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GUIDELINES FOR CLINICIANS

Suppressive Therapy for Genital Herpes

Introduction

Most genital herpes is caused by the herpes simplex virus 2 (HSV-2), although herpes simplex virus 1 (HSV-1) accounts for half the new cases in developed countries. The major concern of HSV is its frequency of recurrences, its chronicity and its effects on patient personal relationships while asymptomatic shedding is an important source of transmission of the virus to other susceptible individuals.

Genital Herpes Recurrences

One characteristic of genital herpes is its ability to recur. Approximately 95% of individuals with HSV-2 on the genitals will experience recurrences. Some recurrences are minor and the patient can treat the episode using local measures such as salt water bathing of the affected area and simple analgesics such as paracetamol.

Antiviral Treatment

Aciclovir, famciclovir and valacyclovir are the three antiviral drugs used to reduce the severity and frequency of episodes. Individuals who experience frequent episodes may wish to start a course of antiviral therapy at the first warning signs (the prodrome) of a recurrence such as itching and pain. This treatment is called 'episodic' oral antiviral therapy. Lastly, some patients experience very frequent and severe HSV recurrences and the aim of the treatment is to prevent recurrences by long-term daily therapy. This is called 'suppressive' (preventative) oral antiviral therapy.

This guideline provides essential evidence based information and guidance on the suppressive treatment of genital herpes simplex virus.

Asymptomatic Viral Shedding

There are two crucial concepts to understanding asymptomatic shedding in genital herpes. The first is that even when genital skin looks and feels normal virus particles may be present and secondly, most people who transmit the virus to others do not know that they are infected and most do not have a readily recognisable lesion present at the time. In women, the anatomical sites of asymptomatic shedding include the cervix, vulva, rectum

and urethra. Asymptomatic cervical shedding has been shown to result both in horizontal and vertical transmission of the infection. In men, asymptomatic shedding may occur on the genital skin and from inside the urethra and rectum. The virus has also been demonstrated in saliva.

Shedding of Virus in HSV-1 and HSV-2 Infections

There are significant differences between genital HSV-1 and HSV-2 infection for both frequency of recurrences and shedding episodes. While HSV-1 is usually acquired via oral-genital contact, it is rarely associated with frequent recurrences and viral shedding. As most people already have HSV-1 infection, genital to genital transmission to new partners is rare. HSV-2 however has a strong tendency to recur, either clinically or asymptotically, and there is a significant risk of sexual transmission to new partners.

Suppressive Antiviral Therapy

There are three antiviral medications, acyclovir (Zovirax, Ozvir, Lovir, Zyclir), famciclovir (Famvir) and valacyclovir (Valtrex), that are used for suppressive treatment of genital herpes simplex. All three drugs prevent replication of the herpes virus by inhibiting the synthesis of DNA. The drugs only act in virus infected cells, which means that oral treatment of herpes is safe, well tolerated and adverse effects are rare. In addition antiviral drugs maintain their efficiency over time.

Research on the prophylactic use of acyclovir for recurrent genital herpes began in the early 1980s. Due to its poor bioavailability famciclovir (a prodrug of penciclovir) was developed. Famciclovir is well absorbed orally, making twice daily oral treatment possible. The third drug, valacyclovir (a prodrug of acyclovir), metabolises into acyclovir in vivo, but has the same mechanism of action as acyclovir. It has the advantage of 54% absorption by mouth. Valacyclovir suppression has also been shown to reduce the risk of transmission. In addition it has been established that once daily dosing of valacyclovir at a dose of 500mg is effective providing a more convenient dosage regime than the other antivirals. However, once daily Valacyclovir is only suitable for individuals who have fewer than ten recurrences a year. It is vital to understand, and to warn patients using suppressive therapy, that antivirals suppress viral shedding but not by 100%. This means that even when suppressive drugs are used, there remains the risk of transmission from an infected individual to a susceptible individual.

The following tables provide the list of drug therapies with dose required for suppressive therapy.

Advantages of Suppressive Therapy

There are many advantages of suppressive therapy. First, most patients will have no recurrences or very few minor episodes whilst on treatment. For most patients this means no pain or discomfort, and no sores or ulcers. Second, prodromal symptoms will cease or be dramatically reduced. Third, many patients will have a marked improvement in psychological and psychosexual wellbeing and their quality of life will also improved. Finally, as mentioned above, suppressive Valacyclovir can reduce the risk of sexual transmission.

Table 1: Suppressive treatment according to immune status

Suppressive Therapy in Immunocompetent Patients			
Diagnosis	Management Strategy	Drug	Dose
Genital herpes type-2	Suppressive Therapy	Valacyclovir	500mg once daily if < 10 recurrences/yr
			1000mg once daily if \geq 10 recurrences/yr
		Famciclovir	250mg twice daily
		Acyclovir	200mg three times daily* (400mg twice a day)

*For 6 months

Suppressive Therapy in Immunocompromised Patients			
Diagnosis	Management Strategy	Drug	Dose
Genital herpes type-2	Suppressive Therapy	Valacyclovir	500mg twice daily
		Famciclovir	500mg twice daily
		Acyclovir [^]	200mg three times daily (400-800mg twice or three times per day)

[^]Advanced symptomatic HIV disease 800mg 4 times daily
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Length of Suppressive Antiviral Courses

Currently there is no clinical evidence for best practice concerning the length of suppressive therapy. As discussed previously a pragmatic approach is needed based on the patient's physical and psychological morbidity. One regime is to provide suppressive therapy to the individual for one year, then stop the drug to assess the need for further therapy. If there is an unacceptable number of recurrences the patient can be placed on another course of suppressive therapy and this can be repeated as necessary.

Dual Method of Prevention

While the role of antivirals for suppression is still being investigated suppression is best achieved by using several methods in combination. Condoms appear to reduce transmission although there is risk of viral particles shedding outside the boundaries of the condom's coverage. It is suspected that the female condom may provide more physical protection.

Specialist Referral when Appropriate

There should be no hesitation on behalf of the treating doctor in referring patients to sexual health and other specialists for expert advice especially if the diagnosis is uncertain and/or testing is unavailable. In addition, if the patient does not respond to treatment as expected an underlying immunosuppressive disorder, for example HIV, should be considered. With regard to pregnancy, a female with genital herpes, or who has a partner with genital herpes, her obstetrician should be alerted to this situation.

The decision whether to allow a vaginal delivery depends on the obstetrician's practice and the presence of lesions at the time of labour. Lastly referral to a psychologist may be needed if the patient is experiencing psychological distress, particularly concerning personal relationships and the impact of the infection and antivirals.

Patient Involvement in Decision Making Concerning the Management of Genital Herpes

Herpes is not curable but is manageable. The responsibility lies with the clinician to provide patients with sufficient information (for example information on the advantages and disadvantages of suppressive treatment)

to allow them to participate fully in management decisions. Considering the variety of physical and psychological factors recurrent genital herpes requires a pragmatic approach to management for each patient.

A practical disadvantage of suppressive therapy centres on pill taking. It is difficult for many patients to remember to take a pill(s) daily for what they may perceive is a non life threatening condition. On the other hand, some patients on suppressive treatment become 'dependent' on it and are reluctant to cease treatment believing episodes will recur. Following on from this we now know that valacyclovir given once daily can control recurrent herpes but that missing one tablet, leaving a 48 hour gap between doses, may lead to a recurrence. This illustrates that clinicians should be flexible about patient preferences for treatment and negotiating treatment regimes at the beginning of a course of suppressive therapy.

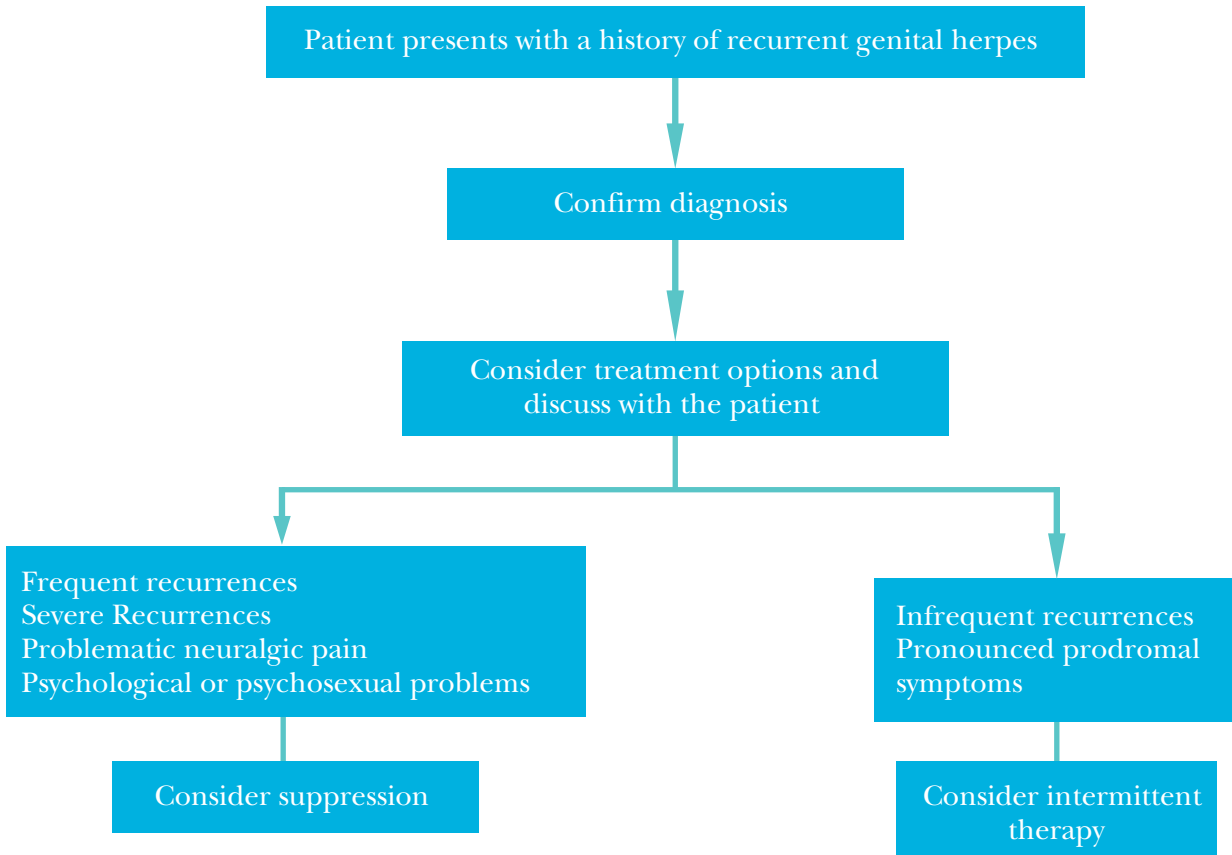
The Best Treatment Reflecting Current Best Practice

Many patients with genital herpes do not require suppressive antiviral therapy. However if suppressive treatment is warranted the antiviral drugs can reduce the number of recurrences and viral shedding by 85-90%.

Individuals with Genital Herpes Who May Benefit from Suppressive Therapy

- Individuals with very frequent outbreaks
- Those with severe prodromal (warning signs) symptoms
- Those that experience severe symptoms, especially pain
- Those that find having recurrences psychologically distressing
- Those entering a new relationship to reduce transmission

Algorithm 1: Suppressive and Intermittent Treatment for Genital Herpes



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