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GUIDELINES

2020 European guideline on the management of genital molluscum contagiosum

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Abstract

Molluscum contagiosum is a benign viral epidermal infection associated with high risk of transmission. The guideline is focused on the sexually transmitted molluscum contagiosum. The diagnosis is clinical with characteristic individual lesions, termed 'mollusca', seen as dome-shaped, smooth-surfaced, pearly, firm, skin-coloured, pink, yellow or white papules, 2 - 5 mm in diameter with central umbilication. Dermoscopy may facilitate diagnosis. Therapeutic options are numerous, including physical treatments (cautery, curettage and cryotherapy), topical chemical treatments (e.g. podophyllotoxin and imiquimod) or waiting for spontaneous resolution in immunocompetent patients. In pregnancy, it is safe to use physical procedures (e.g. cryotherapy). Immunosuppressed patients develop severe and recalcitrant molluscum lesions that may require treatment with cidofovir, imiquimod or interferon. Patients with molluscum contagiosum infection should be offered to be screened for other sexually transmitted infections.

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Introduction and methodology

Molluscum contagiosum is a benign viral epidermal infection associated with high risk of transmission and with an increasing frequency in worldwide populations.[1–3]

This guideline is focused on the genital, sexually transmitted molluscum contagiosum affecting adolescents (from 16 years of age) and adults.

The main objectives include providing clinicians with evidence-based recommendations on diagnosis and treatment as well as prevention strategies against reinfection and onward transmission.

All authors had equally contributed.

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This guideline was developed by reviewing the existing data including the British Association for Sexual Health and HIV (BASHH) guideline (2014)[4] as well as the Centers for Disease Control and Prevention (CDC) recommendations (2015).[5] A comprehensive literature search of publications dating from 1980 to January 2019 was conducted (Appendix 1. Search strategy). Grading of evidence is in compliance with the "European sexually transmitted infection (STI) guidelines: protocol for production and revision April 2020", page 5: "6. Levels of evidence and grading of recommendations: modified GRADE system" (Appendix 2. Grading of evidence). It fulfilled the International Union Against Sexually Transmitted Infections (IUSTI) and the European Dermatology Forum (EDF) standard operating procedures and is supported by the Dermato-venereological Branch of the European Union of Medical Specialists (UEMS). Comments by dermato-venereologist and members of the European Academy of Dermatology and Venereology (EADV), IUSTI and EDF were received, discussed and consensus-agreed.

The guideline was developed in accordance with the agreed IUSTI methodology (https://iusti.org/wp-content/uploads/2020/04/ProtocolForProduction2020.pdf).

Aetiology and Transmission

Aetiology

The lesions of molluscum contagiosum are a benign skin eruption caused by infection with a large DNA virus of the Poxviridae family, Molluscipox genus.[6]

The molluscum contagiosum virus (MCV) has two main subtypes (types 1 and 2) which account for virtually all lesions, although genotypic analysis has also identified other rarer subtypes.[7,8] Type 1 is the most prevalent with variable distribution between different geographical areas.[9–12] Two main clinical presentations are seen: (i) lesions on the face, neck, trunk and arms, seen predominantly in children, and (ii) on the genitals, pubic region, lower abdomen, upper thighs and/or buttocks which appear to be often sexually transmitted and tend to be seen in young adults.[13]

The appearance of the lesions does not vary between subtypes, and individual infections are usually caused by a single subtype (although dual infections have been reported in persons living with HIV (PLWH)[14]). There is no significant difference in the anatomical distribution of subtypes 1 and 2; however, MCV subtype 2 is slightly more common in genital lesions[11,12,15] and also in immunosuppression and HIV infection[10,12,14] where the skin disease can be more severe. Subclinical infection appears common, but the appearance of antibodies in blood seroconversion does not always occur even in symptomatic infections.[16]

Transmission

Transmission is generally caused by direct physical contact, and most evidence is derived from cohort studies in children,[17] but it has also been reported in some contact sports.[18,19] Increased transmission has been reported for swimming and co-bathing, and also fomite spread via the sharing of towels/sponges,[20] with case reports of congenital transmission.[21] In the context of adults, direct skin-to-skin contact during sexual intercourse is the commonest mode of transmission.[1,2]

Clinical findings

Sexually transmitted molluscum contagiosum usually involves the anogenital area including the external genital organs, the inguinal folds, inner thighs or the suprapubic region.[22] Less frequently involved sites are the areola and nipple,[23–27] cervix,[28,29] oral mucosa,[30–34] palms and plantar surfaces of the foot.[35,36]

Incubation typically lasts 2 to 7 weeks but may be as long as 6 months [37].

Characteristic individual lesions, termed 'mollusca',[5] are dome-shaped, smooth-surfaced, pearly, firm, skin-coloured, pink, yellow or white papules, 2–5 mm in diameter with central umbilication.[38] Mechanical evacuation of the mollusca reveals a cheesy material containing degenerated keratinocytes and viral particles.[39]

Dermoscopy may facilitate diagnosis by revealing a central polylobular white-yellow structureless area, surrounded by vessels in a crown pattern.[40,41]

The number of lesions usually varies between 1 and 30 in immunocompetent adults.[42] Lesions may appear grouped as in agminated forms[43] or with linear patterns associated with the isomorphic phenomenon (pseudo-Koebner phenomenon).[44]

Molluscum contagiosum is usually asymptomatic. Local pruritus or discomfort may occur in some cases, increasing the risk of auto-inoculation of other skin sites.[45]

Atypical presentations may include giant,[46] cystic,[47] ulcerated,[48] follicular,[49,50] condyloma acuminatum-like, sebaceous naevus-like,[51] pyogenic granuloma-like,[52] pseudolymphomatous [53], cellulitis or abscess-like lesions.[54,55]

An eczema type reaction, entitled molluscum dermatitis, consisting of erythema, scales and inflamed lesions may appear secondary to a local immune response, and this leads to clinical resolution.[56] In contrast, the appearance of molluscum contagiosum in the setting of atopic dermatitis (eczema molluscatum) may represent a clinical challenge, producing disseminated, inflammatory lesions, covered by scales or haemorrhagic crusts and associated with pruritus.[57,58]

Immunosuppressed patients tend to develop extensive, confluent, giant,[46,59] multiple and/or disseminated[60] lesions. The main causes of immunosuppression associated with molluscum contagiosum include HIV infection,[61] solid organ transplants,[62] immunosuppressive therapy including biologic therapy,[63,64] systemic lupus erythematosus[65] sarcoidosis[66,67] and neoplasia.[68] Giant nodules of molluscum contagiosum have been described as a first clinical manifestation of HIV infection,[69] during the immune reconstitution inflammatory syndrome following initiation of combined antiretroviral therapy in **PLWH**[70] or in the late stages of AIDS.[71]

Other complications of molluscum contagiosum include bacterial superinfection,[72] cellulitis,[54] or chronic conjunctivitis and keratitis in the case of ocular involvement.[73,74]

Congenital molluscum contagiosum via vertical transmission consisting of eyelid or scalp lesions has also been reported.[21,75]

Molluscum contagiosum is a self-limiting disease, the duration ranging from 6 months and 5 years.[76] Persistent infection is usually associated with an immunosuppressed state.[77]

Diagnosis

Clinical

Multiple skin-coloured, sometimes whitish, sometimes umbilicated, non-confluent papules of 2 – 5 mm in size are the diagnostic hallmark. Lesions can develop on all body areas as well as palmar and plantar skin. The distribution is quite variable, and they are often grouped in clusters or distributed linearly because of self-inoculation by microtrauma or scratching. Most of the patients are children between 3 and 10 years of age, and in

adults, they are often restricted to the genital region although they do not always result from sexual transmission. In younger patients, a history or mild lesions of atopic dermatitis are frequently seen and lesions preferentially develop on eczematous skin and may lead to a diagnosis of eczema molluscatum. Single lesions of giant molluscum contagiosum may develop in the inguinal folds or perianal region and can be misdiagnosed as fibroma molle.

Immunodeficiency diseases are risk factors for molluscum contagiosum.

The diagnosis of molluscum contagiosum is usually made on clinical grounds, but dermoscopy and in vivo confocal microscopy may be very useful to aid diagnosis and exclude the differential diagnosis of other types of skin lesion in clinically difficult cases, including cases with inflammation or perilesional inflammation and small lesions. Dermoscopy is more sensitive than visual inspection to highlight the presence of orifices, vessels and specific vascular (crown, radial, flower and punctiform) patterns.[41]

In vivo, confocal microscopy shows a round, well-circumscribed lesion with central round cystic areas filled with brightly refractile material that correlates with the characteristic molluscum bodies seen on histopathological analysis.[78]

Laboratory

Laboratory diagnosis of molluscum contagiosum is not required routinely, as the diagnosis can usually be made on clinical and dermoscopic grounds.

Unclear cases may be confirmed by histological examination, polymerase chain reaction or electron microscopy. Histological examination of molluscum lesions shows a characteristic pattern, which has been described as 'nuts in a sack'. Electron microscopy will reveal the typical brick-shaped virus particles of molluscum contagiosum virus.

Histopathology

Haematoxylin and eosin staining of a molluscum contagiosum lesion typically reveals a crateriform, hyperplastic epidermis or endophytic infundibular hyperplasia that produces a circumscribed cup-shaped pseudotumor containing large cells with granular, eosinophilic, intracytoplasmic molluscum bodies (also known as inclusion bodies or Henderson–Paterson bodies).[79] Inclusion bodies are large, measure up to 35 microns in diameter and are made by millions of virions that compress the keratinocyte nuclei.[80] They progressively enlarge and become basophilic before being disseminated throughout the skin surface.[80] Unusual histological patterns include pseudocystic, giant and pedunculated variants. Disseminated, confluent or atypical, giant lesions may be a sign of immunosuppression, especially HIV infection.[81]

Special stains for inclusion bodies such as Lendrum's phloxine tartrazine reaction or toluidine blue/Giemsa stains are rarely performed because viral inclusions are easily recognizable on routine staining. Special stains have some utility when folliculitis and abscesses following follicular rupture or an intense infiltrate obscure the bodies.[79] Sometimes, a dense dermal lymphocytic infiltrate with CD30-positive cells may mimic anaplastic large cell lymphoma or lymphomatoid papulosis.[64] Molluscum bodies can also be identified by immunohistochemistry on paraffin-embedded, formalin-fixed material,[82] and a cross-reactivity of molluscum bodies with Melan A, a melanocytic marker, has been recently reported.[83]

Immunohistochemical studies, however, are used only for clinico-pathological research and never for diagnostic purposes. Perilesional fibro-oedematous to fibromyxoid stroma and rarely amyloid-like change or anetoderma or metaplastic ossification may occur.[84,85] Follicular induction in the adjacent epidermis should not be mistaken for a basal cell carcinoma.[86] Four per cent of cases can be associated with another lesion such as epidermal cyst and melanocytic naevus potentially obscuring the molluscum contagiosum infection changes.[87,88] Coinfection of molluscum contagiosum virus with other infectious agents such as human papillomavirus or Cryptococcus neoformans in the same lesion, especially in immunocompromised patients, can also occur.[89]

Differential diagnosis

Molluscum contagiosum lesions must be differentiated from other conditions occurring in the context of a possible contagious sexual contact.

In non-immunosuppressed patients, skin lesions mimicking molluscum contagiosum can include genital warts (condyloma acuminata), flat warts, lichen planus, lichen nitidus, secondary syphilis condylomata lata, pyogenic granuloma, ectopic sebaceous glands,[90] dermal cyst, vulvar lymphangioma circumscriptum,[91] keratoacanthoma, basal cell carcinoma and amelanotic melanoma.

In immunosuppressed patients, the following opportunistic skin infections can resemble molluscum contagiosum lesions: *Penicillium marneffei* (penicilliosis),[86] *Cryptococcus neoformans* (cryptococcosis),[92] *Coccidioides spp.* (coccidioidomycosis), *Paracoccidioides brasiliensis*,[93] *Aspergillus fumigatus* (aspergillosis)[94] and *Sporothrix schenckii*.[93] Infection with *Histoplasma capsulatum* (disseminated histoplasmosis) can also manifest with skin lesions looking like molluscum contagiosum.[95]

Molluscum contagiosum can develop on an erythematous background, and the lesions can be wrongly diagnosed as herpes simplex, herpes zoster, acute eczema or (true) Gianotti–Crosti syndrome.[96]

Management

Information, explanation and advice for the patient

Patients who are otherwise well should be advised that molluscum contagiosum is a viral infection of the skin that is harmless

and usually resolves spontaneously in 6–12 months.[97] As it is contagious, they should reduce the local spread of infection by avoiding shaving and waxing **the affected area(s)** and scratching the lesions.

Transmission to others is by direct contact and by fomite spread, so individuals should be advised to cover lesions and not to share towels or bedding[20]; however, the protective effect of condom use appears inconsistent,[98] probably because of lesions on the thighs or in the pubic area. Covering lesions should be recommended if swimming.[20]

Therapy

In immunocompetent patients, it is reasonable to not treat molluscum contagiosum and wait for spontaneous resolution[99] (**GRADE 2, A**); however, many patients with sexually transmitted lesions do in fact request treatment. Indications for active therapy include patient preference, extensive involvement, disease persistence, cosmetic reasons, fear of disease spread and scarring, and symptoms/complications, e.g. pruritus, inflammation and secondary infection.

Although active treatment of molluscum contagiosum may reduce the time to clinical clearance, this should be balanced against the discomfort and side-effects of treatment, particularly so on sensitive genital skin. Patients should be advised that new lesions may continue to erupt for some time even after elimination of all visible lesions, thus requiring further intervention.[4] Associated eczema should be treated with emollients and, if necessary, a topical corticosteroid, particularly when itchy, to reduce the risk of molluscum auto-inoculation by scratching (**GRADE 1, C**).

There are limited data on the relative efficacy of different treatments for molluscum contagiosum and choice of which modality, if any, to select depends on multiple factors including the number and site of lesions, treatment availability, efficacy, mode of application, side-effects, cost, patient and physician preference and experience, and the patient's immune status.[1] Possible modes of action of available therapies include destruction of infected epidermal cells, stimulation of an immune response and direct action against the virus.[8]

Physical Treatments Established physical treatments for genital molluscum include cautery, curettage and liquid nitrogen cryotherapy. Cautery is easy and quick to perform and gives immediate results (**GRADE 1, D**).[99] The resultant small burns typically heal within a few days, do not bleed and leave minimal scarring, provided only the raised part of the lesion is cauterized using light cautery. Pain is a relative limiting factor which may be attenuated by prior application of anaesthetic cream (e.g. EMLA cream 5%—AstraZeneca, Sweden). Curettage of molluscum lesions provides an alternative to cautery[100] (**GRADE 1, C**). Curettage[101] may eliminate lesions more definitively than cautery but is more traumatic and painful, and thus less suitable for genital skin (**GRADE 1, C**). Simply squeezing the molluscum lesions with forceps or piercing them with a small sharp article such as a clean cocktail stick may also be effective; however, there are no formal studies.[102]

Cryotherapy is frequently used in sexual health and dermatovenereology clinics to treat genital molluscum[103] (**GRADE 1, C**), but surprisingly there are no published studies in genital disease. Two studies comparing weekly cryotherapy with topical potassium hydroxide in non-genital molluscum reported clearance rates of over 80% after 4–6 weeks with both modalities.[104,105] Other physical therapies reported in non-genital molluscum include pulsed dye and potassium titanyl phosphate lasers,[106–114] photodynamic therapy[115] and local hyperthermia.[116] However, once again, there are no studies in genital molluscum and the techniques generally require expensive and/or specialized equipment and are less practical for genital skin.

Topical chemical and other treatments Podophyllotoxin may be patient-applied to molluscum lesions using a regime similar to that for viral warts, e.g. twice-daily application for three consecutive days with a break for four days, repeated as necessary until clearance[103,117,118] (**GRADE 1, C**). Other topical chemical treatments reported for non-genital molluscum include salicylic, lactic, glycolic and trichloroacetic acids,[119–122] benzoyl peroxide,[123] hydrogen peroxide,[124] iodine,[125] potassium hydroxide,[104,105,126–128] silver nitrate,[129] nitric oxide,[130] cantharidin,[131–137] lemon myrtle oil,[138] tea tree oil,[139] tretinoin[123,140] and adapalene,[141] with varying evidence for efficacy but none specifically in genital infection (**GRADE 2, D**).

Furthermore, many of these preparations are irritant and inappropriate for sensitive genital skin.

Treatments aimed at stimulating an immune response to the molluscum virus include topical diphencyprone,[142] imiquimod cream,[143–145] intralesional or systemic interferon,[146,147] oral cimetidine[148] and intralesional immunotherapy with candida antigen[149]; however, evidence for efficacy is poor (**GRADE 1, C**). It should be noted that the current imiquimod prescribing information specifically states that efficacy was not demonstrated for molluscum contagiosum in children.[150]

A recent comprehensive Cochrane review of interventions for cutaneous non-sexually transmitted molluscum contagiosum[99] determined that it could provide no reliable evidence-based recommendations for the treatment of molluscum contagiosum at present, except for 5% imiquimod (**GRADE 1, B**). It is concluded that, based on moderate-quality evidence from three unpublished studies with a total of over 800 participants, imiquimod is probably no more effective in terms of clinical cure, makes little or no difference in terms of short-term improvement or local side-effects, but appears to induce more application site reactions compared to vehicle.[105]

Interestingly, in a recent series of four patients,[57] treatment of severe atopic eczema with dupilumab resulted in clearance of coexisting recalcitrant molluscum contagiosum (**GRADE 2, D**).

The authors proposed that selective blockade of T-helper 2 immune responses with dupilumab, leading to subsequent 'normalization' of skin immune and barrier function, may also permit effective innate and cell-mediated mechanisms to clear the molluscum infection.

We conclude that there is a need for well-designed, adequately powered studies to determine best practice for patients with genital molluscum contagiosum. Expectant management is appropriate in most cases, but if treatment is required, the authors consider that cryotherapy, cautery after topical anaesthetic and possibly imiquimod applications are recommended for the treatment of molluscum contagiosum (**GRADE 2, D**) (Fig. 1) (Table 1).

Special cases (pregnancy, HIV+, sexual abuse, other)

Pregnancy/breastfeeding The use of imiquimod or podophyllotoxin is not advised in pregnancy or breastfeeding, but destructive methods, e.g. cryotherapy, are safe. It is advisable to counsel pregnant women about the possibility of vertical transmission.[21]

Sexual abuse The presence of genital molluscum in a child may raise the possibility of sexual abuse, but fomite spread[20] and vertical transmission[1] have both been reported. A study of viral subtypes in one study identified only MCV1 in under 15s[15], but both types have been isolated from genital lesions in adults.

Immunosuppression Severe and recalcitrant molluscum have been described with immunosuppression, particularly in **PLWH**,[151,152] but also with other causes of immunosuppression such as biologic agents[153] and immunosuppression for organ transplants.[154] Multiple or giant lesions can cause significant disfigurement in **PLWH**, and spontaneous clearance is unlikely; however, lesions can resolve with antiretroviral therapy,[155]

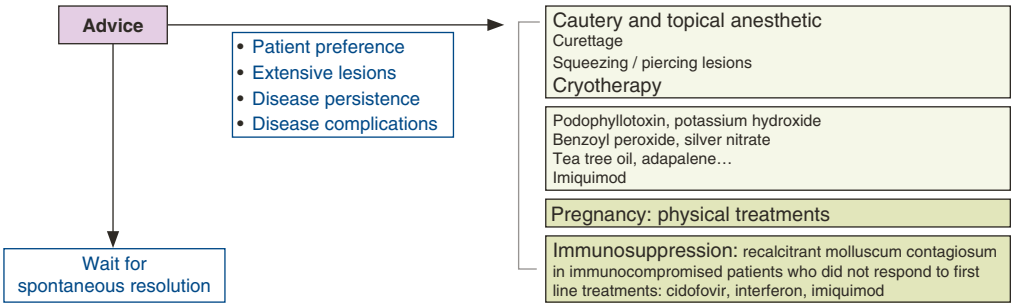

Figure 1 Management of molluscum contagiosum patient.

Table 1 Management of molluscum contagiosum patient—therapeutic recommendations

Recommendation	Symbol	Strength of recommendation
Immunocompetent patients		
We recommend active therapy of genital molluscum contagiosum **in case of** patient preference, extensive involvement, disease persistence, cosmetic reasons, fear of disease spread and scarring, and symptoms/complications	↑↑	Strong recommendation
We recommend no treatment and wait for spontaneous resolution **in other cases**	↑↑	Strong recommendation
Physical Treatments		
Cautery and topical anaesthetic	↑↑	Strong recommendations
Curettage	↑	Weak recommendation
Squeezing/piercing lesions	↑	Weak recommendation
Cryotherapy	↑↑	Strong recommendations
Topical Chemical and Other Treatments		
Podophyllotoxin	↑	Weak recommendation
Potassium hydroxide	↑	Weak recommendations
Benzoyl peroxide, silver nitrate	0	No recommendation
Tea tree oil, adapalene	0	No recommendation
Imiquimod	↑	Weak recommendation
Special cases		
Pregnancy: physical treatments	↑↑	Strong recommendation
Immunosuppression: cidofovir, interferon and imiquimod	↑	Weak recommendation

although inflammatory molluscum lesions have been reported with immune reconstitution.[156] There is a case series reporting the use of topical cidofovir[157] and case reports using intravenous cidofovir,[158] but not specifically for lesions in the genital site. Other treatment modalities which have been reported include imiquimod[159] and interferon[146]; however, there is a lack of evidence to support treatment other than antiretroviral therapy[155] (**GRADE 2, C**).

Reactions to treatment

The destruction of molluscum lesions by physical procedures (cautery, curettage, liquid nitrogen and cryotherapy) induces inflammation of the treated areas, manifested sometimes with pain and oedema.[160] Hair loss and residual hyperpigmentation can occur.[4] In few patients, scars can be observed.[161]

The use of topical chemical treatments (e.g. podophyllotoxin, salicylic, lactic, glycolic and trichloroacetic acids, potassium hydroxide, tretinoin and imiquimod cream) can produce inflammatory side-effects such as burning, pain or pruritus together with small erosions.[162] Postinflammatory dyspigmentation can appear. Cantharidin should be avoided on the genital and perianal regions due to the intense blistering effect.[163] Occasionally, scars can be formed.

Follow-up

Follow-up visits are not usually required.[4] Patients should be informed about the treatment of possible adverse reactions, and a review visit can be scheduled if needed.

Prevention/health promotion

Patients should be made aware of the risk of transmission by sexual contact until completion of treatment and total remission of lesions, since intimate skin-to-skin contact is sufficient for viral transmission.[56,164] Condom use may reduce the risk of transmission, but sufficient data are still lacking in this area.[98]

Patients should also be informed about the possibility of auto-inoculation by scratching or picking their lesions, or of transmission via infected personal items, such as towels, underwear and clothes. Local hygiene, as well as use of disinfectants, may reduce the risk of transmission via fomites.[4] Hair removal of infected areas by shaving or waxing is also considered a risk factor for acquisition or local spread.[165] Bandages used to cover active lesions can be used to reduce the risk of transmission or of auto-inoculation.[5]

The presence of genital molluscum contagiosum requires patients to be offered screening for concomitant sexually transmitted infections.[4]

Patient leaflets consisting of written information of their disease, risk and routes of transmission, and specific treatment regimens should be offered to all patients.

Partner notification

Formal partner notification for genital molluscum contagiosum is not required unless concomitant sexually transmitted infections are diagnosed.[4] However, sexual partners need to be offered appropriate advice about the infection and reassurance yy.[166].

Epidemiological treatment is not required.

Auditable outcomes

- Patients should be offered screening for concomitant sexually transmitted infections: target 95%.
- Treatment based on recommended regimens: selected case.
- Written information offered to patients: target 95%.

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Composition of editorial board

https://iusti.org/wp-content/uploads/2019/12/Editorial_Board.pdf

List of contributing organizations

https://www.iusti.org/regions/Europe/euroguidelines.htm

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Appendix 1.

Search strategy

Publications in English language were searched in the electronic *Resources for Literature Search* for the period 1950 to 2020. Specific keywords combinations were used, and the results were considered of potential interest by reading the titles and abstracts. Those papers were obtained in full text, and the relevant ones were taken into consideration. Priority was given to randomized controlled trial and systematic review evidence. The recommendations were made and graded on the basis of the best available evidence. When the literature search was giving no data, the recommendations were based on the authors' informal consensus. Comments and suggestions arrived during the consultation stage (see https://iusti.org/wp-content/uploads/2020/04/ProtocolForProduction2020.pdf) were analysed by the authors.

Resources for literature search

- PubMed (https://pubmed.ncbi.nlm.nih.gov/)
- Biomedical Reference Collection (via EBSCOhost – https://www.ebsco.com/products/research-databases)
- MEDLINE (via EBSCOhost – https://www.ebsco.com/products/research-databases)

Keywords

Molluscum contagiosum
Combined with AND search
Genital
Sexually transmitted infection
Clinical trial
Dermoscopy
Atypical
HIV
Immunosuppression
Pregnancy
Congenital
Eczema molluscatum
Complications
Epidemiology
Prevention
Partner notification
Epidemiological treatment

Appendix 2.

Grading of evidence

For details regarding the grading of recommendations see "European sexually transmitted infection (STI) guidelines: protocol for production and revision April 2020", page 5: "6. Levels of evidence and grading of recommendations: modified GRADE system":

https://iusti.org/wp-content/uploads/2020/04/ProtocolForProduction2020.pdf