Molluscum contagiosum - IUSTI Guideline

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1. Introduction and methodology

Molluscum contagiosum is a benign viral epidermal infection associated with high risk of transmission and with an increasing frequency in worldwide population [1-3].
This guideline is focused on the genital, sexually transmitted molluscum contagiosum and targets adolescents (from 16 years of age) and adults.
The main objectives include providing clinicians with evidence-based recommendations on diagnosis, treatment of selected cases as well as prevention strategies against reinfection and onward transmission.
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). 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, members of the European Academy of Dermatology and Venereology (EADV), IUSTI, EDF were received, discussed and agreed upon.

2. Aetiology and Transmission

2.1. Aetiology

The lesions of molluscum contagiosum are a benign skin eruption caused by skin 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 in lesions with the actual distribution varying between different geographical series [9-12]. Two main clinical presentations are seen: lesions on the face, neck, trunk and arms, seen predominantly in children, and 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 HIV infection [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 seroconversion does not always occur even in symptomatic infections[16]

2.2. Transmission

Transmission is generally caused by direct physical contact, and most of the 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 with the

sharing of towels / sponges [20], with case reports of congenital transmission [21]. In the context of adults, direct contact during sexual intercourse is the commonest mode of transmission [1,2].

3. Clinical findings

Sexually transmitted molluscum contagiosum usually involves the ano-genital areas including the external genital organs, the inguinal folds, inner thighs or the prepubic region [22]. Less frequently involved sites are represented by the areola and nipple [23-27], cervix [28,29], oral mucosa [30-34] palms and plants [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 content 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 in case of an isomorphic phenomenon (pseudo-Koebner phenomenon) [44].
Molluscum contagiosum is usually asymptomatic. Local pruritus or discomfort may be associated in some cases, increasing the risk of auto-inoculation [45].
Atypical presentations may include: giant [46], cystic [47], ulcerated [48], follicular [49,50], condyloma acuminatum-like, sebaceous nevus-like [51], pyogenic granuloma-like [52], pseudolymphomatous [53], cellulitis or abscess-like [54,55].
An eczema type reaction, entitled molluscum dermatitis, consisting of erythema, scales as well as inflamed lesions of molluscum contagiosum may appear secondary to a local immune response which leads to clinical resolution [56]. In contrast, the appearance of molluscum contagiosum in the setting of atopic dermatitis is presented as eczema molluscatum and may represent a clinical challenge, as disseminated, inflammatory lesions, covered by scales or hemorrhagic crusts and associated with pruritus [57,58].
Immunosuppressed patients tend to develop extensive, confluent, giant [46,59], multiple, disseminated [60] lesions. 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 [69], during the immune reconstitution inflammatory syndrome following initiation of combined antiretroviral therapy in HIV patients [70] or in late stages of AIDS [71].
Other complications of molluscum contagiosum include bacterial superinfection [72], cellulitis [54] or chronic conjunctivitis and keratitis in 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].

4. Diagnosis

4.1. Clinical

Multiple skin-colored, sometimes whitish, sometimes umbilicated, non-confluent papules of 2 – 5 mm in size are the diagnostic hallmark. Lesions can develop on all body areas beside 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 follow a 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 done on clinical grounds but dermoscopy and in vivo confocal microscopy may be very useful to aid diagnosis and differential diagnosis with 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 histopathologic analysis [78].

4.2. Laboratory

Laboratory diagnosis of molluscum contagiosum is not a routine procedure, 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.

5 Histopathology

Hematoxylin and eosin staining of a molluscum contagiosum lesion typically reveals 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 eliminated throughout the skin surface[80]. Unusual histologic 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 obscures 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 signaled [83]. Immunohistochemical studies, however, are used only for clinico-pathological research and never for diagnostic purposes. Perilesional fibroedematous 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 [91]. Four per cent of cases can be associated with another lesion such as epidermal cyst and melanocytic nevus potentially obscuring the molluscum contagiosum infection changes [86, 87]. Coinfection of molluscum contagiosum virus with other infectious agents such as human papilloma virus or Cryptococcus neoformans in the same lesion, especially in immunocompromised patients, should not be ignored [88].

6. 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 [89], dermal cyst, vulvar lymphangioma circumscriptum [90], keratoacanthoma, basal cell carcinoma, amelanotic melanoma.
In immunosuppressed patients the following opportunistic skin infections can resemble molluscum contagiosum lesions: Penicillium marneffei (penicilliosis) [91], Cryptococcus neoformans (cryptococcosis) [92], Coccidioides spp. (coccidiodomycosis), Paracoccidioides brasiliensis [93], Aspergillus fumigatus (aspergillosis) [94] Sporothrix schenckii [93]. Infection with Histoplasma capsulatum (diseminated histoplasmosis) can also manifest with skin lesions looking like molluscum contagiosum [95].
Molluscum contagiosum can develop on erythematous back-ground and the lesions can be wrongly diagnosed as herpes simplex, herpes zoster, acute eczema or (true) Gianotti-Crosti syndrome [96].

7. Management

7.1. 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, and be advised not to squeeze lesions, as the central core contains high levels of virus particles [98]. 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 [99], probably because of lesions on the thighs or in the pubic area. Covering lesions should be recommended if swimming [20].

7.2 Therapy

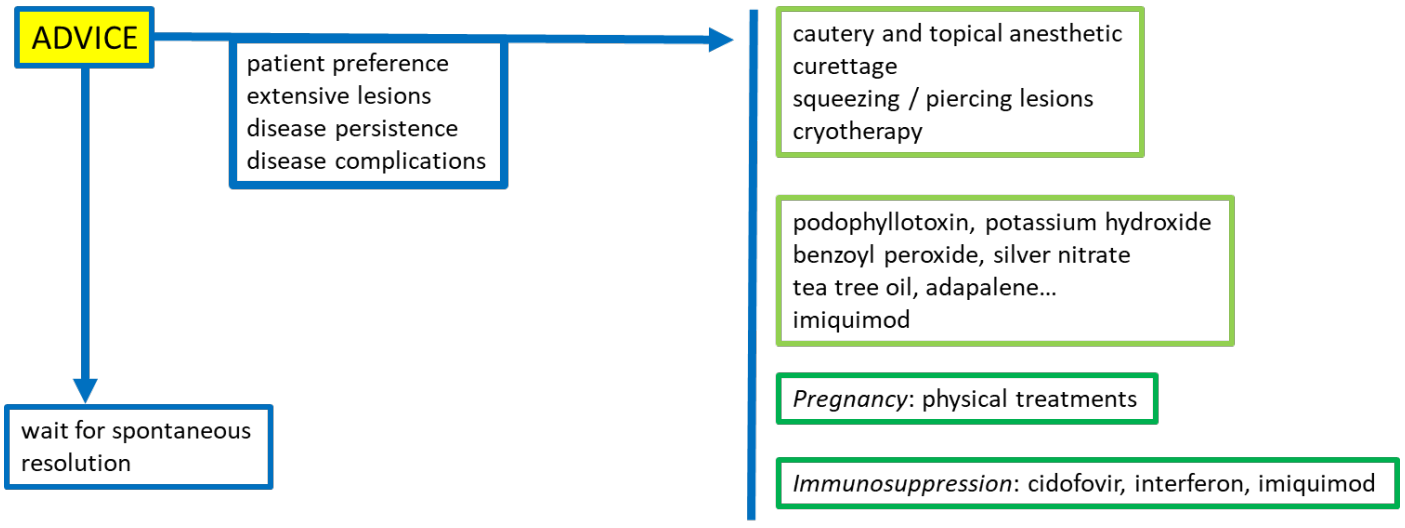
In immunocompetent patients it is reasonable to not treat molluscum contagiosum and wait for spontaneous resolution (100) **(GRADE 2, A)**, however many patients with sexually transmitted disease do in fact request treatment. Indications for active therapy include: patient preference, extensive involvement, 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 autoinoculation by scratching **(GRADE 1, C)**.

There is limited data on the relative efficacy of different treatments for molluscum contagiosum and choice of which modality, if at all, 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).

Figure 1. Management of patient with Molluscum contagiosum



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. 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 cauterised using light cautery. Pain is a relative limiting factor which may be attenuated by prior application of anesthetic cream (e.g. EMLA cream 5% - AstraZeneca, Sweden), as also reported for curettage of molluscum lesions (101) **(GRADE 1, C)**. Curettage (102) 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 **(GRADE 1, C)** however there are no formal studies (103).

Cryotherapy is frequently used in Sexual Health and Dermato-Venereology clinics to treat genital molluscum (104) **(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 (105,106). Other physical therapies reported in non-genital molluscum include pulsed dye and potassium titanyl phosphate lasers (107-115), photodynamic therapy (116) and local hyperthermia (117). However, once again, there are no studies in genital molluscum and the techniques generally require expensive and/or specialised 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 (104,118,119) **(GRADE 1, C)**. Other topical chemical treatments reported for non-genital molluscum include salicylic, lactic, glycolic and trichloroacetic acids (120-123), benzoyl peroxide (124), hydrogen peroxide (125), iodine (126), potassium hydroxide (105,106, 127-129), silver nitrate (130), nitric oxide (131), cantharidin (132-138, lemon myrtle oil (139), tea tree oil (140), tretinoin (124,141) and adapalene (142), 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 (143), imiquimod cream (144,145, 146), intralesional or systemic interferon (147,148), oral cimetidine (149) and intralesional immunotherapy with candida antigen (150), 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 (151).

A recent comprehensive Cochrane review of interventions for cutaneous non-sexually transmitted molluscum contagiosum (100) 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 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 (106).

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 ‘normalisation’ 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 anesthetic and possibly imiquimod applications are recommended for the treatment of molluscum contagiosum (Figure 1).

7.3. 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 transmission1 have both been reported. A study of viral subtypes in one study only identified 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 association with HIV disease [152,153], but also with other causes of immunosuppression such as biologic agents [154] and immunosuppression for organ transplants [155]. Multiple or giant lesions can cause significant disfigurement in HIV infection, and spontaneous clearance is unlikely, however lesions can resolve with antiretroviral therapy [156], although inflammatory molluscum lesions have been reported with immune reconstitution [157]. There is a case series for the use of topical cidofovir [158] and case reports using intravenous cidofovir [159], but not specifically in the genital site. Other treatment modalities which have been reported include imiquimod [160], and interferon [147] however there is a lack of evidence to support treatment other than antiretroviral therapy [156].(level IV, c).

8. Reactions to treatment

The destruction of molluscum lesions by physical procedures (cautery, curettage, liquid nitrogen cryotherapy) induces inflammation of the treated areas, manifested sometimes with pain and oedema [161]. Hair loss and residual hyperpigmentation can occur [4]. In few patients scars can be observed [162].
The use of topical chemical treatments (e.g. podophyllotoxin, salicylic, lactic, glycolic and trichloroacetic acids, potassium hydroxide, tretinoin, imiquimod cream) can produce inflammatory side-effects as burning, pain or pruritus together small erosions [163]. Post-inflammatory dyspigmentation can appear. Cantharidin should be avoided on the genital and perianal regions due to the intense blistering effect [164]. Occasionally scars can be formed.

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

10. 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 [56,165]. Condom use may reduce the risk of transmission, but sufficient data are still lacking in this area [99].
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, clothes etc. 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 [166]. 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 offering patients screening of 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.

11. Partner notification

Formal partner notification in case of genital molluscum contagiosum is not required unless concomitant sexually transmitted infections are diagnosed [4]. However, sexual partners may be offered appointments aiming to provide better explanations of this viral infection and reassurance [167]. Epidemiological treatment is not required.

12. Auditable outcomes

-patients should be offered screening for concomitant sexually transmitted infections: target 100%.

-treatment based on recommended regimens: selected case.

-written information offered to patients: target 100%.

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List of contributing organisations at: www.iusti.org/regions/Europe/euroguidelines.htm

Appendices
Appendix 1
Search strategy
Resources
PubMed (http://www.ncbi.nlm.nih.gov/pubmed)
Biomedical Reference Collection (via EBSCO Host - http://web.ebscohost.com/ehost/)
Medline (via EBSCO Host - http://web.ebscohost.com/ehost/)
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
Levels of evidence
Cf: *Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, et al. Going from evidence to recommendations. BMJ. 2008;336(7652):1049-51.*
Declarations of interest