Vulvar conditions in prepubertal and adolescent girls

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- Labial adhesion
- Vulvovaginitis
- Lichen sclerosis
- Acute genital ulcers

Labial adhesions (aka labial fusion, labial agglutination)

Definition

- Labial adhesions can be defined as agglutination of the labia minora in the midline
- It is a common acquired genital finding in pre-pubertal girls
- It is an acquired pathology and not an alteration in the fetal development and is not associated with genital, urinary or digestive anomalies.

Etiology

- Labial adhesions develop after local irritation of non-estrogenized labial skin, with re-epithelization of closely opposed labia minora resulting in midline fusion
- Vulvar irritation can be caused by:
    - Inappropriate perineal hygiene (poor hygiene or too vigorous cleansing technique)
    - Often connected with the excessive use of perfumed baby wipes or using moistened toilet paper
    - Prolonged use of diapers
    - Trauma
    - Vulvitis / vulvovaginitis
    - Dermatologic conditions e.g. lichen sclerosis, eczemas, psoriasis
- Individual factors: scars pigment (most frequent in blond and red hair girls) racial factor (more frequent in black race)

Prevalence

- 3%, peak incidence 6 months to 3 years
- Never present in newborn (estrogenized vulva)
- Few may persist to the time of puberty (in spite of having reached Tanner II of pubertal development)

Presentation

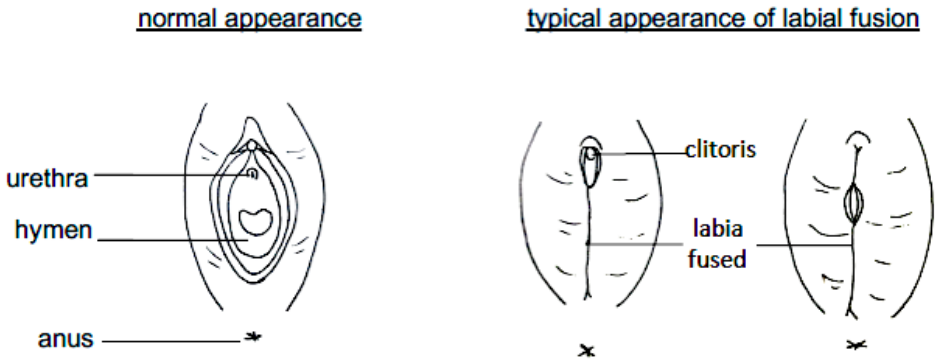
- Asymptomatic labial adhesions (up to 50%)
    - Picked up by caregiver during diaper change or health provider during routine check-up
    - Parents often have concerns regarding possibility of abnormal genitalia
- Symptomatic labial adhesions is more frequent in older patients and can be associated with:
    - Vulvar symptoms:
        - Vulvar irritation: soreness or pain in the genital area
        - Recurrent vaginal discharge

- Urinary symptoms
  - Recurrent urinary tract infection
  - Difficulty with urination
  - Dribbling after voiding or leaking of urine between visits to the toilet
  - Urinary retention (rare)

Diagnosis

- Labial adhesions are diagnosed during physical examination by direct inspection of vulva with Capraro's technique - holding labia between thumb and index fingers as pincers to spread the labia laterally and watch carefully the midline fusion.

- They can be classified based on the varying degree of thickness (from thin and translucent to thick) and degree of extent (from posterior fourchette towards the urethral opening), as
  - Partial labial adhesions
  - Complete labial adhesions (complete adhesions often contain a small pinhole orifice for urine to exit from behind the fused labia)
- More anterior adhesions may occur in older girls with vulvar dermatoses



Differential Diagnosis

- Urogenital sinus
- Vaginal agenesis
- Imperforate hymen

Treatment
Management of labial adhesions is determined by the presence of symptoms

Asymptomatic labial adhesions

- Do not require treatment
- Reassurance and educations of caregivers is the key
- Expected spontaneous resolution without therapy in majority of cases
- Conservative management does not cause adverse clinical outcomes and avoids unnecessary intervention

Symptomatic labial adhesions

- **Topical estrogen or estradiol cream**
  - A small portion of the cream applied twice daily directly to the fusion
    - Gentle, but firm application with fingertip or cotton tipped swab on fusion line (can be accompanied by gentle lateral traction) with several descending movements; the amount is what can be collected from the tube with the swap, being careful not to spread cream on the rest of the vulva to avoid overstimulation
    - Important to show the fusion to the parent and explain the application method
    - The most common reason for medical failure is placement of the cream in the wrong location, placement of too small an amount of cream or too short time of treatment
    - Treatment should be continued until the labial adhesions resolve
  - The mean time to resolution on average is 2 to 6 weeks
    - Resolution with treatment has been reported to be as high as 50%-89% within this time span
  - Recurrence rate is quite high (can reach 55%), and is the highest in asymptomatic patients using diapers
    - Studies reported that over 50% of patients required multiple treatments to obtain resolution
    - One recent RCT showed no statistical difference in complete resolution between use of topical emollient and topical estrogen both with gentle lateral traction.
  - It is important to reassure about safety of treatment and possible rare side effects (caregivers are often worried about systemic effects of estrogen, especially in small children or babies):
    - Irritation and/or redness
    - Can be relieved with hydrocortisone ointment added for few days in the beginning of treatment
    - Vulvar hyperpigmentation, minimal vaginal bleeding and breast bud formation
    - Side effects are reversible and resolve after the cessation of the topical estrogen cream
- **Topical betamethasone 0.05**%
  - Suggested as an alternative or adjunctive topical therapy for labial adhesions
  - The use of betamethasone 0.05% cream twice daily for four to six weeks - efficacy of 68 to 89% reported

- Retrospective study on 0.05% betamethasone vs estrogen cream showed no significant difference
- Care must be taken to avoid prolonged use (greater than three months) to prevent skin atrophy and systemic corticosteroid absorption
- Short-term side effects include erythema, pruritus, and folliculitis, skin atrophy, or fine hair growth.

- **Manual or surgical separation** is traumatic for the children and may cause adhesions to form again; therefore, **FIGIJ recommends very limited use of this practice.**
  - Manual or surgical reparation is rarely indicated and reserved for patients who have complete obstruction of urine flow and for those children in whom estrogen cream cannot be applied for psychosocial reasons or medical treatment has been unsuccessful after an adequate trial
  - May be performed in the office with cooperative patients with topical anesthetic (5 minutes after 5% lidocaine ointment or 30 min after EMLA application) or mild sedation
  - Most often described technique uses a lubricated Q-tip inserted into the opening in the adhesions, which then pulled along the raphe
  - Application of topical estrogen should be implemented to enhance epithelialization and healing for 2 - 4 weeks after manual separation, followed by several months of bland emollient application.
- Evaluation of infection post-labial opening should be considered as clinically indicated
- **Treatment of recurrence** follows the same rules used for treatment of the initial adhesions

Prognosis

- Prognosis is good as most labial adhesions are self-limiting condition
- Spontaneous resolution was reported to occur in 50% of cases within 6 months, 90% of cases within 12 months, and 100% of cases within 18 months
- Patients are expected to outgrow the condition, when endogenous estrogen production commences
- High recurrence rate (7 to 55%) was reported – caregivers should be informed
- Recurrence rate is higher with more severe adhesions, with diaper use, in younger girls, and after recurrent forceful separations

Prevention

- Screening and appropriate treatment of underlying infection reduces risk of recurrence
- Successful treatment should be followed by:
  - Attention to hygiene with daily baths (preferably caregiver should obtain written directions)
  - Application of the bland emollient e.g. A&D Ointment or white petroleum jelly, for 6 to 12 months.
  - Avoidance of trauma, irritation and infection.

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Vulvovaginitis

Definition
Inflammation or irritation of the skin and mucosa of the vulvar and vaginal area, resulting in soreness, itchiness, redness, burning and vaginal discharge

Etiology
75 – 80% cases of vulvovaginitis are non-specific

Contributing factors include:

- Lack of estrogen and barrier (undeveloped labia) in pre-pubertal vulva
- Higher pH
- Poor hygiene
- Exposure to contaminated/dirty water with swimming or bathing
- Urinating style (legs pressed tightly together)
- Obesity
- Foreign body
- Tight-fitting synthetic clothing
- Sexual abuse
- Recurrent respiratory infections
- Parasitic infections such as pinworms (Enterobius)
- Diabetes mellitus

Prevalence

- Most common gynecological referral in pre-pubertal girls
- Peak age: 3-7 years

Presentation

<u>Presentation characteristic of non-specific vulvovaginitis</u>

Symptoms:

- Vaginal discharge may be the only symptom
- Vulvar itchiness and soreness, if reported, usually intermittent or recurrent and of mild or moderate severity (long-standing history)

Signs:

- Non-specific mucoid discharge
- With or without an odor (may be the only sign)
- Minimal or no lesion seen on inspection of the labia and introitus

Presentation characteristic of specific vulvovaginitis

Symptoms:

- Acute onset with pain or soreness, which is often unbearable for a child
- Pinworms typically present with intense nocturnal symptoms

Signs:

- Purulent yellowish-green offensive discharge
- Bleeding or blood-stained discharge is a red-flag sign (may occur in association with foreign body, Shigella or parasitic infections)
- Redness and/or swelling of labia majora and/or minora
- Small erosions and excoriations - may cause dysuria (mistreated as urinary tract infection)

Diagnosis

- Clinical diagnosis based on symptoms and visual signs on examination

Investigations

- Tape test for pinworm
- Vaginal cultures recommended for:
  - Purulent or blood-stained discharge
  - Lack of improvement after implementation of hygienic recommendations

Pathogens causing vulvovaginitis:

- Cultures are often negative or contain non-specific flora or mixed anaerobes, when identified.
- 75-80% vulvovaginitis are non-specific
- The most common pathogens in case of non-specific vulvovaginitis:
  - E. Coli
  - Enterococcus faecalis
  - Proteus mirabilis
- The most common pathogens in case of specific vulvovaginitis:
  - Respiratory flora:
    - Streptococcus pyogenes (group A Streptococcus) – the most common
    - Haemophilus influenzae
    - Staphylococcus aureus
    - Streptococcus pneumoniae
    - Neisseria meningitidis
    - Moraxella catarrhalis

- Enteric flora
  - Shigella
  - Yersinia
- Candida infection:
  - Very rare in toilet-trained prepubertal girls
  - Can occur in children due to recent antibiotic therapy, immunosuppression or diapers.
  - Is frequently wrongly assumed to be the etiology for patients' symptoms
  - Colonization can be present in 3 - 4% of prepubertal patients
- Gardnerella vaginalis
  - Not generally associated with a vaginal discharge in prepubertal girls.
  - Uncommon in sexually inactive girls, but its presence does not indicate sexual exposure
  - A possible relationship with sexual abuse has been disputed.
- Sexually transmitted infections (STIs)
  - Sexual transmission and careful evaluation for potential sexual abuse should be considered
  - Pathogens include: Neisseria gonorrhoeae, Chlamydia trachomatis, Trichomonas vaginalis, Human papillomavirus, Treponema pallidum, and Herpes simplex virus
  - Special considerations for STIs:
  - *Chlamydia trachomatis*: can be transmitted to newborns via exposure to an infected mother's genital flora during vaginal birth and may persist for months to several years
  - *HPV infection* is a sexually transmitted disease, however it does not cause symptoms of vulvovaginitis. The full description of HPV infection is beyond the scope of this Update

Differential diagnosis

- Normal vaginal secretion - *fluor pubertalis*
- Allergy
- Dermatologic skin conditions e.g. lichen sclerosis, psoriasis, eczema
- Trauma
- Abuse
- Vulvodynia
- Pinworms
- Urinary tract infections

Treatment

- Improved vulvar hygiene is the mainstay of treatment
- Perineal hygiene advice preferably provided as a handout (see below for an example of Information for the Caregiver on vulvar/perineal hygiene measures)

Non-specific vulvovaginitis

- Use of barrier cream may be helpful
- No role in antifungal because candidiasis is uncommon

Specific vulvovaginitis

- Oral antibiotics according to vaginal culture results and antibiogram
- If severe symptoms accompany - the symptomatic treatment can be considered, while awaiting culture results:
  - 2% Mupirocin
  - 0.1% Hydrocortisone

Prognosis

- Recurrence is common, especially if measures are not followed
- Caregivers should be informed that vulvovaginitis (except for certain STIs) does not have an adverse effect on reproductive potential of the child

Prevention
Implementation of appropriate hygiene measures is usually sufficient to prevent recurrences and reinfections (see below).

Information for the Caregiver: hygiene measures

1. Toilet hygiene

- Emphasize to wipe front-to-back after each use of toilet, especially after bowel movements.
- Sit on the toilet with knees apart to reduce reflux of urine into the vagina.
- In smaller children use a smaller detachable seat or sit backwards on the toilet (facing the toilet)
- Use white, unscented toilet paper
- Do use not baby wipes or moistened toilet paper
- Children younger than five should be supervised or assisted in toilet hygiene.

2. Body and perineal are hygiene

- It usually suffices to cleanse and rinse the genital area with lukewarm water and gently pat dry
- Bathe a child in clean, warm water for 15 min every day and wash the body just before taking the child out of the tub
- Using hair dryer on the cool setting may be helpful to assist with drying the genital region especially, if irritation is present
- Special hygienic fluids (intimate hygiene gels or soaps) are not recommended for prepubertal girls
- In some countries vinegar baths (a quarter cup per bath) or salt baths are used
- Avoid bubble baths and scented soaps
- Emollients maybe used to protect skin
- In patients with labial adhesion there may the need of special attention to the hygiene, as the remains of urine and cell detritus may accumulate in the pseudo receptacle formed due to the adhesion, and can produce secondary inflammatory processes.

3. Clothes and underwear

- Use of white, cotton underpants is recommended
- Avoid fabric softeners for washing underwear
- Double-rinse underwear after washing to avoid residual irritants.
- Avoid daily use of pantyliners
- Loose fitting wear is recommended, also for sleeping
- Avoid siting in wet swimsuits for longer periods of time after swimming.

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Lichen sclerosis

Definition
Chronic autoimmune inflammatory skin condition with predilection for anogenital area, which if untreated can lead to scarring.

Prevalence

- Two peaks of incidence:
  - Pre-pubertal (10-15%), mean onset 5.4 years;
  - Postmenopausal, mean onset 55.1 years
- Females are more commonly affected comparing to males

Etiology / Pathophysiology

- Uncertain
- Association with autoimmune diseases has been reported (autoimmune thyroiditis, vitiligo, alopecia areata, pernicious anemia, celiac disease)
- Familial cases may suggest genetic predisposition

Presentation
Symptoms

- Vulvar pruritis (itching) as a predominant symptom
- Soreness or burning
- Pain or discomfort in the vulvar area
- External dysuria (up to half)
- Bleeding (a quarter)
- Associated GI symptoms. (secondary constipation)
- Asymptomatic (up to 10%)

Signs:

- Pale and fragile looking skin around vagina and anus (“keyhole”or “figure-of-eight” distribution) often with “cigarette paper” appearance
- White shiny plaques
- Hyperkeratosis
- Hemorrhagic areas within lesions, ecchymoses
- Active of healing fissures in typical areas: anterior to clitoris and in perineal and perianal areas
- Scarring with stenosis of vaginal introitus and resorption of labia minora and clitoral hood

Diagnosis

- Clinical diagnosis based on symptoms and visual signs on examination
- Biopsy not recommended in pediatric population and is reserved for cases if there is
    - A doubt in diagnosis,
    - A suspicion for neoplastic change,
    - Resistance to adequate treatment
    - Atypical extragenital presentations.

Differential diagnosis

- Vulvovaginitis
- Allergy
- Dermatologic skin conditions e.g. psoriasis
- Trauma / abuse
- Vulvodynia
- Pinworms
- UTIs

Treatment

Goals of medical treatment:

- Alleviation of symptoms
- Normalization or improvement in skin texture
- Prevent anatomical changes
- Improve quality of life in long term

Initial treatment:

- Topical corticosteroid therapy
    - Ultrapotent topical corticosteroid (UPTC, e.g. clobetasol propionate 0.05% cream) is recommended as first-line therapy and was found effective for alleviation of symptoms and improvement of signs. The improvement in symptoms usually begins after a one or two-week period of treatment.
    - Less potent topical corticosteroids were also found effective (betamethasone dipropionate 0.05%, mometasone furoate 0.05%, methyloprednisolone aceponate 1%)
    - Ointment formulations of topical corticosteroids are usually preferred as patients sometimes find cream formulations more irritating.
- Topical calcineurin inhibitors (TCIs) can be used as second-line therapy for children with LS, who do not respond to UPTC, as several case reports and case-series have reported the efficiency of TCIs in children. Caregivers should be informed that:
    - This is off-label therapy
    - Tacrolimus ointment and pimecrolimus cream are not indicated for use in children younger than 2 years of age.

- Only tacrolimus 0.03% ointment is indicated for use in children 2 to 15 years of age.

Proposed initial treatment protocol with UPTC:

- UPTC once or twice a day for a month, then every other day for the second month, and twice weekly for the third month

The application and caregivers' education:

- Provision of written instructions for the use of the prescribed therapy.
- Medication should be applied and spread over the affected area
- A small amount of the ointment (approx. 0.25g) should be used
- A caregiver should be shown were to apply the medication before leaving the office
- Provision of written educational materials about lichen sclerosis and discussion about chronicity of the disease
- Caregivers can also be reassured that studies found use of topical steroids safe in this population as non-hair bearing mucous membranes of the prepuberal vulva are relatively resistant to atrophic changes from steroid use.

Side effects and complications of topical corticosteroids:

- Skin irritation from contact sensitization
- Secondary infection
- Telangiectasia
- Skin atrophy

Maintenance therapy:

After initial remission the maintenance therapy is recommended:

- **Medium or low potency topical steroids** (mometasone furoate 0.05%, hydrocortisone acetate 1%) with tapered frequency (one of twice weekly) can be used
- **Topical calcineurin inhibitors (TCIs)** (pimecrolimus, 0.03% tacrolimus) are not first-line therapy for children with lichen sclerosis, however can be used in treatment of disease refractory to UPTC (once or twice daily) or as a maintenance therapy (e.g. on weekends only). Caregivers should be informed about precautions related to *US Boxed Warning*:
  - Continuous long-term use of topical calcineurin inhibitors, including tacrolimus ointment, should be avoided in any age group, and application limited to areas of disease involvement and need to be closely monitored by the health care professional
  - Safety of intermittent use for >1 year has not been established.

Disease monitoring

- Treatment aims to alleviate symptoms and prevent anatomical changes
- The follow-up and maintenance therapy with individualized regimens for children following induction treatment is required to prevent progression or scarring
- First follow-up should be scheduled at 4-6 weeks for review of clinical response

- Subsequent review every 3-6 months thereafter, depending on the use and adherence to maintenance therapy
- Active treatment usually takes two years

Prognosis

- Is not well established in children
- There are studies that suggest that prepubertal lichen sclerosis does not resolve at puberty in some patients hence may result in distortion of vulvar architecture therefore, long term follow-up is advisable in affected children and adolescents
- No studies revealed the incidence of progression to squamous cell carcinoma in children (versus up to 5% reported in adults in old series)

Prevention
Proper genital hygiene with daily baths may be helpful in controlling symptoms and signs, including

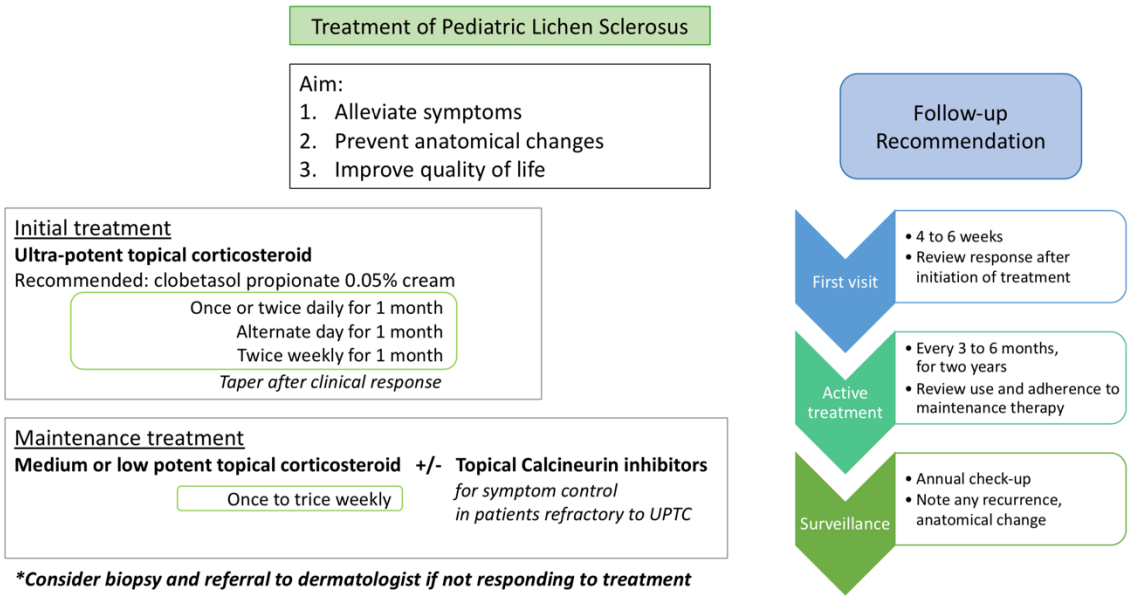
avoidance of:

- Soaps, shampoos and bubble baths with chemical irritants
- Baby wipes, scented detergents and dyed toilet paper
- Feminine douches

using:

- Emollients to the vulvar area.
- Fingertips for washing instead of washcloths
- Cotton underwear (not synthetic)
- Loose pants, skirts, dresses (not tight pants)

Algorithm (updated according to latest NASPAG, spell checked)


Treatment of Pediatric Lichen Sclerosus
Aim:
1. Alleviate symptoms
2. Prevent anatomical changes
3. Improve quality of life
Initial treatment
Ultra-potent topical corticosteroid
Recommended: clobetasol propionate 0.05% cream
Once or twice daily for 1 month
Alternate day for 1 month
Twice weekly for 1 month
Taper after clinical response
Maintenance treatment
Medium or low potent topical corticosteroid +/- Topical Calcineurin inhibitors
Once to trice weekly
for symptom control
in patients refractory to UPTC
*Consider biopsy and referral to dermatologist if not responding to treatment
Follow-up Recommendation
First visit
• 4 to 6 weeks
• Review response after initiation of treatment
Active treatment
• Every 3 to 6 months, for two years
• Review use and adherence to maintenance therapy
Surveillance
• Annual check-up
• Note any recurrence, anatomical change

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Acute Genital Ulcers

Definition:

Painful ulcerative lesions, which can be infectious or non-infectious

Etiology and prevalence

Etiology differs based on presence of sexual activity in patients

Etiology in sexually active patients:

- Genital herpes (30%)
- Non-specific (55%)
- Developing countries: chancroid, syphilis

Etiology in pre-pubertal, sexually inactive girls

- Idiopathic aphthosis
  - Vulvar ulcers sometimes called Lipschutz ulcers, "virginal ulcers", or "aphthous ulcers", are typically seen in girls age 10 to 15 years
  - Uncommon gynecological illness in prepubertal girls
  - The etiology often cannot be determined
  - The most commonly diagnosed cause – in one review was estimated as 70%

- Infectious etiology
  - EBV most commonly found in association with AGU in nonsexually active girls
  - Other viral infections associated with AGU: influenza A, mycoplasma, CMV, mumps
  - Bacterial and fungal: Salmonella, Paratyphoid, Streptococcal, Candida
- Autoimmune / inflammatory
- External factors: trauma, medication related

Presentation

- Acute genital ulcers appear as
  - Single or multiple shallow ulcers, often larger than 1 cm (range 0.3-5 cm), with raised sharply demarcated borders, and purulent base
  - There may be presence of overlying gray exudate (pseudomembrane), adherent gray-brown eschar
  - Impressive secondary erythema and edema may be present
- Typically occur at medial aspects of labia minora, perineum, lower vagina

    - Kissing lesions on opposing surfaces are common
- Often accompanied by prodromal flu-like syndromes
- History of oral ulcers can be present (50%)

Differential diagnosis

- Infectious causes: venereal (HSV or non-venereal (viral, EBV, CMV, influenza, mumps, salmonella, paratyphoid, fungal, bacterial)
- Dermatologic: aphthous, dermatitis (including LS), eczema
- Inflammatory: Crohn's, Bechet's, bullous pemphigoid, pyoderma gangrenosum, pemphigus
- Vulgaris MAGIC syndrome (mouth and genital ulcers with inflamed cartilage), insects
- Drug related lesions: Stevens-Johnson syndrome (SJS) / toxic epidermolytic necrosis (TEN), possible NSAIDs
- Traumatic, sexual injuries
- Neoplastic lesions

Diagnosis

General considerations in approach to evaluation

1. A multidisciplinary approach to evaluation and management should be implemented

2. A detailed history and physical examination (including detailed inspection of oral cavity and skin)

3. Complete blood count with differential should be obtained

4. Culture of the lesion for bacteria and HSV PCR to exclude Herpes simplex virus, even in non-sexually active girls

5. Additional tests for infectious agents can be obtained based on the following algorithm:

<u>Diagnostic algorithm for the first episode</u>

- Assess the risk for infectious cause
    - History of exposure or infected close contacts
    - Severity of associated signs and symptoms
- If severe symptoms not present or non-specific → the idiopathic aphthosis is the most probable diagnosis
- If severe symptom present: persistent fever and fatigue, pharyngitis, lymphadenopathy → consider infectious workup:
    - EBV, CMV, influenza

- Mycoplasma
- Viral cultures of the lesion

- Specialist consultations based on results

Diagnostic algorithm for recurrent genital ulcers

- In the presence of history positive for joint (arthritis), gastrointestinal, ocular (uveitis) or dermatologic symptoms the referral to rheumatology, gastroenterology, ophthalmology or dermatology to rule out associated condition
- If no additional symptoms present refer to algorithm for the first episode

6. In sexually active patients:

- Testing for common causes of genital ulcers, such as HSV and syphilis, as well as other STIs (HIV, gonorrhea, chlamydia, trichomonas) should be implemented
- Testing for other STIs can be considered: hepatitis B and hepatitis C
- Testing for lymphogranuloma venereum, chancroid, or granuloma inguinale
  - If the patient had a known exposure to one of these pathogens
  - If there is a high suspicion for infection based on clinical evaluation

7. A biopsy should only be performed, when a specific dermatologic condition is suspected:

- Results of genital biopsy are likely to show nonspecific inflammatory changes and necrosis

Treatment

1. Usually can be managed in the outpatient setting

- Supportive care
  - Sitz bath (simply lukewarm water) may relieve pain and remove adherent necrotic material
  - Whirlpool therapy once daily for 20 minutes: improves debridement and healing of necrotic ulcers
  - Betadine wash can be used as alternative
  - Avoid alcohol-based solution including Chlorhexidine because of wound irritation and pain
- Pain relief with
  - Local anesthetic: topical xylocaine 2% jelly
  - Pain medication: acetaminophen, narcotics (parenteral if needed)
  - NSAIDs should be avoided during an episode, as they may play a role in acute genital ulcer etiology
- Antibiotics
  - If the ulcers are superinfected

- Steroid treatment
    - Oral steroids may be beneficial in case of recurrent acute genital ulcers or no response to topical therapies (controlled studies are lacking).

2. Hospitalization may be necessary for:
    - Acute urinary retention necessitating bladder drainage
    - Severe pain that is not controlled by conservative measures.
3. Treatment of the underlying cause, if possible
    - In sexually active patients empiric treatment can be initiated based on clinical evaluation and high suspicion of specific cause

Prognosis

- Overall favorable, mostly self-limiting, depending on underlying cause
- These ulcers often heal completely in one to three weeks, but may recur.
- Persistent ulcers can be early non-GI manifestation of Crohn's disease
- Recurrent vulvar ulcers, especially if associated with evidence of systemic involvement and vasculitis (oral lesions, uveitis, arthritis) should suggest the possibility of Behçet’s syndrome

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