type 2. Choices for their treatment should be based on specific conditions.⁵⁹

A case-series study⁶⁰ showed that after an average of 2.61 treatment cycles with intralesional injection of bleomycin (therapeutic dose at 3 U/ml and treatment interval at 3–4 weeks), all of the 250 periungual and subungual warts in 80 patients of whom 26 (32.50%) patients were either with no response to or recurrence after previous treatments were cleared and 65 (81.25%) patients experienced moderate pain during the treatment sessions, 155 (62.00%) treatment sites had transit dyspigmentation, and 3 (1.20%) treatment sites experienced reversible necrosis. An RCT⁶¹ including 42 patients with multiple warts (common warts and plantar warts) compared the bleomycin microneedle patch treatment with cryotherapy and their effective rates were

respectively 55.71% and 55.85%, but patients were more tolerable to microneedle patch for lesser pain during the treatment.

A prospective study⁶² reported that the cure rate of common warts with the injection of 5-FU, lidocaine, and epinephrine mixture (50 mg/ml 5-FU plus with lidocaine and epinephrine mixture at a ratio of 4:1) was higher than that of saline control (64.70% vs. 35.30%, $p < 0.05$). There was no significant difference in the incidence of systemic adverse reactions and treatment-related side effects between the two groups. A case-series study⁶³ included 280 patients with multiple and recalcitrant cutaneous warts (common and mosaic warts) and without any success, they had received at least two other treatments for their lesions. The result showed that lesional injection with 15 mg/ml cidofovir once a month, on average of 3.2 sessions, cleared relapsed and refractory warts in 276 of 280 patients.

An observational study on 90 patients⁶⁴ showed that the overall success rate was 64.44% in treating warts on hands and feet with cryotherapy. The effectiveness of liquid nitrogen cryotherapy for common warts depended on factors including the duration of warts, the number of warts, and the repeated times of treatments. Warts treated by cryotherapy once a week had faster recovery than once every 2–3 weeks while the overall cure rate depended on the total repeated times of treatments rather than the time interval. A meta-analysis on one nonrandomized controlled trial⁶⁵ and two RCTs^{61,66} showed that the effectiveness of liquid nitrogen cryotherapy in the treatment of common warts was significantly higher than noncryotherapy methods ($I^2 = 90\%$, $RR = 2.01$, 95% CI [1.02, 3.97], $p = 0.04$), as topical trichloroacetic acid and intralesional injection of *Candida* antigen. A cohort study⁶⁷ concluded that shorter freezing time (10 s) and interval (2 weeks) of cryotherapy was more effective than longer freezing time (20 s) and intervals (4 weeks), for treating common viral warts on hand and foot.

A case-series study⁶⁸ performed local hyperthermia (once a day for 30 min, for 5 consecutive days, temperature applied was determined by tolerance of the patients, on average, temperatures applied to hand warts was 43.5°C, while that for foot warts was 45.3°C) on patients with common warts who had not received local or systemic treatment in the past 3 months. For patients with multiple lesions, only one target lesion was selected for local hyperthermia. After the treatment, the patients were followed up monthly. After 3 months of follow-up, the total cure rate was 53.85%, and the cure rate for the foot (65.22%) was higher than the hand cure rate (37.50%). Treatment response was not affected by number, gender, and age. All patients had tolerable burning sensations during treatment.

Question 8: What are the recommended clinical treatment methods for flat warts, including generalized, recurrent, and refractory conditions?

Recommendation:

1. 10% 5-aminolevulinic acid photodynamic therapy (5-ALA-PDT) is recommended for the treatment of flat warts. (1B)
2. Lasers and photodynamic therapy could be used to treat multiple flat warts. Lasers include CO₂ laser, PDL (pulsed dye laser), and YAG

laser. Photodynamic therapy (PDT) includes 5-aminolevulinic acid (ALA) or 5-methylaminolevulinic acid (MAL) photodynamic therapy. (2C)

3. Injection of bleomycin or *Candida albicans* antigen is recommended to treat flat warts. (1B)

Summary of the evidence:

Flat warts mostly appear in facial areas of children or young adults. It is commonly caused HPV type 3, 10, 28, and 41. There is no specific antiviral treatment thus far.⁶⁹

A 2017 systematic review⁷⁰ showed that compared with CO₂ laser, ALA-PDT had a lower recurrence rate, fewer adverse reactions, and a better prognosis for treating flat warts ($p < 0.05$). Compared with topical imiquimod cream, ALA-PDT had a higher curative effect, also with a higher incidence of adverse reactions ($p < 0.05$). Compared with liquid nitrogen freezing, ALA-PDT had a better curative effect with a lower recurrence rate and adverse reaction rate ($p < 0.05$). An RCT⁷¹ showed that 10% ALA was more effective than 5% and 20% ALA regarding the complete remission rate after 12 weeks (33.30% vs. 14.30% vs. 26.30%, $p < 0.05$). The rate of hyperpigmentation after 12 weeks was in the descending order of 33.30%, 15.60%, and 12.90% by use of 20%, 5%, and 10% ALA, respectively ($p < 0.05$).

A systematic review in 2016⁷² showed that CO₂, PDL, and Nd: YAG are currently the most studied lasers for the treatment of non-genital verrucae with a response rate of 50.00–100.00% for CO₂ laser, 47.10–100.00% for PDL, and 46.34–100.00% for Nd: YAG laser. PDL was comparable in effectiveness to traditional therapies such as cryotherapy and topical cantharidin. Combination of PDL with drugs such as bleomycin and salicylic acid had higher success rates, PDL had fewer adverse reactions compared with Nd: YAG or CO₂ laser in the treatment of nongenital warts. In 2016, a case series study⁷³ showed that long-pulse 532 nm LP Nd: YAG laser achieved 92.00% complete removal of all warts after one course of treatment. Lesions with longer duration (over 2 years vs. fewer than 6 months) had lower clearance rates (84.00% vs. 98.00%, respectively).

The working panel of the guideline conducted a meta-analysis of four RCTs^{74–77} showing that the effective rate of intralesional injection of *Candida albicans* antigen to treat flat warts was significantly higher than those of other options such as oral isotretinoin, local injection of 5-FU and other microbial antigens ($I^2 = 77\%$, $RR = 0.80$, 95% CI [0.24, 2.72], $p < 0.0001$). While in one of the RCTs⁷⁷, it showed that the cure rate of bleomycin injection was significantly higher than that of *Candida albicans* antigen as well as 5-FU. Side effects included injection pain, local erythema and edema for all, and a few cases of flu-like symptoms in *Candida albicans* antigen recipients.

Question 9: What are the recommended clinical treatment methods for plantar warts, including multiple, recurrent, and refractory conditions?

Recommendation:

1. Local hyperthermia is suggested for patients with plantar warts. (2B)

2. Cryotherapy is suggested for patients with plantar warts. (2B)
3. Long-pulsed 1064 nm Nd: YAG laser combined with topical moisturizing cream treatment or optimized CO₂ laser treatment is recommended for plantar warts. Local injections of recombinant human IL-2 in combination with CO₂ laser are recommended for recalcitrant plantar warts. (1B)
4. Local injections of bleomycin are recommended for the treatment of plantar warts. (1B)

Summary of the evidence:

The plantar wart is a common viral skin disease infected mostly by HPV types 1, 2, 4, 27, and 57, which is challenging because of the frequent recurrences after treatment.⁷⁸

An RCT⁷⁹ applied local hyperthermia at 44°C for 30 min in a session, in a protocol of application on day 1, 2, 3, 17, and 18, on a single target lesion. The results showed that 53.57% of patients with plantar warts and 11.54% of patients in the sham treatment group achieved complete cure ($\chi^2 = 10.718$, $p = 0.001$), 3 months after completion of the treatment protocol. No recurrent case was reported in the study. Additional benefits were the reduction to 80.00% of loading-bearing pain after the treatment and the removal of lesions at distant sites in successful cases. A cohort study⁶⁸ treated plantar warts at local temperatures best tolerated by the patients which ranged from 43.5°C to 47.5°C (average at 45.3°C). By the end of 3 months after the therapy, 15 of 23 (65.22%) cases were cured. The treatment response was not correlated with wart number, sex, age, or temperatures applied.

An RCT⁸⁰ showed that cryotherapy had a significantly higher complete cure rate than the silver tape closure treatment (58.00% vs. 20.00% out of 50 patients in each group) in the scheduled 8 weeks of study. There were no significant differences in response in either group in association with the duration of the disease. The selection of different cryotherapy devices may affect efficacy. An RCT⁸¹ concluded that nitrous oxide freezing had a higher cure rate in the treatment of common warts and plantar warts than the other two commercially available devices (dimethyl ether and propane freezing device and dimethyl ether without or with metal nib device, 82.00%, 47.37%, and 52.78%, respectively, $p = 0.001$). The patients treated were those with a disease duration of no more than 6 months.

A cohort study on 240 patients⁸² showed that the use of moisturizing cream before long-pulse 1064 nanometer Nd: YAG laser treatment achieved a clearance rate of 97.08%, by an average treatment session of 1.3 (range 1–3), 75.80% cleared by one session of treatment.

An RCT⁸³ on the treatment of recalcitrant warts showed that local injection of recombinant human IL-2 combined with CO₂ laser treatment had a higher effective rate 2 months after treatment and a lower recurrence rate than CO₂ laser treatment, cryotherapy, topical fluorouracil ointment and local injection of recombinant human IL-2 (94.00%, 78.00%, 56.00%, 32.00%, and 44.00%, respectively). An RCT⁸⁴ showed that the effective rate of optimized CO₂ laser (out-putting grid spot) treatment and traditional CO₂ laser treatment for plantar warts were 95.71% and 81.54%, respectively ($\chi^2 = 6.858$, $p < 0.05$), after 6 months of follow-up.

An RCT⁸⁵ showed that the cure rate of intralesional bleomycin treatment were 63.02%, superior to that of 48.82% by cryotherapy ($p < 0.05$).

Question 10: What are the recommended clinical treatment methods for CA, including multiple, recurrent, and refractory conditions?

Recommendation:

1. Combination of 5% imiquimod with traditional physical therapy (lasers, cryotherapy) is recommended to treat CA. (1A)
2. Topical treatment is recommended for genital warts with single lesion size less than 5 mm or confluent lesion size less than 10 mm, or a total number of warts less than 15. (1B)
3. ALA-PDT alone is recommended to treat genital warts <5 mm in size. (1B)
4. ALA-PDT combined with traditional physical therapy is recommended to reduce the rate of recurrence. (1B)
5. Surgery is recommended for CA with pedicle or large volumes or recalcitrant. (1A)
6. Destructive physical therapy followed by immunomodulators (imiquimod or recombinant human interferon α -2b) or photodynamic therapy is recommended. (1B)
7. Topical 5% imiquimod or photodynamic therapy is considered for CA with underlining HIV infection. (2C)

Summary of the evidence:

The current principle of treatment of CA is to remove warts as early as possible, improve symptoms, eliminate subclinical infections and latent infections around warts, and reduce recurrence.¹¹ The treatment methods of CA are divided into self-application and office-based treatment. Self-application is mainly topical drugs, including podophyllotoxin and imiquimod. Office-based treatment includes traditional physical therapy (CO₂ laser, microwave, high-frequency electric therapy, and liquid nitrogen freezing), photodynamic therapy, and trichloroacetic acid. Appropriate treatment methods should be based on the overall consideration of the condition of warts, patient selection, treatment cost and feasibility, side effects, and doctor's experience.

Traditional physical therapy has a quick clinical effect on hyperplastic lesions, but the effect of maintaining complete clearance is poor and the risk of recurrence is high.⁸⁶ However, topical treatment with 5% imiquimod is helpful to achieve continuous clearance and reduce recurrence. The combination of these two can effectively clear CA and reduce CA recurrence.⁸⁷ A systematic review in 2020⁸⁷ showed that CO₂ laser combined with 5% imiquimod had a higher clearance rate than CO₂ laser alone (12 weeks after treatment: RR = 1.53, 95% CI [1.38, 1.71], $I^2 = 46\%$; 24 weeks after treatment: RR = 1.90, 95% CI [1.42, 2.53], $I^2 = 73\%$). The clearance rate of wart by electrocautery combined with 5% imiquimod was higher than that by electrocautery alone (RR = 1.62, 95% CI [1.33, 1.97], $I^2 = 0\%$). Microwave combined with 5% imiquimod was better than microwave alone (RR = 2.20, 95% CI [1.26, 3.83], $I^2 = 73\%$). 5% podophyllotoxin and 5% or 3.75% imiquimod cream are the most commonly used topical drugs. 5% podophyllotoxin tincture was topically applied twice a day for 3

consecutive days, followed by withdrawal for 4 days, 7 days as a course of treatment, with a maximum of 4 courses of treatment. In a network systematic review in 2020,⁸⁸ six treatment options, including podophyllotoxin, imiquimod, tea polyphenol ointment, 5-FU, cidofovir, and interferon cream were evaluated, setting the outcome index as complete removal of warts. 0.5% podophyllotoxin ointment or solution was the most effective in clearing the wart and the least recurrent. Meanwhile, in a network meta-analysis⁸⁹ in 2020, 0.5% podophyllotoxin (OR = 1.94, 95% CI [1.02, 3.71]) was significantly more efficacious than 5% imiquimod for lesion clearance.

A 2019 systematic review⁹⁰ showed that topical 0.5% podophyllotoxin solution was superior to 5% imiquimod cream in the treatment of patients with genital warts (OR = 0.07, 95% CI [0.001, 0.36]). In 2019, a systematic review⁹¹ showed that compared with the traditional tincture form of podophyllotoxin, podophyllotoxin nanogel could increase the cure rate (OR = 1.76, 95% CI [1.65, 1.87], $p < 0.00001$), reduce the recurrence rate (OR = -0.32, 95% CI [-0.36, 0.28], $p < 0.00001$), shorten the course of disease (95% CI [-9.41, 9.14], $p < 0.00001$), reduce the adverse reactions such as edema (OR = 0.26, 95% CI [0.29, 0.22], $p < 0.00001$), erosion (OR = 0.25, 95% CI [0.34, 0.17], $p < 0.00001$), pain (OR = 0.35, 95% CI [-0.42, 0.28], $p < 0.00001$), and effectively control HPV subclinical infection (OR = 0.46, 95% CI [0.31, 0.67], $p < 0.00001$).

Meta-analysis of two RCTs^{92,93} showed that the effective rate of topical imiquimod in the treatment of CA was significantly higher than those of other intervention groups ($I^2 = 74.00\%$, RR = 1.60, 95% CI [1.35, 1.89], $p = 0.009$). In 2015, an RCT⁹⁴ studied the clinical effects of 2.5% or 3.75% imiquimod cream in the treatment of male CA for 12 consecutive weeks. The results showed that the clearance rate (CR) of 3.75% imiquimod cream was higher than that of 2.5% imiquimod cream (CR: 18.60% vs. 14.30%, $p < 0.05$).

Photodynamic therapy, as with ALA-PDT, was applied once a week. ALA-PDT therapy had certain advantages in reducing the recurrence rate due to its direct inhibition effect on virus replication.⁹⁵ A systematic review in 2013⁹⁶ showed that the recurrence rate of ALA-PDT was lower than CO₂ laser and cryotherapy with liquid nitrogen for urethral anogenital warts (AGW) (RR = 0.25, 95% CI [0.18, 0.36], $p < 0.05$). The recurrence rate of cervical condyloma in ALA-PDT was lower than that of CO₂ laser (RR = 0.28, 95% CI [0.12, 0.65], $p < 0.05$). A multicenter RCT study⁹⁷ showed that after being followed up for 12 weeks, the recurrence rate of AGW was significantly lower in the ALA-PDT group (10.77% vs. 33.33%, respectively, $p < 0.05$) compared with CO₂ laser group, and again in patients with urethral AGW the recurrence rate was lower in ALA-PDT group than CO₂ laser group (10.53% vs. 36.36%, respectively, $p < 0.05$). A multicenter retrospective study⁹⁸ treated AGW patients using ALA-PDT (once a week for 3 weeks) and assessed the efficacy after each treatment. The results showed increased clearance rates with more treatment sessions. Clearance rates after 1, 2, and 3 weeks of treatment were 68.12%, 81.16%, and 95.27%, respectively, $p < 0.001$. Small warts (<5 mm) had a higher clearance rate than warts of >5 mm (97.74% vs. 88.73%, $p < 0.001$). The recurrence rates varied at different locations of warts and perianal warts had the highest recurrence rates while those at labia had the lowest ones (30.23% vs.

11.54%, respectively). The adverse reactions included redness, pain, erosion, ulcer, and pigmentation, and the incidence rates were 7.72%, 8.10%, 2.26%, 0.94%, and 0.19%, respectively. There was no reported case of urethral malformation and sexual dysfunction. One clinical observation⁹⁹ showed that after treatment for 1, 2, and 3 weeks, the clearance rate of warts with ALA-PDT was higher than cryotherapy with liquid nitrogen at rates of 73.23% vs. 53.19% (at week 1), 85.83% vs. 63.83% (at week 2), and 93.70% vs. 70.21% (at week 3), all $p < 0.01$. After 3 months of follow-up, the recurrence rate of ALA-PDT was lower than cryotherapy with liquid nitrogen (10.17% vs. 45.45%, $p < 0.01$).

A systematic review in 2014¹⁰⁰ revealed that ALA-PDT combined with liquid nitrogen cryotherapy had a higher cure rate (OR = 4.82, 95% CI [3.33, 7.00], $p < 0.01$) and lower recurrence rate (OR = 0.32, 95% CI [0.21, 0.50], $p < 0.01$) compared with the liquid nitrogen freezing alone in patients with AGW. Two systematic review^{96,101} showed that the local application of ALA-PDT combined with CO₂ laser had a lower recurrence rate than using CO₂ laser alone after a 12 weeks follow-up (RR = 0.20, 95% CI [0.09, 0.44], $p < 0.05$) in 13 RCTs and a 24 weeks follow-up (RR = 0.23, 95% CI [0.11, 0.51], $p < 0.05$) in 7 RCTs. What's more, the combined treatment had a lower incidence and severity of adverse reactions, and patients were well tolerated.¹⁰¹ In a single-arm clinical trial,¹⁰² 98 patients with warts were treated with laser ablation and then applied to three sessions of ALA-PDT treatments. The results showed that 92 cases (93.88%) were completely cured. After 3 months of follow-up, 18 (18.37%) cases had relapsed lesions near the treatment sites. A meta-analysis of six RCTs¹⁰³⁻¹⁰⁸ showed that the cure rate of ALA-PDT combined with conventional physical treatments was higher than those of conventional physical treatment alone ($I^2 = 89\%$, RR = 1.33, 95% CI [1.09, 1.63], $p = 0.005$). ALA-PDT combined with conventional physical treatments had lower recurrence rates than those of conventional physical treatment alone, in 1 month ($I^2 = 0\%$, RR = 0.20, 95% CI [0.13, 0.32], $p < 0.00001$), 2 months ($I^2 = 0\%$, RR = 0.16, 95% CI [0.11, 0.22], $p < 0.00001$), and 3 months ($I^2 = 0\%$, RR = 0.25, 95% CI [0.19, 0.34], $p < 0.00001$).^{101,104,105}

Surgical resection is suitable for the treatment of pedicled or massive warts, recalcitrant warts, and warts with repeated attacks in a short time. In a network meta-analysis on anogenital warts in 2020,⁸⁸ surgical resection achieved the best effect in removing the lesions (RR = 10.54, 95% CI [4.53, 24.52]), as compared with other methods like 5-FU, ablation, ablation and imiquimod, cidofovir, 9% citric acid, or CO₂ laser. A systematic review⁹⁰ published in 2019, in which the outcome index was no recurrence of CA, showed that surgery had the best effect in reducing recurrence risk after thorough removal of CA compared with cryotherapy, 5% imiquimod cream, 0.5% podophyllotoxin solution, and 20-25% podophyllate.

Perianal CA is difficult to remove and the recurrence rate is high. The meta-analysis results of two RCTs^{109,110} showed the effective rate of the combined treatment group (recombinant human interferon α -2b injection combined with liquid nitrogen cryotherapy or CO₂) was significantly higher than that of liquid nitrogen cryotherapy or CO₂ group alone ($I^2 = 85\%$, RR = 1.47, 95% CI [1.04, 2.06], $p = 0.03$) and the recurrence rate was lower ($I^2 = 89\%$, RR = 1.33, 95% CI [1.09, 1.63], $p = 0.005$).

AGW concurrent with HIV infection is more prone to malignant transformation and more difficult to treat. Traditional therapy such as CO₂ laser, microwave, high-frequency electric therapy, and liquid nitrogen freezing treatment often fails and the recurrence rate is high. An RCT¹¹¹ compared the efficacy of ALA-PDT with topical 5% imiquimod cream for AGW with HIV infections, along with standard anti-HIV therapy during the trial. ALA-PDT had a higher cure rate (84.00% vs. 52.00%, $p < 0.05$), lower recurrence rate (16.00% vs. 48.00%, $p < 0.05$), and reduced incidence of adverse reactions related to skin and mucosal injury ($p < 0.05$), but the treatment-related pain was more severe ($p < 0.05$). A case-series study¹¹² observed the cure rate 20 weeks after treatment with microwave therapy combined with imiquimod cream topical application (topical application after 1 week of microwave treatment) in AGW patients concurrent with HIV infection. The results showed that in patients with CD4⁺T lymphocyte number $\geq 350 \times 10^6/L$, the cure rate was 89.55%, and CD4⁺T lymphocyte below that number was 72.09%. A cohort study¹¹³ focusing on different methods for the treatment of patients with anal CA complicated with HIV infection showed that 1 year after treatment, the cumulative recurrence rates were 6.15% (4/65, 95% CI [2, 15], error data in original study) by electroresection, 11.11% (3/27, 95% CI [4, 28]) by infrared coagulation, and 11.11% (1/9, 95% CI [2, 44]) by imiquimod. After 10 years of follow-up, cumulative recurrence rates were 46.15% (95% CI [35, 58]) by electroresection, 55.56% (95% CI [37, 72]) by infrared coagulation, 55.56% (95% CI [27, 81]) by imiquimod, and 50.00% (1 case, 95% CI [1, 91]) by cryotherapy.

Question 11: What are the recommended clinical treatment methods for epidermodysplasia verruciformis (EV)?

Recommendation:

1. 5-FU and imiquimod could be used topically for early stage EV with lesions few in numbers and small in size. (2D)
2. Retinoic acids could be taken orally and topically when the lesions spread all over the body. (2D)
3. Refractory lesions could be treated with electrocautery and cryotherapy. (2D)
4. Surgery removal is suggested for patients with severe keratinized lesions, precancerous lesions, and squamous cell carcinoma. (2D)
5. All patients need sun protection education and guidance on sun protection. (1D)

Summary of the evidence:

Verrucous epidermal dysplasia is a rare chronic disease characterized by genetic susceptibility to HPV, manifesting as highly pleomorphic and disseminated lesions. Solar keratosis frequently occurs after 30 years of age, and half of them evolve into squamous cell carcinoma. There is currently no specific treatment, and different treatment methods are chosen according to the manifestations of the skin lesions. Above all, sun protection is necessary to prevent malignant transformation.

In a case report, two 23-year-old female patients with multiple flat EV lesions on the face were topically applied 5-FU combined with imiquimod once a day and three days per week, and the area and

numbers of warts were reduced, while recurrent after 1 year.¹¹⁴ A 40-year-old female EV patient with generalized lesion was treated with oral Isotretinoin combined with Tazarotene gel, and the lesions subsided significantly (no long-term follow-up).¹¹⁵ A 16-year-old female patient with generalized skin lesions on the face and neck was treated with systemic ganciclovir, BCG polysaccharide nucleic acid, and the skin lesions were treated with electrocautery and cryotherapy. A proportion of the lesions were removed while there were remaining ones on several sites of the body.¹¹⁶ A 50-year-old male patient with severe hyperkeratotic plaques on the face and limbs was diagnosed with clinical manifestation and HPV 51 DNA positivity. Surgical resection removed the plaques over his hands. There was no recurrence in a 1-year follow-up.¹¹⁷ A case report described a 56-year-old female patient with brown flat verrucous papules all over the body for 40 years. She developed multiple lesions histologically confirmed Bowen's disease, which was surgically removed.¹¹⁸

Question 12: How should children (under the age of 18) with cutaneous warts be treated?

Recommendation:

1. Intralesional *Candida* antigen immunotherapy is suggested for children with recalcitrant and multiple warts. (2C)
2. Children with CA could be treated with 5-ALA -PDT combined with high-frequency electrocautery. (2C)
3. Children with recalcitrant CA around the anus could be treated with local thermotherapy. (2D)
4. Children with common warts can be treated with 5% imiquimod cream. (1B)
5. Monochloroacetic acid (MCA) is recommended for children with plantar warts. (1B)

Summary of the evidence:

Cutaneous warts are estimated to occur in up to 10% of children and young adults, with the greatest incidence between 12 and 16 years of age. Warts occur more frequently in girls than in boys. Common warts represent 70% of skin warts and occur primarily in children, whereas plantar and flat warts occur among slightly older populations.¹¹⁹

The first-line treatment of skin warts includes topical use of salicylic acid and cryotherapy, but cryotherapy may cause pain and blisters and require repeated treatment, which limits its use in children. Intralesional immunotherapy is a promising method for the treatment of multiple or refractory warts in children, which can remove distant warts with minimal side effects, with cure rates of 23.30–95.20%.¹²⁰

An RCT¹²¹ compared the efficacy of MMR (measles, mumps, and rubella) vaccine ($n = 15$), *Candida* antigen intralesion injection ($n = 15$), and saline control ($n = 10$) in 40 cases of children with anogenital warts. Of 15 patients in the treatment groups, 73.33% (MMR) and 80.00% (*Candida* antigen) achieved complete clearance, respectively, compared with saline control (1 out of 10 patients, 10.00%). There was no statistically significant difference between the MMR vaccine and the *Candida* antigen group. Adverse reactions were mild, and there was no recurrence after 6 months of follow-up.

An RCT¹²² compared the efficacy of high-frequency electrocautery combined with 5-ALA-PDT and high-frequency electrocautery alone for treating CA in children. The result showed that the effective rates were not statistically different between the two groups (90.91% vs. 88.89%, $p > 0.05$), while the combination method had a significantly lower recurrence rate than the high-frequency electrocautery group alone (13.64% vs. 44.44%, $p < 0.05$).

A case report showed¹²³ that local thermotherapy at 44°C successfully cured a 2.5-year-old child with multiple CA around the anus, who failed several previous treatments. The treatment started once a day for 3 consecutive days, each treatment for 30 min, plus two sessions of treatment 2 weeks later. Then the treatment was conducted once a week for 5 weeks when the volume of the body of the wart started to decrease. Two more additional treatments were given, and in 4 months, all the lesions disappeared without recurrence the months to follow.

An RCT¹²⁴ compared the effect of MCA and cryotherapy on common warts. The cure rates were 40/92 (43.48%, 95% CI [34, 54]) for MCA and 50/93 (53.76%, 95% CI [44, 64]) for cryotherapy (risk difference (RD): 10%, 95% CI [-25, 4.0], $p = 0.16$), at week 13th after initiation of treatment. MCA could effectively replace cryotherapy, which could avoid pain and reduce blisters during treatment but could not avoid pain after treatment. In regard to plantar wart, cure rates were 49/106 (46.23%, 95% CI [37, 56]) for MCA and 45/115 (39.13%, 95% CI [31, 48]) for cryotherapy combined with self-daily applied salicylic acid (RD 7.10%, 95%CI [-5.9, 20], $p = 0.29$). MCA had similar efficacy but it could reduce the pain, blister, and burden of treatment.

Question 13: How should pregnant women with cutaneous warts be treated?

Recommendation:

1. Podophyllotoxin and imiquimod are not recommended for CA during pregnancy, but trichloroacetic acid can be used. (1A)
2. CA during pregnancy could be treated by liquid nitrogen cryotherapy or surgery. (2C)
3. Cesarean section is recommended when large warts may block the birth canal or cause massive bleeding. (1C)
4. CA during pregnancy could be treated with local thermotherapy. (2C)

Summary of the evidence:

Compared with the nonpregnancy patient, CA during pregnancy has rapid growth, a high recurrence rate and is easy to ulcerate and bleed, possibly due to changes in hormone levels in pregnant women, a genital environment conducive to HPV reproduction, limited clinical medication, and decreased immune function.¹²⁵

Chinese guidelines for the diagnosis and treatment of CA in 2014¹⁰ and an expert consensus in 2017¹¹ recommended that pregnant women with CA should be treated as early as possible. Podophyllotoxin and imiquimod were not recommended.¹³ Podophyllotoxin and imiquimod were prohibited during pregnancy because their fetal ter-

atogenic effect was grade C for pregnancy medication classified by FDA.¹²⁶ However, a cohort study¹²⁷ showed that there was no statistical relationship between podophyllotoxin exposure and nonexposure groups in birth defects, spontaneous abortion, preterm delivery, and stillbirth. The study concluded that the use of podophyllotoxin during pregnancy (the dose of podophyllotoxin was not specified in this cohort study, and exposure was based on the prescription of the drug) did not increase the risk of adverse fetal outcomes. However, sufficient evidence from RCT trials on podophyllotoxin use in pregnant women are needed. Similarly, although medical reports^{128–131} indicated that the use of imiquimod during pregnancy did not show adverse fetal outcomes, there was still a lack of large-scale human trials, so it was not recommended as a first-line drug for pregnant women.¹³² A comparative study¹³³ showed that by combination therapy of CO₂ laser and 85% trichloroacetic acid in treating 32 pregnant women with genital condylomas, 96.88% patients (31/32) achieved successful eradication with only maternal postoperative complications being pyelonephritis (1/32, 3.13%). The differences in obstetric complications such as premature rupture of membranes, premature onset of labor, and cesarean delivery between the case group ($n = 32$) and control group ($n = 64$) were not significant.

A retrospective study¹³⁴ showed that liquid nitrogen cryotherapy combined with proanthocyanidins dressings (2–3 times a day for 1 week, 20 min for each dressing) cleared all visible CA in 46 pregnant women, with the recurrence rates of 2.17% in 1 month and 10.87% in 3 months.

The existence of warts rarely changed the mode of production, and cesarean section could be performed only when warts block the birth canal. The only serious complication of transvaginal delivery was respiratory papillomatosis in infants and young children, which was relatively rare (4/million).¹³⁵

A report¹³⁶ applied hyperthermia at 44°C for 30 min a day, 3 days in a row, and 2 sessions of treatment after a week. CA in two cases of pregnant women had been cleared 4 and 5 weeks after the last treatment, respectively. No apparent side effects were reported except slight burning pain. There was no recurrence during the 6-month follow-up.

4 | DISCUSSION

4.1 | Summary

This guideline covers several main types of cutaneous and mucosal HPV infectious diseases including common warts, flat warts, plantar warts, genital warts, and EV. Treatment for the special population such as children and pregnant women was also involved. Some clinical questions have been redefined and explained. The guideline aims to systematically and effectively guide the clinical management of warts, achieve better clinical outcomes for patients with HPV infectious skin diseases, improve the overall levels of medical services for skin warts, and reduce medical costs and economic burden.

4.2 | Dissemination, implementation, and evaluation

Once the guideline is released, the guideline development team will mainly disseminate and promote the guideline in the following ways: (I) introduce it in relevant academic conferences; (II) organize guideline promotion special sessions in a planned way to ensure that medical practitioners fully understand and correctly apply the guidelines; (III) conduct research in the next 2 years to understand the dissemination of the guidelines and evaluate the impact of the implementation of the guidelines on clinical decision-making and patient outcomes. However, as a rule, the choice of a treatment method is decided on consensus between the practitioner and the patient, as well as practitioners' evaluation of the specificity of a patient. The strength of the recommendation and levels of evidence may offer certain help.

4.3 | Strengths and limitations

The guidelines for HPV infectious skin diseases are formulated by evidence-based methods. The guideline working groups have strictly followed the standards and procedures of evidence-based guidelines formulation required by international organizations, selected specific problems in the clinical practice of HPV infectious diseases, and conducted a systematic search. The evidence body is formed after a systematic search and assessment, and based on patient preferences and values, as well as cost-benefit factors, combined with the practical experience of multidisciplinary clinical experts. A high-quality evidence-based guideline has been formulated with evidence-based medicine support, patient-based, clinical problem-oriented features.

Meanwhile, limitations exist such as low-level evidence support of certain recommendations. Especially for EV, the included literature is mainly case reports so recommendations are formulated restrictively with less representativeness. For responders of the survey, specialists at the Department of Obstetrics and Gynecology were not concluded while they were also clinical practitioners of this guideline. Due to the cross-disciplines nature, treatments of HPV infectious skin diseases have not included HPV vaccines. Only literature in English and Chinese were covered in the guideline and exclusion of literature in other languages may cause bias.

5 | CONCLUSIONS

This guideline covers aspects of the diagnosis and treatment of cutaneous warts such as diagnostic gold standard, transmission routes, laboratory tests, treatment principle, clinical cure criterion, definitions, and treatments of common warts, flat warts, plantar warts, CA, and EV. Recommendations about special populations such as children and pregnant women are listed. It is a comprehensive and systematic evidence-based guideline and we hope this guideline could systematically and effectively guide the clinical practice of cutaneous

warts and improve the overall levels of medical services. We will update this guideline around 2025 according to the requirement of the international guide.

ACKNOWLEDGMENTS

We thank Doc. Yan Wu, Doc. Yiping Zhao and Doc. Dongxin Shi (Department of Dermatology, The First Hospital of China Medical University) for team organization of evidence-based medicine course study and submission material preparation. We appreciated instructions of guideline development by Shouyuan Wu, Qiangqiang Guo, Hui Lan, and Juanjuan Zhang (School of Public Health, Lanzhou University).

CONFLICT OF INTEREST

All members of this guideline working group have signed a conflict of interest declaration form when determining to participate in the guideline work. All authors have confirmed that they have no potential conflicts of interest.

ORCID

Yaolong Chen  <https://orcid.org/0000-0002-7338-4418>

Xing-Hua Gao  <https://orcid.org/0000-0001-8809-8564>

REFERENCES

1. Loo SK, Tang WY. Warts (non-genital). *BMJ Clin Evid*. 2014;2014.
2. Ockenfels HM. Therapeutic management of cutaneous and genital warts. *J Dtsch Dermatol Ges*. 2016;14(9):892-899.
3. Ringin SA. The effectiveness of cutaneous wart resolution with current treatment modalities. *J Cutan Aesthet Surg*. 2020;13(1):24-30.
4. Al-Eitan LN, Alghamdi MA, Tarkhan AH, Al-Qarqaz FA. Genome-wide identification of methylated CpG sites in nongenital cutaneous warts. *BMC Med Genomics*. 2020;13(1):100.
5. Gross GE, Werner RN, Becker JC, et al. S2k guideline: hPV-associated lesions of the external genital region and the anus—anogenital warts and precancerous lesions of the vulva, the penis, and the peri- and intra-anal skin (short version). *J Dtsch Dermatol Ges*. 2018;16(2):242-255.
6. Gilson R, Nugent D, Werner RN, Ballesteros J, Ross J. 2019 IUSTI-Europe guideline for the management of anogenital warts. *J Eur Acad Dermatol Venereol*. 2020;34(8):1644-1653.
7. Sterling JC, Gibbs S, Haque Hussain SS. British association of dermatologists' guidelines for the management of cutaneous warts 2014. *Br J Dermatol*. 2014;171(4):696-712.
8. Lacey CJN, Woodhall SC, Wikstrom A, Ross J. 2012 European guideline for the management of anogenital warts. *J Eur Acad Dermatol Venereol*. 2013;27(3):e263-e270.
9. Chinese society of dermatology and venereology, China dermatologist association, Chinese association of rehabilitation dermatology and venereology. Guideline for the Clinical Management of Anogenital Warts in China (2021). *Chin J Dermatovenereol*. 2021;35(04):359-374.
10. Liu QZ. Guidelines for diagnosis and treatment of condyloma acuminatum (2014). *Chin J Dermatol*. 2014;47(08):598-599.
11. Lu XN, Xu JH. Expert consensus on the treatment of condyloma acuminatum (2017). *J Clin Dermatol*. 2018;47(02):125-127.
12. Xue FX, Liu HT, Liu ZH. Expert consensus on diagnosis and treatment of human papillomavirus infection in female lower genital tract. *Chin J Pract Gynecol Obstetr*. 2015;31(10):894-897.
13. Workowski KA, Bolan GA, Centers for Disease C, et al. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep*. 2015;64(RR-03):1-137.

14. Canfield SE, Dahm P. Rating the quality of evidence and the strength of recommendations using GRADE. *World J Urol*. 2011;29(3):311-317.
15. Shea BJ, Hamel C, Wells GA, et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. *J Clin Epidemiol*. 2009;62(10):1013-1020.
16. Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
17. Whiting PF. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med*. 2011;155(8):529-536.
18. Wells G, editor. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses. Symposium on Systematic Reviews. Beyond the Basics; 2014.
19. Chen YL, Yang KH, Yao L, et al. Progress in GRADE system methodology. *Chin J Evid Based Pediatr*. 2013;8(01):64-65.
20. Chen YL, Yao L, Norris S, et al. Application of GRADE in systematic reviews: necessity, frequently-asked questions and concerns. *Chin J Evid-based Med*. 2013;13(12):1401-1404.
21. Jaeschke R, Guyatt GH, Dellinger P, et al. Use of GRADE grid to reach decisions on clinical practice guidelines when consensus is elusive. *BMJ*. 2008;337:a744.
22. Becker M, Neugebauer EAM, Eikermann M. Partial updating of clinical practice guidelines often makes more sense than full updating: a systematic review on methods and the development of an updating procedure. *J Clin Epidemiol*. 2014;67(1):33-45.
23. Chen YL, Wang XQ, Wu QF, et al. Survey on update condition of clinical practice guidelines in China. *Chin J Evid-based Med*. 2014;14(02):178-183.
24. Steben M, Garland SM. Genital warts. *Best Pract Res Clin Obstet Gynaecol*. 2014;28(7):1063-1073.
25. Sedlacek TV, Cunnane M, Carpiello V. Colposcopy in the diagnosis of penile condyloma. *Am J Obstet Gynecol*. 1986;154(3):494-496.
26. Gross G, Pfister H, Hagedorn M, Gissmann L. Correlation between human papillomavirus (HPV) type and histology of warts. *J Invest Dermatol*. 1982;78(2):160-164.
27. Vyas NS, Pierce Campbell CM, Mathew R, et al. Role of histological findings and pathologic diagnosis for detection of human papillomavirus infection in men. *J Med Virol*. 2015;87(10):1777-1787.
28. Kumar B, Gupta S. The acetowhite test in genital human papillomavirus infection in men: what does it add? *J Eur Acad Dermatol Venereol*. 2001;15(1):27-29.
29. Schultz RE, Skelton HG. Value of acetic acid screening for flat genital condylomata in men. *J Urol*. 1988;139(4):777-779.
30. Liu R, Hou JL, Chen XC, et al. Evaluation of HPV subclinical infection in patients with condyloma acuminatum by acetowhite test. *Chin J Dermatol*. 2008(05):331-332.
31. Milecki T, Michalak M, Milecki J, et al. Polish medical students' knowledge regarding human Papillomavirus's ways of transmission, risk of cancer development and vaccination, and their intention to recommend vaccination. *Vaccines (Basel)*. 2021;9(7):776.
32. Burchell AN, Tellier P-P, Hanley J, Coutlée F, Franco EL. Human papillomavirus infections among couples in new sexual relationships. *Epidemiology*. 2010;21(1):31-37.
33. Zhou BB, Zhang LN, Fan YY, et al. A prospective study on the types of human papillomavirus infection during pregnancy and vertical transmission from mother to child. *Prog Obstet Gynecol*. 2012;21(03):208-210+14.
34. Palma S, Gnambs T, Crevenna R, Jordakieva G. Airborne human papillomavirus (HPV) transmission risk during ablation procedures: a systematic review and meta-analysis. *Environ Res*. 2021;192:110437.
35. Park IU, Introcaso C, Dunne EF. Human papillomavirus and genital warts: a review of the evidence for the 2015 centers for disease control and prevention sexually transmitted diseases treatment guidelines. *Clin Infect Dis*. 2015;61(Suppl 8):S849-S855.
36. Schultz RE, Miller JW, Macdonald GR, et al. Clinical and molecular evaluation of acetowhite genital lesions in men. *J Urol*. 1990;143(5):920-923.
37. Mao Y, Liu JF, Guan CP, et al. Detection of human HPV typing in condyloma acuminatum by different sampling methods. *Chin Prev Med*. 2012;13(04):236.
38. De Koning MNC, Khoe LV, Eekhof JAH, et al. Lesional HPV types of cutaneous warts can be reliably identified by surface swabs. *J Clin Virol*. 2011;52(2):84-87.
39. Anic GM, Messina JL, Stoler MH, et al. Concordance of human papillomavirus types detected on the surface and in the tissue of genital lesions in men. *J Med Virol*. 2013;85(9):1561-1566.
40. Dong H, Shu D, Campbell TM, Frühauf J, Soyer P, Hofmann-Wellenhof R. Dermatoscopy of genital warts. *J Am Acad Dermatol*. 2011;64(5):859-864.
41. Zhang Y, Jiang S, Lin H, Guo X, Zou X. Application of dermoscopy image analysis technique in diagnosing urethral condylomata acuminata. *Anais Brasileiros Dermatol*. 2018;93(1):67-71.
42. Friis S, Kjaer SK, Frisch M, Mellemkjaer L, Olsen JH. Cervical intraepithelial neoplasia, anogenital cancer, and other cancer types in women after hospitalization for condylomata acuminata. *J Infect Dis*. 1997;175(4):743-748.
43. Nordenvall C, Chang ET, Adami H-O, Ye W. Cancer risk among patients with condylomata acuminata. *Int J Cancer*. 2006;119(4):888-893.
44. Mi X. Investigation of cervical high-risk human papillomavirus infection in patients with condyloma acuminatum and research on clinical and subclinical infection treatment of human papillomavirus, PhD, Peking Union Medical College; 2012.
45. Fan SR, Peng YT. 2010 U.S. centers for disease control guidelines for the treatment of human papillomavirus infection. *Chin Gen Pract*. 2011;14(14):1513-1514.
46. Geng JX, Huang HY, Liu JH, et al. Expert consensus on HPV infection and HPV-associated diseases (2017). *J Med Postgra*. 2017;30(12):1238-1241.
47. Guidelines for clinical diagnosis and prevention of Condyloma Acuminatum (1). *Chin J AIDS STD*. 2015;21(02):172-174.
48. Westfechtel L, Werner RN, Dressler C, Gaskins M, Nast A. Adjuvant treatment of anogenital warts with systemic interferon: a systematic review and meta-analysis. *Sex Transm Infect*. 2018;94(1):21-29.
49. Werner RN, Westfechtel L, Dressler C, Nast A. Anogenital warts and other HPV-associated anogenital lesions in the HIV-positive patient: a systematic review and meta-analysis of the efficacy and safety of interventions assessed in controlled clinical trials. *Sex Transm Infect*. 2017;93(8):543-550.
50. Nofal A, Marei A, Ibrahim Al-SM, Nofal E, Nabil M. Intralesional versus intramuscular bivalent human papillomavirus vaccine in the treatment of recalcitrant common warts. *J Am Acad Dermatol*. 2020;82(1):94-100.
51. Redzic N, Benoy I, Vanden Broeck D, Bogers JP. Efficacy of AV2-salicylic acid combination therapy for cutaneous warts: study protocol for a single-center randomized controlled trial. *Contemp Clin Trials Commun*. 2020;17:100534.
52. Park JY, Park BW, Cho EB, Park EJ, Kim KH, Kim KJ. Clinical efficacy of diphenylcyclopropanone immunotherapy as monotherapy for multiple viral warts. *J Cutan Med Surg*. 2018;22(3):285-289.
53. Giuliodori K, Campanati A, Liberati G, et al. Lifelong widespread warts associated with human papillomavirus type 70/85: a new diagnostic entity? *Acta Dermatovenereol Alp Pannonica Adriat*. 2016;25(1):11-13.
54. Beutner K, Friedman-Kien A, Artman N, et al. Patient-applied podofilox for treatment of genital warts. *Lancet*. 1989;1(8642):831-834.
55. Ebrahim HM, Asaad AM, El Desoky F, Morsi HM. Bacillus Calmette-Guerin polysaccharide nucleic acid vs Bacillus Calmette-Guerin

- vaccine in the treatment of warts: a comparative, double-blind, controlled study. *Dermatol Ther*. 2021;34(1):e14549.
56. Snast I, Kaftory R, Lapidoth M, et al. Combined pulsed dye laser and systemic retinoids for the treatment of hypertrophic resistant warts among organ transplant patients. *Lasers Med Sci*. 2020;35(7):1653-1657.
 57. Shi L, Luo M, Zhang F, et al. Photothermal therapy enhanced the effectiveness of imiquimod against refractory cutaneous warts through boosting immune responses. *J Biophotonics*. 2019;12(2):e201800149.
 58. Aziz-Jalali M-H, Ghafarpour G, Rezaei MR, Heshmatzadeh Behzadi A, Rohani Nasab M, Nilforoushzadeh MA. Efficacy of intralesional bleomycin in the treatment of resistant warts. *J Skin Stem Cell*. 2014;1(1).
 59. Kollipara R, Ekhlasi E, Downing C, Guidry J, Lee M, Tying S. Advancements in pharmacotherapy for noncancerous manifestations of HPV. *J Clin Med*. 2015;4(5):832-846.
 60. Singal A, Grover C. Efficacy and safety of intralesional bleomycin in the management of ungual warts. *Skin Appendage Disord*. 2020;6(6):346-350.
 61. Ryu HR, Jeong H-R, Seon-Woo H-S, et al. Efficacy of a bleomycin microneedle patch for the treatment of warts. *Drug Deliv Transl Res*. 2018;8(1):273-280.
 62. Yazdanfar A, Farshchian M, Fereydoonnejad M, et al. Treatment of common warts with an intralesional mixture of 5-fluorouracil, lidocaine, and epinephrine: a prospective placebo-controlled, double-blind randomized trial. *Dermatol Surg*. 2008;34(5):656-659.
 63. Broganelli P, Chiaretta A, Fragnelli B, Bernengo MG. Intralesional cidofovir for the treatment of multiple and recalcitrant cutaneous viral warts. *Dermatol Ther*. 2012;25(5):468-471.
 64. Khaled A, Ben Romdhane S, Kharfi M, et al. Assessment of cryotherapy by liquid nitrogen in the treatment of hand and feet warts. *Tunis Med*. 2009;87(10):690-692.
 65. Abdel Meguid AM, Abdel Motaleb AA, Abdel Sadek AMI. Cryotherapy vs trichloroacetic acid 90% in treatment of common warts. *J Cosmet Dermatol*. 2019;18(2):608-613.
 66. Attwa E, Elawady R, Salah E. 'Cryo-immuno-therapy' is superior to intralesional Candida antigen monotherapy in the treatment of multiple common warts. *J Dermatolog Treat*. 2020;32:1-8.
 67. Muhaidat JM, Al-Qarqaz FA, Alshiyab DM, Alkofahi HS, Khader Y, Ababneh MY. Comparison of the efficacy and safety of two cryotherapy protocols in the treatment of common viral warts: a prospective observational study. *Dermatol Res Pract*. 2020;2020:2309309.
 68. Gao XH, Gao D, Sun XP, et al. Non-ablative controlled local hyperthermia for common warts. *Chin Med J (Engl)*. 2009;122(17):2061-2063.
 69. James WD. *Andrews' Diseases of the Skin: Clinical Dermatology* 10th ed. Saunders Elsevier; 2006.
 70. Li XM, Ding YG, Wei RL, et al. A meta-analysis of the efficacy of 5-aminolevulinic acid-photodynamic therapy for flat warts. *J Clin Dermatol*. 2017;46(05):313-317.
 71. Li Q, Jiao B, Zhou F, et al. Comparative study of photodynamic therapy with 5%, 10% and 20% aminolevulinic acid in the treatment of generalized recalcitrant facial verruca plana: a randomized clinical trial. *J Eur Acad Dermatol Venereol*. 2014;28(12):1821-1826.
 72. Nguyen J, Korta DZ, Chapman LW, Kelly KM. Laser treatment of nongenital verrucae: a systematic review. *JAMA Dermatol*. 2016;152(9):1025-1034.
 73. Alshami MA, Mohana MJ, Alshami AM. Long-pulsed 532-nm neodymium-doped yttrium aluminium garnet laser for treatment of facial plane warts in 160 Yemeni patients. *Dermatol Surg*. 2016;42(11):1273-1278.
 74. Nofal A, Khedr A, Fathy M. Combined oral isotretinoin and Candida antigen versus either agent alone in the treatment of plane warts. *J Dermatolog Treat*. 2020:1-6.
 75. Fawzy MM, Nofal A, Alakad R. Intralesional antigen immunotherapy for the treatment of plane warts: a comparative study. *Dermatol Ther*. 2020;33(6):e13807.
 76. Nassar A, Mostafa M, Khashaba SA. Photodynamic therapy versus candida antigen immunotherapy in plane wart treatment: a comparative controlled study. *Photodiagnosis Photodyn Ther*. 2020;32:101973.
 77. Hodeib AAE, Al-Sharkawy BG, Hegab DS, Talaat RAZ. A comparative study of intralesional injection of *Candida albicans* antigen, bleomycin and 5-fluorouracil for treatment of plane warts. *J Dermatolog Treat*. 2021;32(6):663-668.
 78. Basavarajappa SJ, Subramaniyan R, Dabas R, et al. A comparative study of topical 5% 5-fluorouracil with needling versus 30% trichloroacetic acid with needling in the treatment of plantar warts. *Indian Dermatol Online J*. 2021;12(3):412-416.
 79. Huo W, Gao XH, Sun XP, et al. Local hyperthermia at 44 degrees C for the treatment of plantar warts: a randomized, patient-blinded, placebo-controlled trial. *J Infect Dis*. 2010;201(8):1169-1172.
 80. Abdel-Latif AA, El-Sherbiny AF, Omar AH. Silver duct tape occlusion in treatment of plantar warts in adults: is it effective? *Dermatol Ther*. 2020;33(3):e13342.
 81. Walczuk I, Eertmans F, Rossel B, et al. Efficacy and safety of three cryotherapy devices for wart treatment: a randomized, controlled, investigator-blinded, comparative study. *Dermatol Ther (Heidelb)*. 2018;8(2):203-216.
 82. Alshami MA, Mohana MJ. Novel treatment approach for deep palmo-plantar warts using long-pulsed 1064-nm Nd:YAG laser and a moisturizing cream without prior paring of the wart surface. *Photomed Laser Surg*. 2016;34(10):448-455.
 83. Wu D, Mo B, Huang C. Comparison of the efficacy and safety of five therapeutic Regimens for intractable plantar warts. *Chin J Derm Venereol*. 2014;28(11):1200-1202.
 84. Jin CL. Clinical study on optimization of CO₂ laser therapy for plantar warts. *Chin J Derm Venereol*. 2011;25(03):245-246.
 85. Zhao XM. Assessment of efficacy of pingyangmycin in the treatment of verruca plantaris. *Chin J Lepr Skin Dis*. 2015;31(11):689-690.
 86. Schofer H, Tatti S, Lynde CW, et al. Sinecatechins and imiquimod as proactive sequential therapy of external genital and perianal warts in adults. *Int J STD AIDS*. 2017;28(14):1433-1443.
 87. Feng C, Li W, Wang X, et al. A systematic review evaluating the efficacy and safety of a combination of ablative treatment and self administered treatment versus ablative treatment alone for external anogenital warts. *Int J Dermatol*. 2020;59(10):1210-1216.
 88. Bertolotti A, Ferdynus C, Milpied B, Dupin N, Huiart L, Derancourt C. Local management of anogenital warts in non-immunocompromised adults: a network meta-analysis of randomized controlled trials. *Dermatol Ther (Heidelb)*. 2020;10(2):249-262.
 89. Jung JM, Jung CJ, Lee WJ, et al. Topically applied treatments for external genital warts in nonimmunocompromised patients: a systematic review and network meta-analysis. *Br J Dermatol*. 2020;183(1):24-36.
 90. Barton S, Wakefield V, O'mahony C, Edwards S. Effectiveness of topical and ablative therapies in treatment of anogenital warts: a systematic review and network meta-analysis. *BMJ Open*. 2019;9(10):e027765.
 91. Ni J, Wang D, Wang S. Meta-analysis of randomized controlled trials of podophyllotoxin nanogel in the treatment of condyloma acuminatum. *Int J Clin Exp Med*. 2019;12(11):12647-12657.
 92. Baker DA, Ferris DG, Martens MG, et al. Imiquimod 3.75% cream applied daily to treat anogenital warts: combined results from women in two randomized, placebo-controlled studies. *Infect Dis Obstet Gynecol*. 2011;2011:806105.
 93. Murray ML, Meadows J, Dore CJ, et al. Human papillomavirus infection: protocol for a randomised controlled trial of imiquimod cream (5%) versus podophyllotoxin cream (0.15%), in combination with quadrivalent human papillomavirus or control vaccination in the

- treatment and prevention of recurrence of anogenital warts (HIPvac trial). *BMC Med Res Methodol*. 2018;18(1):125.
94. Rosen T, Nelson A, Ault K. Imiquimod cream 2.5% and 3.75% applied once daily to treat external genital warts in men. *Cutis*. 2015;96(4):277-282.
95. Wu DX, Wu LF, Yu HY. Meta-analysis of 5-aminolevulinic acid photodynamic therapy for preventing recurrence of condyloma acuminatum. *Chin J Lepr Skin Dis*. 2012;28(10):754-756.
96. Ying Z, Li X, Dang H. 5-aminolevulinic acid-based photodynamic therapy for the treatment of condylomata acuminata in Chinese patients: a meta-analysis. *Photodermatol, Photoimmunol Photomed*. 2013;29(3):149-159.
97. Tu P, Zhang H, Zheng H, et al. 5-Aminolevulinic photodynamic therapy versus carbon dioxide laser therapy for small genital warts: a multicenter, randomized, open-label trial. *J Am Acad Dermatol*. 2021;84(3):779-781.
98. Zhang Z, Lu XN, Liang J, et al. Evaluation of photodynamic therapy using topical aminolevulinic acid hydrochloride in the treatment of condylomata acuminata. *Int J Clin Exp Med*. 2015;8(4):6517-6521.
99. Li J, Liu YX, Zheng HY, et al. A clinical observation of aminolevulinic acid photodynamic therapy for condyloma acuminatum. *Chin J AIDS STD*. 2010;16(06):585-586+98.
100. Wu WY, Su ZG, Shi X. Systematic analysis of liquid nitrogen freezing combined with aminolevulinic acid photodynamic therapy in the treatment of condyloma acuminatum. *Chin J Dermatol*. 2014;47(05):361-362.
101. Jiang Y, Shi BJ, Liu JJ, et al. Efficacy of photodynamic therapy plus CO₂ laser combination therapy for patients with condyloma acuminatum: meta-analysis. *Chin J Derm Venereol*. 2012;26(09):815-817+46.
102. Hu S, Yang Y, Jiang B, et al. Treatment of condyloma acuminatum using the combination of laser ablation and ALA-PDT. *Photodiagn Photodyn*. 2019;25:193-196.
103. Liu LH, Wang YF. ALA-PDT combined with microwave in the treatment of condyloma acuminatum has good efficacy and safety. *Genom Appl Biol*. 2018;37(11):4909-4913.
104. Xu Q, Shen LL. 20% 5-aminolevulinic acid photochemotherapy combined with liquid nitrogen frozen therapy in treatment of condyloma acuminatum patients. *Chin J New Drugs Clin Rem*. 2015;34(12):935-939.
105. Shi H, Zhang X, Ma C, et al. Clinical analysis of five methods used to treat condylomata acuminata. *Dermatology*. 2013;227(4):338-345.
106. Long XC, Huang B, Zhou QZ, et al. Comparison of the efficacy of YAG laser and combined 5-aminolevulinic acid photodynamic therapy in the treatment of condyloma acuminatum. *J Clin Dermatol*. 2011;40(02):116-117.
107. Yang G, Yin LP, Mei LH. Clinical observation of 5-aminolevulinic acid photodynamic therapy combined with CO₂ laser in the treatment of condyloma acuminatum. *Chin J Der Venereol*. 2010;24(07):643-644.
108. Zhu LY, Chen B, Xuan X, et al. 222 cases of condyloma acuminatum treated by photodynamic combined electrocautery. *Chin J Dermatol*. 2010(05):366-367.
109. Han LL, Lu SJ. Clinical study of liquid nitrogen frozen combined with α -2b interferon in the treatment of anal condyloma acuminatum. *Chin J Clin Pharmacol*. 2015;31(06):447-449.
110. Ma WY. Efficacy observation of recombinant human interferon α -2b injection in the treatment of condyloma acuminatum in elderly patients. *China Pharm*. 2010;21(38):3610-3611.
111. Huang A, Luo H, Zhang L, et al. Effect of photodynamic therapy on condyloma acuminata combined with HIV for 25 patients. *Chin J Derm Venereol*. 2018;32(06):733-736.
112. Hu RX, Lu SH, Lu C, et al. Clinical analysis of microwave combined with imiquimod for 110 anal condyloma patients with HIV/AIDS. *Chin J Derm Venereol*. 2012;26(11):1010-1011+7.
113. Vela S, Videla S, Ornelas A, et al. Effectiveness of physically ablative and pharmacological treatments for anal condyloma in HIV-infected men. *PLoS One*. 2018;13(8):e0199033.
114. Yoshida R, Kato T, Kawase M, Honda M, Mitsuishi T. Two sisters reveal autosomal recessive inheritance of epidermodysplasia verruciformis: a case report. *BMC Dermatol*. 2014;14:12.
115. Liu ZL, Shi YJ, Liu XG. A case of verrucous epidermal dysplasia treated with isotretinoin combined with tazarotene gel. *Chin J Dermatol*. 2003(04):58.
116. Zhang HY, Zhang Y, Li LX, et al. Epidermodysplasia Verruciformis: a case report and review of literature. *Chin J Derm Venereol*. 2014;28(01):65-66+104.
117. Liu W, Ma D-L. Severe epidermodysplasia Verruciformis. *Mayo Clin Proc*. 2020;95(9):2035.
118. Ye H, Han SX, Wang H, et al. A case of epidermodysplasia verruciformis complicating multiple Bowen disease. *Chin J Derm Venereol*. 2016;30(03):286-288.
119. Plasencia JM. Cutaneous warts: diagnosis and treatment. *Prim Care*. 2000;27(2):423-434.
120. Fields JR, Saikaly SK, Schoch JJ. Intralesional immunotherapy for pediatric warts: a review. *Pediatr Dermatol*. 2020;37(2):265-271.
121. Nofal A, Alakad R. Intralesional immunotherapy for the treatment of anogenital warts in pediatric population. *J Dermatolog Treat*. 2020:1-5.
122. Zhang XN, Su BB. Analysis on the curative effect of 5-aminolevulinic acid-photodynamic therapy combined with high-frequency electrocautery in treatment of condyloma acuminata in children. *Maternal and Child Health Care of China (Chin)*. 2015;30(04):628-629.
123. He CC, Sun YZ, Qi RQ. Successful treatment of perianal warts in children with local hyperthermia: a case report. *Dermatol Ther*. 2020;33(4):e13634.
124. Bruggink SC, Gussekloo J, Egberts PF, et al. Monochloroacetic acid application is an effective alternative to cryotherapy for common and plantar warts in primary care: a randomized controlled trial. *J Invest Dermatol*. 2015;135(5):1261-1267.
125. Liu ZH. Human papillomavirus infection in pregnancy. *Zhongguo Shiyong Fuke Yu Chanke Zazhi*. 2011;27(08):588-591.
126. Patel VM, Schwartz RA, Lambert WC. Topical antiviral and antifungal medications in pregnancy: a review of safety profiles. *J Eur Acad Dermatol Venereol*. 2017;31(9):1440-1446.
127. Andersson NW, Andersen JT. Association between fetal safety outcomes and exposure to local podophyllotoxin during pregnancy. *JAMA Dermatol*. 2020;156(3):303-311.
128. Maw RD. Treatment of external genital warts with 5% imiquimod cream during pregnancy: a case report. *Bjog-Int J Obstet Gy*. 2004;111(12):1475.
129. Einarson A, Costei A, Kalra S, Rouleau M, Koren G. The use of topical 5% imiquimod during pregnancy: a case series. *Reprod Toxicol*. 2006;21(1):1-2.
130. Ciavattini A, Tsiroglou D, Vichi M, Di Giuseppe J, Cecchi S, Tranquilli AL. Topical Imiquimod 5% cream therapy for external anogenital warts in pregnant women: report of four cases and review of the literature. *J Matern-Fetal Neo M*. 2012;25(7):873-876.
131. Audisio T, Roca FC, Piatti C. Topical imiquimod therapy for external anogenital warts in pregnant women. *Int J Gynaecol Obstet*. 2008;100(3):275-276.
132. Workowski KA, Berman SM. Centers for disease control and prevention sexually transmitted diseases treatment guidelines – introduction. *Clin Infect Dis*. 2007;44:S73-S76.
133. Schwartz DB, Greenberg MD, Daoud Y, Reid R. Genital condylomas in pregnancy: use of trichloroacetic acid and laser therapy. *Am J Obstet Gynecol*. 1988;158(6 Pt 1):1407-1416.
134. Yang L-J, Zhu D-N, Dang Y-L, Zhao X. Treatment of condyloma acuminata in pregnant women with cryotherapy combined with proanthocyanidins: outcome and safety. *Exp Ther Med*. 2016;11(6):2391-2394.

135. Lacour DE, Trimble C. Human papillomavirus in infants: transmission, prevalence, and persistence. *J Pediatr Adolesc Gynecol*. 2012;25(2):93-97.
136. Huo W, Di Z-H, Xiao B-H, Qi R-Q, Weiland M, Gao X-H. Clearance of genital warts in pregnant women by mild local hyperthermia: a pilot report. *Dermatologic Therapy*. 2014;27(2):109-112.

How to cite this article: Zhu P, Qi R-Q, Yang Y, et al. Clinical guideline for the diagnosis and treatment of cutaneous warts (2022). *J Evid Based Med*. 2022;15:284-301.
<https://doi.org/10.1111/jebm.12494>

APPENDIX WORKING TEAM

Steering committee: Xinghua Gao (The First Hospital of China Medical University), Yaolong Chen (Evidence-Based Medicine Center, School of Basic Medical Sciences, Lanzhou University), Hongduo Chen (The First Hospital of China Medical University), Wanqing Liao (Shanghai Changzheng Hospital), Qianjin Lu (The Second Xiangya Hospital of Central South University), Jie Zheng (Ruijin Hospital), Jianzhong Zhang (Peking University People's Hospital), Xuejun Zhang (Anhui Medical University), and Jinghe Lang (Peking Union Medical College Hospital).

Consensus expert group: Hao Cheng (Sir Run Run Shaw Hospital), Lingyu Fu (The First Hospital of China Medical University), Xinghua Gao (The First Hospital of China Medical University), Heng Gu (Chinese Academy of Medical Sciences and Peking Union Medical College), Li He (First Affiliated Hospital of Kunming Medical University), Hongzhong Jin (Peking Union Medical College Hospital), Quanzhong Liu (Tianjin Medical University General Hospital), Lin Ma (Beijing Children's Hospital), Ruiqun Qi (The First Hospital of China Medical University), Youlin Qiao (Peking Union Medical College), Yuping Ran (West China Hospital), Zhu Shen (Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital), Ping Song (Guang'anmen Hospital), Gang

Wang (Xijing Hospital), Xiuli Wang (Shanghai Skin Disease Hospital), Yan Wu (The First Hospital of China Medical University), Shengxiang Xiao (The Second Affiliated Hospital, School of Medicine, Xi'an Jiaotong University), Jinhua Xu (Huashan Hospital), Huilan Yang (General Hospital of Southern Theatre Command of PLA), Rongya Yang (General Hospital of Beijing Military Command of PLA), Furen Zhang (Shandong Provincial Hospital for Skin Diseases & Shandong Provincial Institute of Dermatology and Venereology), Kang Zeng (Nanfang Hospital), Ping Tu (Peking University First Hospital), Yuzhen Li (Second Affiliated Hospital of Harbin Medical University), Xiang Chen (Xiangya Hospital), Aijun Chen (The First Affiliated Hospital of Chongqing Medical University), Junling Zhang (Tianjin Academy of Traditional Chinese Medicine Affiliated Hospital), Shanshan Li (The First Hospital of Jilin University), Zhirong Yao (Xinhua Hospital), Weihua Pan (Second Affiliated Hospital of Naval Medical University), Songmei Geng (The Second Affiliated Hospital of Xi'an Jiaotong University), and Juan Tao (Union Hospital, Tongji Medical College, Huazhong University of Science and Technology).

Secretarial group: Peiyao Zhu, Yang Yang, Xu Han, Yiping Zhao, Dongxin Shi, Yunqiu Gao (The First Hospital of China Medical University), Jianjian Wang, Qiangqiang Guo, Shouyuan Wu, Hui Lan, and Juanjuan Zhang (Evidence-Based Medicine Center, School of Basic Medical Sciences, Lanzhou University).

Evidence evaluation group: Xueli Niu, Yao Lu, Tianxin Cong, Yanjun Li, Congcong He, Xinyun Fan, Ze Wu, Wenzhen Hu, Kangle Fu, Yining Wang, Qu Qi, Donghong Sun, Xiaoxue Yang, Jiali Yin, Yifei Liu, Yiping Zhao, Gaiyang Xu, Mingsui Tang, Chang Fu, Jingyi Li, Weibao Lu, Qixin Han, Shuzhen Ren, Dongxin Shi, Sitong Liu, Meihui Shi, Weitong Yan, Peihong Sun, Jing Zeng, Chengfei Zhuang, Jingyu Wang, Peiyao Zhu, and Xu Han (The First Hospital of China Medical University).

External review group: Xing-Hua Gao, Rui-Qun Qi, Yang Yang and Peiyao Zhu (The First Hospital of China Medical University), Yaolong Chen, Jianjian Wang, Shouyuan Wu, Qiangqiang Guo, Hui Lan, and Juanjuan Zhang (Evidence-Based Medicine Center, School of Basic Medical Sciences, Lanzhou University).