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Therapeutic Moisturizers in Eczema and Xerosis Management

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Introduction

Eczema is a chronic relapsing dermatitis and, as such, it is imperative to maintain the hydration and barrier function of the skin in these patients with daily moisturizer use. Emollients have long been used to maintain the skin barrier function in patients with eczema (atopic dermatitis). Ceramide and urea-based moisturizers have been shown to be beneficial in reducing transepidermal water loss (TEWL), improving barrier function, and maintaining hydration of the stratum corneum layer of the epidermis; thus, they should be considered a mainstay of treatment in patients with xerosis (dry skin) and eczema.

Overview of Eczema

Eczema is a chronic, pruritic, inflammatory skin disease with wide ranging severity; it is usually the first manifestation of atopic disease. Eczema is a major public health problem worldwide that commonly presents during early infancy and childhood, but can persist or start in adulthood (prevalence in children is 10-20% and 1-3% in adults).[1] Prevalence has increased by two to threefold during the past 30 years in urban areas and industrialized countries, but it remains much lower in rural and less industrialized regions.[2]

- The causes of eczema are not completely understood, but dysfunction of the skin barrier, likely the result of both genetic and environmental factors, and immune dysregulation are important in its pathophysiology.[3]
- Acute eczema presents as erythematous patches, papules, plaques, and excoriations secondary to scratching; there may also be weeping of serous exudate. Chronic lesions have the same characteristics, with the addition of lichenification, fissures, and occasional alopecia.[4]
- Partly due to the ease of accessibility for scratching, infantile eczema predominantly involves extensor surfaces of the arms and legs, face, and trunk. Scaling, exudate, and fissures are also common findings in infants.
- In adults, flexural areas, face and neck, wrists, and the dorsal areas of the hands and feet are the most commonly affected regions.

Treatment Rationale

The major goal of disease management is to reduce the frequency and severity of flares, and prolong periods of remission. Comprehensive long-term management addresses both skin barrier dysfunction and immune dysregulation, but also includes patient and caregiver education, flare prevention through trigger avoidance and hydration, as well as pharmacologic and non-pharmacologic therapies.[3]

- Non-pharmacologic patient-specific strategies include removal of allergens (e.g., foods, pet dander, pollen), identification of trigger factors (e.g., stress, low humidity), and a balanced intake of dietary nutrients.[5]

ALSO IN THIS ISSUE: **Review of Conventional Systemic Therapies for Severe Psoriasis** *(page 4)* & **Review of Management Options for Genital Herpes Infections** *(page 7)*

- Short (5-10 minutes) tepid baths or showers can help to hydrate the skin. A soft towel should be used to pat dry without rubbing, a moisturizer is applied within 3 minutes.
- Particularly during infancy, a higher intake of vitamin A may reduce the incidence of eczema seen in children with a positive family history of atopy. The use of *Lactobacillus* during pregnancy and while nursing may postpone the onset of eczema in infants and children.[5]
- Pharmacologic therapy includes the use of emollients, topical corticosteroids, and topical calcineurin inhibitors.
- For mild eczema, over-the-counter (OTC) emollients and topical corticosteroids, e.g., hydrocortisone 0.5% (low potency) and clobetasone 0.05% (mid potency) are available for self-treatment.
- Physicians can emphasize to patients that the goals of self-treatment are to stop the itch-scratch cycle, maintain skin hydration, and avoid or minimize factors that can trigger or aggravate eczema.
- An ideal moisturizer is one that performs four functions:[6]
  1. repair the skin barrier,
  2. maintain skin integrity and appearance,
  3. reduce transepidermal water loss (TEWL),
  4. restore the lipid barrier's ability to attract, hold, and redistribute water.
- It is appropriate for patients or caregivers to consult a physician if OTC treatments are not providing adequate relief, eczematous lesions appear to be infected, or the patient's sleep is frequently disturbed by pruritus.[5]

Available Therapeutic Moisturizers

Ceramide-based Moisturizers

- Recent biochemical findings indicate that disturbances of epidermal lipid compartment structures (particularly of ceramides) account for the defects in barrier function of atopic dry skin.[7]
- Optimal barrier function requires the presence of sufficient extracellular lipids to form a competent lamellar bilayer system of the stratum corneum.[7]
- Ceramides, which consist of different sub-fractions of lipids, represent one of the major lipid constituents of the extracellular lipids and are functionally important for the stability of the multilamellar bilayer system.
- Studies have revealed that ceramides are reduced in the whole atopic population, but particularly in those individuals in an active phase of the disease.[8]
- A reduction of ceramides has been inversely correlated with TEWL, which can result in chronically dry skin.
- Topical ceramide supplementation controls ceramide deficiency and improves the overall skin condition.[6]
- Their benefits are derived from prophylactic and regular use, which may reduce the need for topical corticosteroids and calcineurin inhibitors, and possibly mitigate the side-effects from these medications.
- OTC ceramide-based moisturizers include Impruv® cream and Cetaphil Restoraderm™ lotion. CeraVe® and TriCeram® are currently available in the U.S. only, however, CeraVe® is due to be launched in Canada soon.

Prescription Ceramide-based Moisturizers

- These consist of a higher percentage (compared to OTC brands) combination of ceramides, cholesterol, and fatty acids that mimic those naturally found in the skin.[9]
- EpiCeram® was approved by Health Canada in September 2009 as a Class 2 medical device for use as a non-steroidal lipid barrier emulsion to manage burning and itching symptoms associated with dry skin conditions, such as eczema.
  - In a study involving 113 children with moderate to severe atopic dermatitis, similar efficacy to a mid-strength topical corticosteroid was demonstrated.[9]
  - This multi-lipid emulsion has a favourable safety profile and does not appear to have substantial restrictions for use, such as treatment duration or patient age.
- Prescription ceramide-dominant formulations include EpiCeram® cream (available in Canada and the U.S.) as well as Atopiclair® and MimyX® (available in the U.S. only).

Urea-based Moisturizers without Hydrocortisone

- Urea-based moisturizers are OTC formulations that are indicated for xerotic skin with or without pruritus.
- Urea works by enhancing the water-binding capacity of the stratum corneum and long-term treatment with urea has been demonstrated to decrease TEWL.[10]
- Application of these moisturizers is recommended shortly after bathing, while the skin is still wet.
- The short-term therapeutic effects of urea-based moisturizers are apparent in patients even after 1 week of daily application in those with dry skin and eczema.[11]
- It has also been shown that long-term urea application reduces the susceptibility to skin irritation from sodium lauryl sulfate, a surfactant commonly used in many soaps, shampoos, detergents, and toothpastes.
- The protective effect (after prolonged application) of urea-containing moisturizers has promising clinical ramifications, such as reduction of contact dermatitis from irritating stimuli.[10]
- Higher concentration urea-based formulations induce more prominent keratolytic (softening/shedding) activity that can increase skin irritation. A lower concentration is generally used on the face and body, whereas a higher concentration may be applied to thickened skin areas (e.g., feet).
- OTC urea-based moisturizers include various strengths of urea: 5% (e.g., Eucerin® cream); 10% (e.g., Uremol® 10 cream or lotion, Eucerin® lotion or cream, Urisec™ cream); 12% (e.g., Uresec™ lotion); 20% (e.g., Uremol® 20 cream); 22% and 40% urea creams.
- Urea 40% cream is a potent keratolytic that is not suitable for use as a regular moisturizer.

Urea-based Moisturizers with Hydrocortisone

- Urea-based moisturizers with hydrocortisone are prescription strength formulations and are effective for xerotic skin with inflammation and mild eczema.[4]
- Topical corticosteroids are effectively used for controlling active skin inflammation in eczema. The lowest effective potency of topical corticosteroids is always preferred for the local treatment of lesions.

- Combining an emollient with a corticosteroid has been shown to be effective. A cohort study found that the addition of 10% urea to a commercially prepared steroid cream gave better results in treating subacute atopic eczema than the steroid cream alone.[12]
- Side-effects from topical steroids are directly related to the potency of the compound and the length of use.
- Potential risks from long-term topical steroid use include fungal infections, impetigo, viral warts, and herpes simplex. As well, discontinuation of topical corticosteroids may lead to a flare of symptoms.
- Low-potency hydrocortisone 1% cream has been found to be quite safe for cutaneous use.
- Prescription-based urea moisturizers containing 10% urea with 1% hydrocortisone are available in lotion or cream preparations (e.g., Uremol® HC).

Diabetic Skin Care Management

- Xerosis of the feet is a common skin condition; incidence increases with age, exposure to dry winter conditions, and physiological changes that alter circulatory supply to the lower extremities (e.g., diabetes).
- People with diabetes have a high incidence of xerosis of the feet, especially on the heels.
- While assessing for predictors of foot lesions in diabetic patients, one study found that 82.1% of this cohort had skin with dryness, cracks, or fissures.[11] An unpublished survey of 105 consecutive patients with diabetes conducted by one of the authors revealed that 75% had clinical manifestations of dry skin.
- Dry skin often leads to cracks and fissures that can act as portals of entry for bacteria. These cracks and fissures are associated with an increased risk of cellulitis and foot ulceration that, if left unchecked, can eventually lead to amputation.
- Xerosis of the feet in diabetic individuals can be controlled with the regimented use of moisturizers.[11]
- Healthcare providers should routinely inspect the feet of diabetic patients and encourage daily moisturization.
- Urea has been found to be a potent skin humidifier (by decreasing TEWL) and descaling agent.
- Studies of diabetic patients revealed that urea is safe and effective in controlling xerosis of the feet and showed longer-lasting effect than other emollient creams.[11]
- Urea cream works as a keratinolytic and helps in the treatment of corns and calluses of the feet.[13] This can be functionally important as these hyperkeratotic papules can be uncomfortable, and even painful, thereby restricting physical activity in affected individuals.

Conclusion

Eczema is a chronic relapsing dermatitis and, as such, it is imperative to maintain the hydration and barrier function of the skin in these patients with daily moisturizer use. Ceramide and urea-based moisturizers have been shown to be beneficial in reducing TEWL, improving barrier function, and maintaining hydration of the stratum corneum layer of the epidermis, and thus, should be a mainstay of treatment in patients with dry skin and eczema. Failure to adequately moisturize the skin can lead to a flare of symptoms or an increased incidence of infections. However, adherence to a schedule of regular moisturizer use is associated with improved patient quality of life outcomes (e.g., reduced pruritus, improved sleep patterns, less depression) and a reduction in the severity and frequency of eczematous flares.[14]

References

1. Simpson EL. *Curr Med Res Opin* 26(3):633-40 (2010 Mar).
2. Leung DYM, et al. *Lancet* 361(9352):151-60 (2003 Jan).
3. Levy ML. *Curr Med Res Opin* 23(12):3091-103 (2007 Dec).
4. Ahuja A. *South Med J* 96(11):1068-72 (2003 Nov).
5. Carbone A, et al. *Ann Pharmacother* 44(9):1448-58 (2010 Sep).
6. Anderson PC, et al. *Curr Opin Pediatr* 21(4):486-90 (2009 Aug).
7. Chamlin SL, et al. *J Am Acad Dermatol* 47(2):198-208 (2002 Aug).
8. Di Nardo A. *Acta Derm Venereol* 78(1):27-30 (1998 Jan).
9. Madaan A. *Drugs Today* 44(10):751-5 (2008 Oct).
10. Flynn TC, et al. *Clin Dermatol* 19(4):387-92 (2001 Jul).
11. Trung H, et al. *Ostomy Wound Manage* 48(5):30-6 (2002 May).
12. Hindson TC. *Arch Dermatol* 104(3):284-5 (1971 Sep).
13. Hogan DJ, et al. Corns: treatment and medication. Available at: http://emedicine.medscape.com/article/1089807-treatment. Accessed: September 30, 2010.
14. Loden M. *J Eur Acad Dermatol Venereol* 19(6):672-88 (2005 Nov).

Review of Conventional Systemic Therapies for Severe Psoriasis

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Introduction

Psoriasis is a chronic inflammatory cutaneous disorder that can significantly affect patient quality of life (QoL). Although the exact pathogenesis remains to be elucidated, immunologic abnormalities with an increase in immune mediators are likely primary contributing factors. Most patients have mild disease that can be adequately managed by topical therapy. However, a subset of the psoriatic population with severe disease requires phototherapy and/or systemic treatment. Due to its chronic and recalcitrant course, a combinational approach (including topical, systemic, and nondrug interventions) is often necessary for successful long-term management.

Of the conventional systemic agents, acitretin, cyclosporine, and methotrexate are the most commonly used. In the new era of biologics, these agents remain as valuable therapeutic options for severe psoriasis. Recent studies have also provided insights into enhanced efficacy and safety when these drugs are used in combination with the biologics. A review of these conventional systemic antipsoriatic agents will be discussed.

As family physicians frequently serve on the frontlines of patient care and are instrumental in managing comorbidities associated with psoriasis, it may be helpful to be aware of more aggressive approaches. However, because systemic treatment carries a higher risk for adverse effects, moderate to severe cases are best co-managed with dermatologists, who are more familiar with the use of these agents.

Disease Overview

- Psoriasis is a common multisystem disease that affects the skin and may involve the joints.
- Immune dysregulation of T cells results in overactivation, triggering an inflammatory response that leads to the accelerated production of epidermal cells.
- Build-up of the epidermis produces red, scaly, and well demarcated plaques of variable size.
- Psoriasis can affect any part of the body, including the scalp, elbows, knees, lower back, and nails, but the face is usually unaffected.
- Chronic lesions, particularly of the hands and feet, can result in persistent dryness, hyperkeratosis (thickening of the other layer of the skin), itching, fissuring, and infection.

Prevalence

- Genetic factors increase disease susceptibility.
- It affects about 2-3% of the general population.[1]
- Up to 35% of people with psoriasis have moderate to severe disease.[2]
- It may eventually progress to the joints (arthritis). Up to 30% of Canadians with psoriasis develop psoriatic arthritis.[3]

Types of Psoriasis[4]

- Plaque – chronic plaque psoriasis is the most common variant, affecting more than 80% of the psoriatic patient population.[5]
- Guttate – multiple small (5-15 mm) red lesions are round or oval, and drop-like in shape. Lesions appear suddenly and will typically cover the trunk, arms, legs, face, and scalp. It is often associated with streptococcal infection.
- Inverse – also known as flexural psoriasis occurs in the creases and folds of the skin, such as the armpits, groin, and under the breasts. The lesions are characterized by smooth, well defined red patches, but scaling is generally minimal or absent.
- Pustular – a rare form that can be localized to the palms and soles or become generalized. Although pustules are seen, they do not indicate an infection.
- Erythrodermic – a very rare form; most of the skin's surface is affected by inflammation, redness, and scaling. It can be fatal due to associated complications.

Severity Assessment

- Psoriasis Area Severity Index (PASI) is widely used in clincial trials.
- One common method for measuring psoriasis severity is based on the percentage of affected body surface. For example, one palm-sized lesion represents 1% of body surface area (BSA).[4]
  - Mild psoriasis affects <3% of BSA.
  - Moderate psoriasis affects 3%-10% of BSA.
  - Severe psoriasis affects >10% of BSA.
- The measure of social, emotional, and fuctional impairment resulting from psoriasis is critical.

- The Dermatology Life Quality Index (DLQI) questionnaire is a commonly used tool to assess patient reported outcomes.
- In a questionnaire study, investigators assessed the extent of psychosocial comorbidity and functional impairment in 43 psoriasis patients.[6]
  - About 48% of psoriasis patients reported adverse impacts on social functioning, leading to decreased work efficiency in 51% and to workplace distress in 63%.[6]
  - Stress in the home environment and interpersonal relationships were reported by 70%.[6]

Comorbidities

- Psoriasis can significantly impact a patient's QoL, e.g., loss of productivity, depression, and an increased incidence of malignancy.[7]
- Associated comorbidities include cardiovascular disease and metabolic syndrome, which may be linked to the underlying chronic inflammation.
- Psoriasis patients have demonstrated an increased prevalence of obesity, dyslipidemia, and insulin resistance.

Treatment Rationale

Formulation of an effective treatment strategy will depend on several factors, including findings from diagnostic investigations, extent and severity of psoriasis, treatment history, age, and patient preferences. Aside from achieving tangible improvements, the adopted therapeutic approach must also minimize QoL impairment, such as discomfort, disability, and heighten self-consciousness, which can lead to social avoidance behaviours. Consequently, early diagnosis and ongoing medical and adjunctive care are crucial for controlling chronicity and disease severity.

Biologics represent the newest class of antipsoriatic agents, although their advent has revolutionized the treatment of moderate to severe psoriasis, long-term safety remains to be established and their high cost can be prohibitive. The common traditional systemic agents (i.e., acitretin, cyclosporine, and methotrexate) continue to have a place in the management of severe psoriasis and novel combined uses have emerged.

Acitretin

Acitretin is a second generation aromatic retinoid (a vitamin A derivative). Acitretin is prescribed mainly for men and also for post-menopausal women. Due to its teratogenic potential, premenopausal women are generally excluded as treatment candidates. Acitretin's mechanism of action includes inhibiting cell replication by controlling cellular differentiation within the epidermis. It reduces inflammation and influences the growth rate of skin cells.

Advantages and Benefits

- Convenient once daily oral dosing.
- Very helpful as an adjunct to phototherapy.
- Acitretin may be the safest oral systemic agent for psoriasis, apart from its teratogenic risk that persists 2-3 years following treatment discontinuation.[8]
- Highly effective for treating pustular (including palmoplantar psoriasis) or erythrodermic forms of psoriasis; less effective as monotherapy for plaque psoriasis.
- Acitretin usually does not cause organ damage, which is a side-effect with other medicines (such as methotrexate and cyclosporine), therefore, it can be used for long-term maintenance therapy.
- Unlike other systemic therapies for psoriasis, it does not suppress the immune system.
- Relatively safe for long-term treatment.
- For psoriasis patients with a history of melanoma, acitretin should be considered as a therapeutic option.

Risks and Side-Effects

- Onset of response is usually 2-4 months.
- Combination treatment with phototherapy or biologic agents is superior to monotherapy.
- Side-effects include dryness and irritation of the skin, lips, eyes, nose, and mucous membrane surfaces. Frequent use of a moisturizer is essential to help reduce the irritation.
- Other adverse side-effects include elevation of cholesterol and triglyceride levels, liver toxicity, bone changes, and alopecia.
- As birth defects can occur with retinoids, acceptable method(s) of birth control must be practiced by and discussed with the patient. Because of its relatively long bioelimination, even following treatment cessation, female patients must continue to avoid pregnancy for the next 2-3 years.
- The main issue with compliance is to minimize side-effects through inclusion of topical agents and phototherapy.
- Due to the medication's drying effects, starting with a lower dose may ease the intensity.

Cyclosporine

Cyclosporine is an immunosuppressant that is also frequently used in organ transplantation. Although it is a very effective antipsoriatic agent, cyclosporine is generally reserved for patients with severe, disabling, or recalcitrant psoriasis (also referred to as a crisis drug), owing to its cost and potentially serious side-effect profile (e.g., renal impairment). Cyclosporine offers rapid disease control in severe cases by suppressing the body's immune system and slowing the rapid production of skin cells.

Advantages and Benefits

- Treatment is administered orally 1-2 times daily.
- Onset of effect is rapid (4-8 weeks); improvement is often seen within the first 4 weeks.
- Highly effective for severe psoriasis, especially helpful for treating acute flare-ups.
- It can be used intermittently in short-term courses or combined with other topical and systemic therapies.
- Multiple short courses are prescribed to reduce the potential for toxicity.

Risks and Side-Effects

- Long-term use leads to kidney damage, although the damage is often reversible with treatment cessation.
- Total duration of therapy should not exceed 1-2 years to avoid severe adverse systemic effects.
- Regular assessments through blood and urine tests, and blood pressure monitoring are required throughout treatment.

- Rebounds are common if the dosage is tapered or when the medication is stopped.
- Side-effects include flu-like symptoms, nausea, diarrhea, hair growth, high blood pressure, numbness and tingling, and kidney damage.
- Because cyclosporine suppresses the body's immune system, there is an increased risk of infections and certain cancers, such as skin cancer and lymphomas, but reported incidences usually involve use in organ transplantation where the medication is administered long-term and at higher doses.
- Cyclosprine cannot be used at the same time with psoralen + UVA (PUVA) or UVB phototherapy, methotrexate or other immunosuppressive agents, coal tar, or radiation therapy.
- As a potent immunosuppressive agent, increasing the risk of skin cancer, patients being treated with cyclosporine should be advised to take sun-protective measures, i.e., as applying a broad-spectrum sunscreen daily and wearing long-sleeved clothing and hats.

Methotrexate

Methotrexate (MTX) is an antimetabolite drug that has been in use since the 1950s. It continues to be one of the most widely prescribed drugs for treating severe psoriasis. MTX is effective against diseases that are affected by abnormally rapid cell growth (e.g., psoriasis, rheumatoid arthritis, and cancer). It helps to control psoriasis by reducing immune responses and slowing joint destruction. MTX is usually given after other medications have been tried unsuccessfully.

- The mechanism of action is the interference with DNA synthesis repair and cellular reproduction.
- Antifolate agents, such as MTX, impair the function of folic acid (a B vitamin) that is essential for cellular activity.
- MTX is usually administered orally once weekly at doses ranging from 2.5-25 mg or occasionally by injection.
- It can be administered either as a single dose or in a split dose 12 hours apart for 3 doses.

Advantages and Benefits

- Reasonably effective, convenient dosing, and relatively inexpensive
- Improvements are noticeable following 6-8 weeks of therapy.
- MTX can be used for longer periods of time in comparison with other agents (such as cyclosporine), but patients must be regularly monitored for potentially serious side-effects.
- MTX can also enhance the effect of UVB phototherapy.

Risks and Side-Effects

- Side-effects include headache, skin irritation (itch and rash), hair loss, mouth sores, upset stomach, nausea, low white blood cell count, and fatigue.
- Long-term MTX use can cause serious liver damage. Routine blood tests assessing hepatic function may not detect the damage, hence, a liver biopsy may be necessary every 1.5-2 years while undergoing treatment.
- Long-term risks include birth defects, kidney damage, bone marrow toxicity, and bone marrow suppression (rare, but potentially life-threatening).
- There are many drugs (e.g., non-steroidal anti-inflammatory drugs) that can adversely interact with MTX.
- MTX can cause birth defects and miscarriages, resultantly, women with child-bearing potential taking the drug must use a reliable method of contraception.
- To mitigate the risk of liver damage, patients must be advised not to consume alcohol while on therapy.

Phototherapy

- For generalized psoriasis, UVB phototherapy offers an effective option that allows both rapid disease control and long-term maintenance.[8]
- Narrowband UVB may be more effective than broadband.
- Use of low doses of acitretin enhances both therapeutic benefits of UVB and PUVA.
- MTX may also improve the effect of UVB.
- Phototherapy in combination with acitretin not only improves efficacy, but may also reduce long-term side-effects and the number of required treatments.
- For patients unresponsive to phototherapy or who find the treatment schedule too demanding, MTX can be an effective alternative.

Conclusion

Effective ongoing management of patients with severe psoriasis requires knowledge of available therapies, including mechanism of action, potential toxicity, and appropriate monitoring. Combinational, rotational, and sequential therapeutic methods that aim to improve overall efficacy while reducing the toxicity of the chosen medications are the goals of treatment. Optimal patient care also requires continued education and support, as well as addressing quality of life concerns. It is important to encourage patients to be involved in therapeutic decision-making and to report any side-effects that they are experiencing, in order that symptoms can be mitigated with dose adjustments, the addition of other treatments, or even temporary discontinuation of therapy.

References

1. Griffiths CE, et al. *Lancet* 370(9583):263-71 (2007 Jul 21).
2. Thomas VD, et al. *J Am Acad Dermatol* 53(2):346-51 (2005 Aug).
3. The Arthritis Society. Psoriatic Arthritis. Available at: http://www.arthritis.ca/types%20of%20arthritis/psoriatic%20arthritis/default.asp?s=1. Accessed: December 21, 2010.
4. National Psoriasis Foundation. Facts about psoriasis. Available at: http://www.psoriasis.org/NetCommunity/Document.Doc?id=352. Accessed: December 21, 2010.
5. Pathirana D, et al. *J Eur Acad Dermatol Venereol* 23(Suppl 2):1-70 (2009 Oct).
6. Gaikwad R, et al. *Indian J Dermatol Venereol Leprol* 72(1):37-40 (2006 Jan-Feb).
7. Gottlieb AB, et al. *J Dermatolog Treat* 19(1):5-21 (2008).
8. Feldman S. *Dermatol Online J* 6(1):4 (2000 Sep).

Review of Management Options for Genital Herpes Infections

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Introduction

Genital herpes is a common sexually transmitted infection caused by the herpes simplex virus (HSV). HSV type 2 (HSV-2) causes approximately 60% of the primary genital HSV infections in Canada.[1] However, the type 1 strain (HSV-1), traditionally associated with oral herpes, is capable of causing a similar clinical picture. It is estimated that 20% to 40% of Canadians are HSV-2 seropositive, while studies have consistently shown that the great majority are unaware of their disease status.[1] Although treatment exists, there is currently no cure for genital herpes and infection is, therefore, lifelong. Consequently, patients should be informed about clinical signs and symptoms of genital herpes, as this may help them to recognize symptomatic infection and seek early treatment, thereby contributing to improved management and therapeutic efficacy.

Brief Overview of the Disease

- Transmission of genital herpes occurs when there is direct contact with secretions or skin of a person who is actively shedding virus.
- The clinical course of genital herpes varies greatly from patient to patient; up to 75% of infected individuals are asymptomatic.[1]
- Polymerase chain reaction (PCR) testing has demonstrated that viral shedding occurs on up to 40% of asymptomatic days.[2]
- Asymptomatic viral shedding leads to a precarious situation in which individuals can unwittingly transmit the disease to sexual contacts.
- Symptomatic genital HSV infection is manifested 7-10 days after exposure by a prodrome of tingling and pain that precedes the lesions by up to a day.
- The initial or primary outbreak is generally more severe and may have multiple genital or anorectal ulcerations. Recurrent episodes are usually less intense and of shorter duration.
- Clinical presentation includes developed clusters of papules on an erythematous base, which then become vesicles, pustules, and later erosions. During initial infection, these lesions crust over by day 7-14 and generally heal by the fourth week without scarring.
- An initial episode is often accompanied by dysuria, urinary retention, tender inguinal and femoral lymphadenopathy, as well as systemic symptoms that can include fever, malaise, and headache.
- After the initial infection, the virus remains latent in the sacral dorsal root ganglion and, at variable intervals, travels back down the nerve root and causes asymptomatic shedding or mucocutaneous outbreaks that are usually less intense than the initial episode.[3]
- Recurrent episodes can be triggered by stress, infection, trauma, or menstruation, and have a prodrome of burning and tenderness for 2 hours to 2 days, followed by papules and vesicles lasting 4-15 days until re-epithelialization.[2]
- In the first year after infection, an untreated patient will experience an average of four further episodes.
- Complications associated with genital HSV infection include:[3,4]
  - disseminated HSV
  - aseptic meningitis
  - autonomic dysfunction with urinary retention
  - vertical transmission from an infected mother to her newborn
  - increased risk of HIV transmission.

Diagnosis

- Diagnosis is usually made clinically, but laboratory tests should be used to confirm the diagnosis. This can be done with viral culture, HSV detection, or serology.[3]
- To obtain a sample from an active clinical lesion for laboratory analysis:
  - choose the most recent of the vesicles and gently lift the roof of the vesicle with a needle tip or scalpel blade to expose the underlying material
  - instill collected swab in viral culture media and send to the lab as per usual practice (takes 5 days to culture)
  - alternatively, transfer swab to a glass slide and send for immediate direct immunofluorescence testing (rapid detection).
- Type specific serology can be done, however, this can only be used to determine past infection or asymptomatic HSV infection; this test is helpful for determining between HSV-1 and HSV-2.[4]

- A Tzanck smear showing multinucleated giant cells has been used historically, but may not always be practical in a clinic setting.
- Consider testing for other bacterial causes of ulcerative lesions, such as *Treponema pallidum* and *Haemophilus ducreyi*, depending on the demographics of the population.[3]

Treatment Rationale

- Treatment is aimed at reducing patient discomfort, transmission of the virus, duration of the outbreak, and risk of complications.
- Treatment should be initiated as soon as possible without waiting for laboratory results (ideally within 72 hours of symptom onset in order to minimize duration and severity of illness).
- Conservative measures include analgesics and sitz baths to alleviate the pain.
- Intermittent urinary catheterization may be necessary if urinary retention results from autonomic dysfunction.

Available Treatments

Topical Therapy

- Although oral agents are the standard of practice in the treatment of genital herpes, topical administration of 5% acyclovir is an option for those patients who do not wish to receive oral therapy, who are on multiple oral medications (e.g. elderly, multiple comorbidities), or if cost is an issue. It allows prompt and convenient treatment to be initiated by the patient when symptoms first develop.
- Topical therapy with 5% acyclovir can be used for initial outbreaks; treatment must be started during the prodromal stage (Table 1).
- Randomized double-blind, placebo controlled studies have shown that topical acyclovir 5% in an ointment or cream base reduces viral shedding, time to healing, duration of pain, and new lesion formation for initial episode of genital herpes.[5-7]
- Many other topical agents are currently being investigated, including immune response modifiers, other antivirals, microbicides, and oligodeoxynucleotides with variable results reported.[2]

Oral Therapy

- There are three oral anitviral agents available: acyclovir, valacyclovir, and famciclovir (Tables 1, 2 and 3).
- Efficacy for all three agents is comparable with respect to duration and severity of the lesions, as well as reduction in the incidence of complications, such as meningitis.

Drug	Dose	Duration
Acyclovir	400 mg PO 3 times/day or 200 mg PO 5 times/day	7-10 days
Valacyclovir	1000 mg PO 2 times/day	7-10 days
Famciclovir	250 mg PO 3 times/day	7-10 days
Acyclovir (topical)*	Apply liberally to affected area 4-6 times/day	7-10 days

Table 1: Suggested treatment for initial episode genital herpes[2]
** If oral agent cannot be used, consider topical acyclovir for initial outbreaks*

Drug	Dose	Duration
Acyclovir	400 mg PO 3 times/day	5 days
	800 mg PO 2 times/day	5 days
	800 mg PO 3 times/day	2 days
Valacyclovir	500 mg PO 2 times/day	3 days
	1000 mg PO once/day	5 days
	2000 mg PO 2 times/day	1 day (not FDA approved)
Famciclovir	125 mg PO 2 times/day	5 days
	1000 mg PO 2 times/day	1 day

Table 2: Episodic therapy for recurrent herpes[2]

Drug	Dose	Duration
Acyclovir	400 mg PO 2 times/day	Daily
Valacyclovir	500 mg PO once/day	Daily
	500 mg PO 2 times/day	
	1000 mg PO once/day	
Famciclovir	250 mg PO 2 times/day	Daily

Table 3: Suppressive therapy for recurrent herpes[2]

- Decisions about which agent to use is dependent upon dosing and price, with acyclovir being the least expensive and valacyclovir requiring less frequent dosing.
- Suggested duration for treatment is 7-10 days, however, this should be extended if lesions are not healed or new lesions are developing.
- Recurrent episodes will require therapy and can be treated according to the severity and frequency of outbreaks.
- Episodic therapy (Table 2) is suitable for patients with mild or infrequent outbreaks.
- Suppressive therapy (Table 3) is required for patients with either severe or frequent episodes (> 6 episodes per year).

Intravenous (IV) Therapy

- Only acyclovir is available for IV administration and should be reserved for use in severe cases, immunocompromised patients, or in patients with complications requiring hospitalization.
- The dose is 5-10 mg per kg body weight every 8 hours.[2]

Conclusion

Genital herpes is a chronic sexually transmitted infection that has the potential to cause both physical and psychological distress. The disease is spread by direct contact and manifests either asymptomatically or with pain and lesions that begin as clusters of papules and develop into vesicles or ulcerations. Diagnosis is usually clinical, but is best confirmed with swab sample testing. Treatment should be initiated as soon as possible after symptom onset and aims to reduce the severity and duration of symptoms, as well as the risk of complications. Oral antivirals are the mainstay of treatment, but in patients who are unable or unwilling to use these agents, topical 5% acyclovir may be a therapeutic option, particularly for managing initial symptoms of HSV outbreaks. Adjunctive therapies include analgesics and sitz baths. IV acyclovir is reserved for the most severe cases requiring hospitalization and/or in immunocompromised patients.

References

1. Steben M, et al. *Can J Hum Sex* 6(2):127-34 (1997).
2. Viera MH, et al. *Int J Dermatol* 49(7):733-49 (2010 Jul).
3. Gupta R, et al. *Lancet* 370(9605):2127-37 (2007 Dec 22).
4. Sen P, et al. *BMJ* 334(7602):1048-52 (2007 May 19).
5. Corey L, et al. *N Engl J Med* 306(22):1313-9 (1982 Jun 3).
6. Kinghorn GR, et al. *Antiviral Res* 3(5-6):291-301 (1983 Dec).
7. Thin RN, et al. *Br J Vener Dis* 59(2):116-9 (1983 Apr).

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