MAJOR ARTICLE

Recommendations for the Selective Use of Herpes Simplex Virus Type 2 Serological Tests

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Background. Herpes simplex virus (HSV) type-specific serological tests are now widely available, but indications for their use have not been well defined. The California Sexually Transmitted Diseases (STD) Controllers Association convened a committee of clinicians and researchers to make recommendations for the use of type-specific HSV type 2 (HSV-2) serological tests.

Methods. By means of a systematic review of the literature, evidence to support screening in selected high-risk groups was compiled. Screening recommendations were developed by applying standard screening criteria to each specific population.

Results. The committee concluded that, in addition to serological testing for the diagnostic evaluation of patients with symptoms, screening of asymptomatic patients is likely to be beneficial among the following groups: those at high risk for STDs and human immunodeficiency virus (HIV) infection who are motivated to reduce their sexual risk behavior, HIV-infected patients, and patients with sex partners with genital herpes. In contrast, universal screening for HSV-2 infection in pregnant women is unlikely to be beneficial.

Conclusions. The targeted use of HSV-2 serological tests for specific diagnostic situations and selected populations should benefit patients, providers, and the community. Until more data become available, these recommendations provide justification for selective diagnostic and screening uses of HSV-2 serological tests.

Genital herpes is one of the most prevalent sexually transmitted diseases in the United States, with a documented seroprevalence of herpes simplex virus (HSV) type 2 (HSV-2) of 22% in the general population [1]. Approximately 90% of persons with HSV-2 antibodies do not know they are infected [1]. Recent evidence demonstrates that most people infected with HSV-2 shed the virus from a variety of genital areas asymptomatically [2]. There is concern that this population of sexually active, infected persons without a diagnosis of herpes acts as a reservoir for the continued spread of herpes [3].

The advent of type-specific serological tests has provided tools to aid in the diagnosis of genital ulcer disease and has made screening for herpesvirus infections possible. The tests can distinguish between antibodies to HSV-2, the virus most associated with genital ulcers, and HSV type 1 (HSV-1), the virus most frequently associated with childhood-acquired orolabial disease. Some experts recommend type-specific screening in certain populations [3–5], whereas others cite insufficient evidence and recommend against its use [6, 7]. Although there is less controversy surrounding the use of type-specific serological tests for the diagnostic evaluation of patients with symptomatic disease, there is potential for confusion among providers regarding the timing and interpretation of these tests [8].

At present, no evidence-based guidelines exist for the use of type-specific serological tests as a screening tool. The most recent guidelines for screening for herpes from the United States Preventive Services Task Force (USPSTF) and the American College of Obstetrics and Gynecology were made before the commercial availability of type-specific serological tests [9, 10]. Other groups, including the Centers for Disease Control and Prevention (CDC), have made recommendations re-

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garding the use of type-specific serological tests based primarily on expert opinion without a clear rationale [5, 11].

Inappropriate use of screening tests can rob people of their perceived health, cause unnecessary or harmful interventions, and waste valuable health care resources [12]. The California Sexually Transmitted Diseases (STD) Controllers Association and California Department of Health Services STD Control Branch, recognizing the need for carefully considered guidelines for the use of type-specific herpes serological tests, convened a committee to make evidence-based recommendations. The literature review presented here provides the rationale for the clinical practice guidelines released in 2003 [13].

LITERATURE REVIEW AND DEVELOPMENT OF RECOMMENDATIONS

In December 2001, the STD Controllers Association with the STD Control Branch established an ad hoc HSV committee to make evidence-based guidelines for the use of type-specific herpes serological tests. The committee consisted of 7 members with expertise in the field of STDs and public health.

The literature search strategy included a search of the MEDLINE database (National Library of Medicine) for published articles related to herpes, herpes screening, type-specific serological tests, herpes and HIV, herpes in pregnancy, neonatal herpes, condom efficacy, behavior intervention efficacy, and antiviral suppression. In addition, bibliographies of identified articles and unpublished manuscripts from HSV researchers were reviewed. The committee named patients with genital symptoms the diagnostic population and identified 4 target screening populations: patients at high risk for STDs and HIV infection, HIV-infected patients, patients in partnerships or considering partnerships with HSV-2–infected people, and pregnant women. Articles selected for full review discussed herpes or herpes serological tests in the identified diagnostic or screening populations, addressed type-specific herpes tests in the diagnosis of genital symptoms, or contained information relevant to herpes screening criteria. Evidence was organized into the following categories by screening criteria [14]: prevalence and impact of HSV-2 infection, potential serious adverse effects of an unrecognized infection—including transmission risk to an uninfected partner, availability of a suitable diagnostic test, reduction of complications and improvement of patient and community health as a result of early detection and intervention, adverse consequences to screening, and cost-effectiveness. No new literature was reviewed after January 2003 except for previously reviewed unpublished manuscripts that became published. The committee developed a rating system for screening recommendations adapted from the USPSTF (table 1) [9]. Because of the high seroprevalence of HSV-1 antibodies in the general population, and the paucity of genital HSV-1 research, the HSV committee limited the review and recommendations to HSV-2 serological tests.

DIAGNOSIS OF SYMPTOMATIC GENITAL HERPES

The committee determined 3 situations in which HSV-2 serological tests may assist in the diagnosis of genital herpes: patients presenting with a culture-negative recurrent lesion, a history suggestive of herpes without visible lesions, and the first presentation of genital lesions when results of culture or antigen detection are negative or unavailable (table 2) [8, 15, 16]. Direct testing of the lesion with culture or antigen detection should always be done first to establish HSV as the etiologic agent [17]. If these tests yield negative results or are unavailable or if there is no lesion amenable to testing, HSV-2 serological tests can assist in the diagnosis of a suspected symptomatic herpesvirus infection. Note that results of serological testing from an early time point in infection may yield falsely negative results because of the lag time in seroconversion [18]. Testing for HSV-1 infection as part of the diagnostic evaluation of genital symptoms has limited utility because of the high prevalence of HSV-1 antibodies in the adult population but may be useful if HSV-2 testing yields negative results and there is high suspicion of a herpes infection. Additional discussion of the diagnostic workup of symptomatic disease can be found in the clinical practice guidelines [13].

GENERAL CONSIDERATIONS IN SCREENING

Several issues were relevant to all screening groups: test performance, potential adverse consequences of screening, and cost-effectiveness. Currently available type-specific serological tests detect the majority of primary infections by 12 weeks and have a sensitivity of 93%–99% and a specificity of 94%–98% [4, 18]. Time to seroconversion for available tests has not been adequately determined but may differ by commercial test and by patient population [18]. Testing before seroconversion will cause false-negative results. Because these tests are not 100% specific, there is a risk of false-positive test results, and confirmatory testing may be necessary [5]. Non–type-specific serological tests should not be used, because they cannot distinguish between HSV-1 and HSV-2 [8].

There appear to be minimal adverse consequences to screening. The actual serological test is a simple venipuncture. Because symptomatic genital herpes can result in depression and ongoing emotional stress [19], there is concern about the potential psychosocial impact of newly diagnosed herpes infection through screening. An American Social Health Association survey of the perceived trauma of a potential herpesvirus infection showed that two-thirds of respondents thought the diagnosis would be "very traumatic" [20]. However, there is some evidence that nonpregnant, sexually active people will likely have

Table 1. System for rating strength of recommendations regarding serological testing for herpes simplex virus type 2.

Rating	Strength of the recommendation and rationale
A	Should always be offered; both strong evidence for efficacy and substantial benefit supports recommendation for use
B	Should generally be offered; moderate evidence of efficacy, or limited evidence with expert consensus, supports a general recommendation for use
C	Should be offered to select patients; evidence for efficacy is insufficient to support a general recommendation for use
D	Should generally not be offered; moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use
E	Should never be offered; strong evidence for lack of efficacy or for adverse outcome supports a recommendation against use

minimal to no psychosocial dysfunction after the diagnosis of asymptomatic herpesvirus infection [21–23].

The cost-effectiveness of herpes screening has not yet been fully evaluated. At present, the lack of quantitative data on the impact of herpes and herpes interventions limits these analyses.

SCREENING RECOMMENDATIONS

Medical organizations recommend against universal screening of the general population for HSV-2 infection. Reviewers concurred with the 2002 CDC [5] and the 1996 USPSTF [9] recommendations that screening of the general population would not be useful, given that the vast majority of infected people are asymptomatic and without significant medical complications. Screening of targeted populations, however, may be appropriate.

Patients at increased risk for STDs and HIV infection. Reports of prevalence of HSV-2 infection in patients attending STD clinics range from 14% to 69% [24]. HSV-2 infections are associated with at least a 2-fold increased risk of acquisition of HIV [25]. The annual incidence of HSV-2 ranges from roughly 3% per year in those undergoing repeated HIV testing [26] to 11% per year in a public STD clinic population [27]. Patients at risk for STDs or HIV infection include those with high-risk sexual behaviors or a current or recent acute bacterial STD. Identification of patients with HSV-2 infection who are at high risk for other STDs provides an opportunity to reduce their risk of acquiring HIV infection and of transmitting HSV-2. Potential interventions include counseling regarding risk reduction, condom use, and use of antiviral suppressive therapy.

No studies have specifically investigated whether knowledge of herpesvirus infection decreases risk behavior in individuals. Good evidence exists that risk-reduction counseling decreases incident bacterial STDs in patients at STD clinics [28, 29]; however, the impact on incident HSV infection is less clear [27]. Studies evaluating the effectiveness of behavioral interventions among men who have sex with men who exhibit high-risk sexual behavior have yielded mixed results [30, 31].

Consistent and correct use of male condoms is protective against HIV infection and effective in reducing risk of transmission of HSV-2 infection among heterosexuals. A prospective study of couples with discordant HSV infection status showed that condoms offered protection to women when used for >25% of sex acts but failed to protect men from acquiring herpes [32]. An unpublished study of adults at high risk for STDs demonstrated that condoms were protective against HSV-2 infection for men and women if used for >65% of sex acts [33].

There is evidence that suppressive therapy for herpes decreases transmission of HSV-2 infection. Suppressive therapy with acyclovir decreases subclinical HSV-2 shedding in symptomatic patients [34]. Recently, Corey et al. [35] demonstrated that treatment of symptomatic HSV-2–infected patients with daily valacyclovir therapy decreased the risk of HSV-2 seroconversion in uninfected regular partners by 50%, from 3.8% to 1.9%, over a period of 8 months. The effectiveness of daily suppressive therapy to prevent transmission of herpes in this population has not been evaluated, and the impact on infection rates for nonregular partners is problematic to study.

No studies to date have demonstrated that treatment of HSV-2–infected persons with antiviral suppressive therapy reduces acquisition of HIV infection. Theoretically, suppressive therapy for herpes may limit portals of HIV entry by decreasing the frequency of mucosal ulceration or skin breakdown. Trials are underway to address this question, but results are not expected for several years.

On the basis of these findings, the committee determined that screening is likely to be beneficial to selected patients at risk for STDs or HIV infection (recommendation C in table 2). Among patients motivated to reduce their sexual risk behavior, HSV-2 serological tests could be used as an adjunct to risk-reduction counseling.

HIV-infected patients. HSV-2 infections are highly prevalent among HIV-infected patients, with >80% of HIV-infected men who have sex with men and >60% of HIV-infected het-

erosexuals coinfected with HSV-2 [36]. HSV infection is a significant cause of morbidity and mortality in persons with HIV infection. HSV infection may also accelerate the course of HIV disease progression [37].

Genital herpes may facilitate transmission of HIV infection. There is biological plausibility that symptomatic HSV-2 infections increase HIV transmission, because high titers of HIV have been found in HSV-2 genital lesions [38] and persons with dual HSV-2 and HIV infections have more frequent symptomatic and asymptomatic reactivations of herpes [39]. Symptomatic and asymptomatic reactivations of herpes also increase the rate of HIV transcription and virus loads [40, 41]. It is less clear whether asymptomatic HSV-2 infections in HIV-infected persons contribute to HIV transmission. Gray et al. [42] retrospectively studied the probability of HIV transmission in discordant couples and found that, although symptomatic genital ulcer disease increased the risk of HIV transmission, HSV-2 antibodies in the HIV-infected partner were not associated with an increased risk of HIV transmission.

The first goal of screening for HSV-2 infection in HIV-infected persons would be to identify persons at higher risk of transmitting HIV infection because of an unrecognized HSV-2 coinfection. Potential interventions to prevent the spread of both HIV and HSV infections include risk-reduction counseling, consistent and correct use of condoms, and antiviral suppressive therapy for herpes. Suppressive therapy for herpes significantly reduces HSV-2 shedding from HIV-infected persons and may therefore decrease transmission of herpes [43]. A trial investigating whether treating HSV-2– and HIV-coinfected patients with daily acyclovir can decrease HIV transmission to HIV-uninfected partners was recently started (C. L. Celum, personal communication).

The second goal of screening HIV-infected persons for HSV-2 would be to improve the health of HSV-2– and HIV-coinfected patients. Previously unrecognized symptoms of recurrent herpes might be identified after screening, thus making the patient a candidate for suppressive therapy. Acyclovir has been shown to decrease levels of HIV-1 RNA in plasma [40], and high doses of acyclovir have shown a survival benefit for HIV-infected patients [44]. At present, there is no clear indication for treatment of asymptomatic herpes in patients with HIV infection. Additional prospective, controlled studies demonstrating a benefit from HSV suppression on HIV progression are needed before suppressive therapy for herpes can be recommended for coinfected patients. The contribution of this approach to increasing levels of acyclovir-resistant HSV is unclear and would need further investigation.

The third goal of screening HIV-infected patients would be to identify persons negative for HSV-2 antibodies who are at increased risk of acquiring HSV-2 infection. HIV-infected patients have a 4-fold higher risk of becoming HSV-2–infected than do uninfected people [25, 45, 46]. General counseling against reduction of risks for STDs may reduce incident herpesvirus infection in these persons [27].

Table 2 Summary of recommended uses for serological tests for herpes simplex virus type 2 for diagnosis and screening.

Recommended for diagnostic evaluation of:
A culture-negative, recurrent lesion
A history suggestive of herpes without visible lesions
A first presentation of genital lesions when culture or antigen test results are negative or unavailable and acquisition was likely to have been ⩾6 weeks earlier.
Recommended for screening of (rating):[a]
Patients at risk for sexually transmitted disease/HIV (C)
HIV-infected patients (B)
Patients with a partner with genital herpes (B)
Pregnant women (D)

[a] See table 1 for definitions of ratings.

On the basis of these findings, the committee determined that HSV-2 screening is likely beneficial to HIV-infected patients and should generally be offered (recommendation B in table 2).

Patients in partnerships or considering partnerships with HSV-2–infected people. Screening patients whose partners or potential partners are known to have genital herpes may assist patients in sexual health decisions. The yearly risk of acquisition in heterosexual couples aware of their serodiscordance ranges from ~4% to 10% per year, with women at highest risk [35, 47, 48].

Strategies to decrease acquisition of herpes in known HSV-discordant couples include risk-reduction counseling, consistent and correct condom use, and suppressive therapy for the infected partner. Evidence from 2 prospective, observational studies demonstrates low rates of condom use among serodiscordant heterosexual couples, despite education that condoms are protective against transmission of HSV-2 [32, 48]. Suppressive therapy for the symptomatic HSV-2–infected partner was shown to halve transmission of herpes in heterosexual couples [35]. Additional research about the impact of compliance on transmission, the acceptability of chronic therapy, and the generalizability to other populations would be helpful.

Screening to identify concordance between couples is beneficial for partners' sexual decision-making but may have little impact on public health. Identification of concordance could decrease condom use and potentially increase risk of acquiring other STDs, but there is no evidence to support this. General STD counseling should be done if concordance is identified, as well as counseling regarding risk of transmission of herpes in future or concurrent partnerships, perinatal transmission of herpes after acquisition in late pregnancy, and acquisition of HIV.

On the basis of these findings, the committee determined that screening is likely to be beneficial for patients in partnerships or considering partnerships with HSV-2–infected people and should generally be offered (recommendation B in table 2).

Pregnant women. The incidence of neonatal herpes in the United States ranges from 11 to 33 cases per 100,000 persons [49–51]. It is often a devastating disease, with >50% of affected infants having moderate or severe neurological impairment and with a 20% overall mortality rate [52]. Approximately 90% of all neonatal herpesvirus infections are transmitted during delivery, and HSV-2 is implicated in more than one-half (55%) of neonatal herpesvirus infections [53, 54]. More than 80% of infants with neonatal herpes are born to women without any history of symptomatic herpes during that pregnancy or at delivery [53]. The risk of neonatal HSV transmission is highest at delivery from women with a primary infection so close to term that antibodies have not yet developed (30%–50%) and lowest from women with an established genital herpesvirus infection for which protective antibodies already exist (<0.04%) [52, 55–57].

The natural history of women at risk for neonatal transmission of herpes was provided by a prospective study by Brown et al. [55] of 7046 pregnant women who were seronegative for either HSV-1 or HSV-2 who were observed through delivery. Ninety-four women who were infected with herpesvirus during their pregnancy had seroconversion (i.e., developed antibodies) before delivery; none of them delivered infected infants. Nine women were infected so close to labor that they were still seronegative for antibodies to herpesvirus at delivery; 4 of them delivered infants with neonatal herpes. This study illustrated the low risk of transmission once antibodies develop and the high morbidity of perinatal primary HSV infections. Of note, HSV-1 was responsible for one-half of the neonatal HSV infections in this study. HSV-1 appears to be more virulent to neonates than is HSV-2, and maternal HSV-1 antibodies do not appear to be as protective [54].

Serological screening programs for herpes in pregnant women designed to target women at highest risk of vertical transmission would need to identify HSV-2–negative women at risk of acquiring herpes late in pregnancy. Evidence suggests that the women with highest-risk pregnancies may be the least likely to receive a prenatal HSV screening; 5 of 9 women with primary HSV infection at delivery studied by Brown et al. [55] received no prenatal care or prenatal care at an outside facility. Screening of partners may also be difficult: >45% of husbands of pregnant women in a middle- to upper-class private practice obstetrical community refused HSV serological testing [58]. Possible interventions once a pregnant patient is identified at risk for HSV-2 infection are counseling regarding risk reduction, consistent correct condom use, abstinence, or antiviral therapy for the HSV-2–infected sex partner(s).

Although condoms decrease transmission of genital herpes from men to women if used regularly [32], behavior change in discordant couples is particularly difficult to achieve [32, 48]. In a prospective study that examined the risk of herpes seroconversion in uninfected pregnant women with HSV-2 antibody–positive husbands, the majority of discordant couples did not adopt safer-sex practices [58]. Despite education to abstain from sex or use condoms to prevent maternal acquisition of HSV-2, one-half of the 18 couples reported having sex a mean of 5.5 times per month and never using condoms. Discordant pregnant couples who did use condoms had a lower risk for seroconversion than did those who had unprotected sex (relative risk reduction, 45%) [58].

The effectiveness of treating partners with suppressive therapy for herpes to prevent transmission of herpes to susceptible pregnant women has not been evaluated. However, because daily suppressive therapy has been shown to reduce rates of transmission in discordant couples, an appealing management strategy to reduce the risk of maternal acquisition of herpes near term is suppressive therapy for the male partner, paired with regular condom use [35].

Serological screening in pregnancy would also identify asymptomatic HSV-2–infected women at low risk of virus transmission at delivery. Historically, these women were targeted for delivery by cesarean section when signs or symptoms of recurrence were present at labor, thereby bypassing the vaginal canal and preventing vertical transmission. Although this remains the current standard of care [10], no firm data support this strategy. In a recent study by Brown et al. [54], cesarean section appeared to be protective against neonatal herpesvirus infection in the univariate analysis but showed no benefit in the multivariate analysis. Surveillance data show that 20%–30% of infected infants are born by cesarean section, with 8% of infected infants born to women with intact membranes [53, 59]. Additional evidence by Prober et al. [56] demonstrated that infants born to mothers with recurrent herpes have high protective neutralizing antibodies to HSV-2 and low risk of acquiring herpes; 0 of 34 infants exposed to vaginal HSV-2 developed herpesvirus infections. In a cost-effectiveness analysis of maternal and neonatal outcomes associated with cesarean section in women with recurrent herpes, assuming a 1% vertical transmission rate, >1580 excess cesarean sections would be done to prevent 1 severe neonatal HSV-2 infection and 0.57 maternal deaths caused for every neonatal death prevented [57].

The use of antiviral suppressive therapy by women with recurrent herpes has not been shown to affect the incidence of neonatal herpes. Because the incidence of neonatal herpes is so low in this population, it is difficult to evaluate adequately this intervention's effectiveness. Two small, randomized, con-

trolled trials have shown that acyclovir treatment late in pregnancy reduces the frequency of cesarean sections among women with recurrent genital herpes by diminishing the frequency of clinical recurrences at term [60, 61]. Acyclovir's safety in pregnancy has not been well established [5], although no adverse fetal outcomes have been reported to the acyclovir registry [62]. The routine use of acyclovir in pregnancy is still not recommended [10].

A potential consequence of universal screening of asymptomatic pregnant women would be the identification of asymptomatic HSV-2–infected women without any clear need for intervention. There is no indication for suppressive therapy for asymptomatic pregnant women with HSV-2 antibodies. Additionally, women identified as theoretically at risk for neonatal transmission may then be at risk for unnecessary prophylactic cesarean deliveries. Marrazzo et al. [63] found that women with a known history of herpes who were asymptomatic during pregnancy were 20% more likely to have a delivery by cesarean section than were pregnant women without herpes in hospitals at which cesarean section rates were >20%, although results were not statistically significant.

A cost-effectiveness analysis of screening for HSV-2 infection in pregnancy to prevent neonatal herpes estimated that the cost to prevent 1 case of moderate to severe neonatal herpes ranged from $891,000 to $4 million. The authors concluded that screening from a public health perspective was ill advised [64].

On the basis of these findings, the committee determined that universal screening would not be useful to pregnant women and should generally not be offered (recommendation D in table 2). Asymptomatic pregnant women whose partners have known genital HSV-2 infection, as well as HIV-positive pregnant women, should generally be offered type-specific serological testing.

CONCLUSIONS

To our knowledge, these recommendations represent the first evidence-based rationale for the use of selective HSV-2 serological testing. These are the first to review critically the existing literature on HSV-2 prevalence, morbidity, detection, treatment, and prevention to better understand the impact of screening for this potentially stigmatizing, incurable viral STD on patients, their partners, and the community.

Strong evidence exists that HSV-2 infection is highly prevalent in sexually active populations, is responsible for severe neonatal morbidity, and is related to and may be a cofactor for HIV acquisition and transmission. Targeted HSV-2 screening will have individual and public health benefits if used in conjunction with proven interventions, such as risk-reduction counseling and antiviral suppressive therapy. Highly motivated patients at risk for STDs and HIV infection, HIV-infected patients, and patients with HSV-2–infected partners will likely benefit most from the determination of their serostatus. There is less evidence that screening of all pregnant women will be beneficial to the individual patient, the newborn, or the community, and it may be potentially harmful. HSV-2 serological tests, in conjunction with culture or direct antigen detection, can be useful in the diagnosis of symptomatic genital disease.

The committee concurs with the CDC that education about herpes and its prevention and counseling regarding transmission is necessary for all people being tested or screened for HSV-2 infection [5]. Ideally, both pre- and posttest counseling should be done. In pretest counseling, the provider can determine the patient's preparedness for the diagnosis of a chronic infection and motivation to reduce sexual risk behavior if HSV-2 infection is diagnosed. Posttest counseling can provide support and reassurance to patients with positive test results and can educate them about the natural history of the disease and its transmissibility. Those identified as uninfected with HSV-2 can be informed about preventing future acquisition of herpes and other STDs.

These recommendations are based on the strength of existing evidence and expert opinion. There are many important gaps in the evidence. No studies have directly assessed the impact of HSV-2 serological screening in the populations discussed. Studies are needed that demonstrate the efficacy of interventions, including herpes-specific risk-reduction counseling and herpes antiviral suppression therapy, in preventing transmission of HIV and HSV. Although the efficacy of suppressive therapy for herpes to prevent HSV-2 transmission has been demonstrated, real-world effectiveness should be assessed. The paucity of research concerning HSV-1 should be corrected by examining the impact of genital HSV-1 in HIV infection and neonatal herpes and the efficacy of antiviral suppression for HSV-1.

The targeted use of HSV-2 serological tests for specific diagnostic situations and selected populations should benefit patients, providers, and the community. Patients at highest risk for acquiring and transmitting genital herpes can be identified so that providers and public health departments can direct limited resources to the patients who will benefit the most.

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