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Management of Herpes in Pregnancy

This Practice Bulletin was developed by the ACOG Committee on Practice Bulletins—Obstetrics with the assistance of Lisa Hollier, MD. The information is designed to aid practitioners in making decisions about appropriate obstetric and gynecologic care. These guidelines should not be construed as dictating an exclusive course of treatment or procedure. Variations in practice may be warranted based on the needs of the individual patient, resources, and limitations unique to the institution or type of practice.



Genital herpes simplex virus (HSV) infection during pregnancy poses a risk to the developing fetus and newborn. Genital herpes infection occurs in one in five women in the United States. Because many women of childbearing age are infected or are becoming infected with HSV, the risk of maternal transmission of this virus to the fetus or newborn is a major health concern. The purpose of this document is to outline the spectrum of maternal and neonatal infection, including risks of transmission, and provide management guidelines supported by appropriately conducted outcome-based research. Additional guidelines based on consensus and expert opinion also are presented to permit a review of most clinical aspects of HSV.

Background

Etiology

Herpes simplex virus is a double-stranded DNA virus that can be differentiated into HSV type 1 (HSV-1) and HSV type 2 (HSV-2) based on the glycoproteins in the lipid bilayer envelope. Glycoprotein G2 is associated with HSV-2, and glycoprotein G1 is associated with HSV-1. Herpes simplex virus type 1 is the primary etiologic agent of herpes labialis, gingivostomatitis, and keratoconjunctivitis. Most genital infections with HSV are caused by HSV-2, but genital HSV-1 infections are becoming increasingly common, particularly among adolescent and young women (1).

Herpes simplex virus is transmitted from person to person through direct contact. Infection is initiated when the virus contacts mucosa or abraded skin. The incubation period after acquisition of HSV-1 or HSV-2 ranges from 2 days to 12 days. Herpes simplex virus then replicates in the epidermis and dermis, with resulting cellular destruction and inflammation. During the initial infection, the virus gains access to the sensory neurons, and then the infection becomes latent

in the sensory ganglia. Reactivation of viral replication occurs and may manifest clinically as recurrent ulcerative lesions or subclinically as asymptomatic viral shedding. Both the cellular and humoral immune systems play an important role in controlling this viral infection (2).

Herpes virus has a characteristic protein coat, and each of the viral types has identifiable proteins. Type-specific antibodies to the viral proteins develop within the first several weeks of infection and persist. Antibodies to HSV can be detected by most assays within 2–3 weeks after infection with the virus (3).

Genital infection with HSV is a primary infection when HSV-1 or HSV-2 is detected in individuals with no evidence of antibodies to either viral type in the serum. An outbreak is considered a nonprimary first episode when one viral type is detected in an individual with serologic evidence of past infection with the other viral type. Recurrent episodes are characterized by isolation of HSV-1 or HSV-2 in the presence of antibodies of the same serotype.

Incidence

Herpes simplex virus infection of the genital tract is one of the most common sexually transmitted infections. The true incidence of genital HSV infection is not known because it is not a reportable disease. It is estimated that approximately 45 million adolescent and adult Americans have been infected with HSV-2 (4). In a large, national serologic study, it was found that approximately 26% of women had serologic evidence of HSV-2 infection (4). It should be emphasized that serologic studies of HSV-2 underestimate the prevalence of genital herpes because HSV-1 also causes genital disease.

Most individuals who are infected with HSV are unaware that they have contracted the virus. Only approximately 5–15% of infected individuals report recognition of their infection (4, 5). The increasing burden of infection has important implications for health care providers. The number of initial visits to physicians' offices as a result of genital HSV infection increased from approximately 75,000 per year in 1978 to nearly 270,000 per year in 2004 (6). Risk factors for HSV infection include female gender, duration of sexual activity, minority ethnicity, previous genital infection, family income, and number of sex partners (4, 7).

Whereas HSV-2 is virtually always a genital pathogen, HSV-1 is increasingly recognized as the etiologic agent of genital herpes infection. Up to 80% of new genital infections among all women may be caused by HSV-1 (8, 9). This increase in initial infections with HSV-1 is particularly pronounced in the adolescent and young adult populations. In these populations, genital infection with HSV-1 may have surpassed new genital infection with HSV-2 (1).

Among women with serologic test results that indicate susceptibility to HSV infection, the incidence of new HSV-1 or HSV-2 infection during pregnancy is approximately 2% (10). Approximately 10% of women who are HSV-2 seronegative have partners who are seropositive and are at risk for transmission of HSV-2 during the pregnancy (11). Consistent with nonpregnant patients, most new infections in pregnant patients are asymptomatic (10). The timing of infection is relatively evenly distributed, with approximately one third of women becoming infected in each trimester (10). Among women with recurrent genital HSV, approximately 75% can expect at least one recurrence during pregnancy, and approximately 14% of patients will have prodromal symptoms or clinical recurrence at delivery (12, 13).

Neonatal herpes usually is acquired during the intrapartum period through exposure to the virus in the genital tract, although in utero and postnatal infections are rare but can occur. Approximately 80% of infected infants are born to mothers with no reported history of HSV infection (14). Although the actual incidence is unknown because neonatal herpes infection is not a reportable disease, estimates suggest that approximately 1,200–1,500 cases occur each year in the United States (15). Approximately one third to one half of cases of neonatal herpes are caused by HSV-1 (15, 16). Neonatal HSV infections can be classified as disseminated disease (25%); central nervous system disease (30%); and disease limited to the skin, eyes, or mouth (45%) (14). Mortality has decreased substantially over the past two decades, decreasing to 30% for disseminated disease and 4% for central nervous system disease. Approximately 20% of survivors of neonatal herpes have long-term neurologic sequelae (17).

Clinical Considerations and Recommendations

► *How can the diagnosis of herpes simplex virus be established?*

All suspected herpes virus infections should be confirmed through viral or serological testing. A diagnosis of genital herpes based on the clinical presentation alone has a sensitivity of 40% and specificity of 99% and a false-positive rate of 20% (18). The tests used to confirm the presence of HSV infection can be divided into two basic groups: 1) viral detection techniques and 2) antibody detection techniques. Primary viral DNA testing techniques are viral culture and HSV antigen detection by polymerase chain reaction (PCR). The antibody detection techniques include the use of both laboratory-based

and point-of-care serologic tests to detect the presence of antibodies to either HSV-1 or HSV-2. With viral detection techniques, negative results do not rule out the presence of infection. The diagnosis of HSV should be confirmed either serologically or with viral culture.

Isolation of HSV in cell culture is the preferred virologic test for patients who seek medical treatment for genital ulcers or other mucocutaneous lesions and allows differentiation of the type of virus (HSV-1 versus HSV-2) (18). The sensitivity of this test is limited because of several issues related to sampling and transportation of the specimen (19). Primary lesions are more likely than recurrent lesions to yield positive cultures (80% versus 40% of patients, respectively) (20, 21). Additionally, as the lesions heal, they are less likely to be culture positive (21). Thus, a positive genital culture provides conclusive evidence of genital HSV infection; however, a negative result does not exclude the presence of infection. When a genital specimen is collected for HSV culture, the vesicles should be unroofed, if present, and vesicular fluid should be collected.

Polymerase chain reaction techniques involve the amplification of particular sequences of DNA or RNA before detection and can thus detect evidence of viral DNA at low concentrations. Because of the increased sensitivity of PCR, unroofing vesicles is unnecessary. In one very large study, PCR results were three to five times more likely to be positive than were cultures (19). Cultures were more likely to be positive at increasing concentrations of virus, as demonstrated by a linear relationship between the proportion of positive cultures and copy numbers of HSV DNA in samples. Polymerase chain reaction techniques are commercially available and can differentiate between HSV-1 and HSV-2. Polymerase chain reaction provides increased sensitivity over culture (19, 20, 22) and may ultimately replace culture as the standard of care for diagnosis. Presently, however, there are no interlaboratory standards that ensure that identical specimens processed in different laboratories will yield identical results. Additionally, the PCR tests are not U.S. Food and Drug Administration (FDA) approved for clinical testing of genital specimens (18).

For patients who do not present with active lesions or whose lesions have negative culture or PCR test results, accurate type-specific serologic assays that accurately distinguish between HSV-1 and HSV-2 antibodies are now commercially available. Currently, there are several FDA-approved type-specific tests, and others are under development (see box). The sensitivity of these assays varies from 93–100% and specificity from 93–98% (23). The predictive value of a positive test result is influenced by the prevalence of the disease in

U.S. Food and Drug Administration- Approved Type-Specific Tests

Laboratory-based assays

- HerpeSelect-1 and 2 ELISA IgG
- HerpeSelect 1 and 2 Immunoblot IgG
- Captia HSV-1 and 2 ELISA

Rapid tests (formerly known as the POCkit test)

- BiokitHSV-2 Rapid Test
- Sure-Vue HSV-2

the population tested. In a high-risk population, the positive predictive value for the ELISA test results was 80–94% (24, 25). Repeat testing, using a different type-specific assay, has been shown to increase the positive predictive value of a single test result, and this may be especially important in populations with low HSV prevalence (24).

Because HSV-2 is an uncommon cause of oral infection, detection of HSV-2 antibodies is virtually diagnostic of genital HSV infection (26). Conversely, detection of HSV-1 antibodies alone may represent orolabial infection or may be indicative of genital infection. Correlation with direct viral identification techniques and the patient's symptoms is important.

► ***How can primary herpes simplex virus infection be distinguished from a nonprimary first episode during pregnancy?***

It is not possible to distinguish primary from nonprimary herpes simplex virus infection on the basis of clinical findings alone (27). Diagnosis is based on the combination of positive viral detection and negative serologic test results or evidence of seroconversion.

A primary outbreak in the first trimester of pregnancy has been associated with neonatal chorioretinitis, microcephaly, and skin lesions in rare cases (28). Although HSV has been associated with an increased risk for spontaneous abortion, recent studies do not support such a risk (29).

► ***How should a primary outbreak be managed in pregnancy?***

At the time of the initial outbreak, antiviral treatment may be administered orally to pregnant women to reduce the duration and the severity of the symptoms as well as reduce the duration of viral shedding (Table 1) (30). In patients who have severe disease, oral treatment can be

Table 1. Recommended Doses of Antiviral Medications for Herpes in Pregnancy

Indication	Acyclovir	Valacyclovir
Primary or first-episode infection	400 mg orally, three times daily, for 7–10* days	1 g orally, twice daily, for 7–10* days
Symptomatic recurrent episode	400 mg orally, three times daily, for 5 days or 800 mg orally, twice daily, for 5 days	500 mg orally, twice daily, for 3 days or 1 g orally, daily, for 5 days
Daily suppression	400 mg orally, three times daily, from 36 weeks estimated gestational age until delivery	500 mg orally, twice daily, from 36 weeks estimated gestational age until delivery
Severe or disseminated disease	5–10 mg/kg, intravenously, every 8 hours for 2–7 days, then oral therapy for primary infection to complete 10 days	

*Treatment may be extended if healing is incomplete after 10 days.

Adapted from Sexually transmitted diseases treatment guidelines, 2006 [published erratum appears in MMWR Recomm Rep 2006;55:997]. Centers for Disease Control and Prevention. MMWR Recomm Rep 2006;55(RR-11):1–94.

extended for more than 10 days if lesions are incompletely healed at that time (18).

Acyclovir may be administered intravenously to pregnant women with severe genital HSV infection or with disseminated herpetic infections. Case reports have associated significant improvement in expected survival with acyclovir treatment in cases of pregnant women with disseminated HSV, herpes pneumonitis, herpes hepatitis, and herpes encephalitis (31–33).

Primary genital herpes infection during pregnancy constitutes a higher risk for perinatal transmission than does recurrent infection. The risk of vertical transmission to the neonate when a primary outbreak occurs at the time of delivery is approximately 30–60% (10, 15). Several factors likely contribute to the increased risk. First, when women have acquired infection near the time of delivery, there is likely reduced transplacental passage of protective HSV-2 specific antibodies. Higher titers of neutralizing antibodies in the neonate have been associated with a reduced risk of neonatal infection (34). Second, neonatal exposure to the virus in the genital tract may be increased. The genital viral shedding in women with primary infection is of higher concentration and longer duration than shedding that occurs with recurrent episodes. Women with primary herpes that is untreated have a mean duration of viral shedding of 15 days (30). In addition, cervical shedding was detected by viral culture in 90% of women with primary infection (30).

Data regarding interventions to reduce vertical transmission in the specific setting of primary herpes are limited. One randomized trial of acyclovir versus placebo given from 36 weeks of gestation until delivery to women with their first episode of genital herpes infection during pregnancy found a significant reduction in clinical recurrences at delivery (35). The number of cesarean

deliveries for clinical herpes recurrences was reduced; however, the total number of cesarean deliveries in the treatment and placebo groups was similar. The number of deliveries was insufficient to evaluate efficacy of antiviral treatment to prevent neonatal herpes. Evidence of the effectiveness of cesarean delivery before labor for the prevention of vertical transmission is lacking.

► *How should recurrent herpes simplex virus infection in pregnant women be managed?*

All women should be asked early in pregnancy about symptoms of genital herpes, including prodromal symptoms. Women with a history of herpes should be examined for external herpetic lesions when they present for evaluation in labor and delivery (6).

Among women with recurrent lesions at the time of delivery, the rate of transmission with a vaginal delivery is only 3% (36). For women with a history of recurrent disease and no visible lesions at delivery, the transmission risk has been estimated to be 2/10,000 (15, 36). The low risk is in part attributed to the presence and transplacental passage of antiherpes antibodies (15, 34, 36). Cesarean delivery is not indicated in women with a history of HSV in the absence of active genital lesions or prodromes.

The efficacy of suppressive therapy during pregnancy to prevent recurrences near term has been evaluated in numerous studies (13, 35, 37–41). Because many of the individual trials were small, a recent systematic review of randomized controlled trials was performed to assess the effectiveness of acyclovir suppression therapy given to prevent a clinical recurrence at delivery, cesarean delivery for recurrent genital herpes, and the detection of HSV at delivery (42). The risk of recurrence at

delivery was reduced by 75%, and the rate of cesarean delivery for recurrent genital herpes was reduced by 40% for women who received suppression therapy after 36 weeks of gestation. Viral detection at delivery using culture or PCR was reduced by 90% among treated women, but shedding was not completely eliminated (in one trial, virus was detected in one woman receiving acyclovir) (13). There were no cases of neonatal herpes in any of the studies. Several trials demonstrating similar efficacy of valacyclovir have been published since the meta-analysis (12, 43). Women with active recurrent genital herpes should be offered suppressive viral therapy at or beyond 36 weeks of gestation. The doses of antiviral medication used in the randomized trials in pregnancy are higher than the corresponding doses in nonpregnant women. (Table 1.) Although neutropenia is a recognized, transient complication of acyclovir treatment of neonatal HSV infection, it has not been reported following maternal suppressive therapy (17). The acyclovir concentrations at which neutropenia occurred were approximately 5–30 times higher than were observed in umbilical vein plasma in a pharmacokinetic study of valacyclovir in pregnancy (44).

► ***What medications are available for treatment of herpes simplex virus infection during pregnancy?***

There are three antiviral agents that are commonly used to treat HSV infections. Acyclovir, famciclovir, and valacyclovir are all FDA pregnancy category B medications. These drugs are all approved for the treatment of primary genital herpes, the treatment of episodes of recurrent disease, and the daily treatment for suppression of outbreaks of recurrent genital herpes.

Acyclovir is a nucleoside analogue that enters virally infected cells and acts specifically to inhibit the viral thymidine kinase and, thus, DNA replication. The bioavailability of oral acyclovir is approximately 20%, which necessitates more frequent dosage intervals (45). Valacyclovir is a prodrug of acyclovir and is rapidly converted to acyclovir after metabolism in the liver. The bioavailability of acyclovir after doses with valacyclovir is approximately 54% (46). This is three to five times higher than achieved with oral acyclovir and, at a dose of 1 gm, approximates levels achieved with intravenous doses of acyclovir. The pharmacokinetics of both drugs have been evaluated in pregnancy. After doses of acyclovir and valacyclovir, there was evidence of acyclovir concentration in the amniotic fluid but no evidence of preferential fetal drug accumulation (44, 47). Famciclovir also is a prodrug that is rapidly transformed into penciclovir in the body. The bioavailability of the

active drug from an oral dose is approximately 77%, so the dosage interval is less frequent than with acyclovir (48). There are no published data on the use of famciclovir in pregnancy.

Development of viral resistance to acyclovir has not been a problem in immunocompetent patients. In two large, laboratory-based studies, a very low prevalence of acyclovir resistance in viruses isolated from immunocompetent patients has been estimated (0.3–0.6%), whereas acyclovir-resistant HSV infections occur more commonly among patients who are immunocompromised (6–7%) (49, 50).

There are no documented increases in adverse fetal effects because of medication exposure (39, 50, 51). The manufacturer of acyclovir and valacyclovir, in cooperation with the Centers for Disease Control and Prevention, maintained a registry for exposure to these drugs during pregnancy through 1999. More than 700 infants reported were exposed to acyclovir during the first trimester, and there was no increase in adverse fetal or neonatal effects, although the safety has not been definitely established (18). There are insufficient data on valacyclovir and famciclovir exposure in the pregnancy registry for analyses (52). Topical therapy offers limited benefit and should be discouraged.

► ***Is there a role for routine screening for genital herpes during pregnancy or at delivery?***

In the past, screening referred to the use of a viral detection method, most commonly culture, to assess whether viral shedding was present. Asymptomatic shedding during the antepartum period does not predict asymptomatic shedding at delivery (53, 54). Thus, routine antepartum genital HSV cultures in asymptomatic patients with recurrent disease are not recommended.

With the advent of serologic tests that can reliably detect disease in asymptomatic patients, screening now refers to the detection of HSV infection. Maternal HSV screening has been proposed to reduce neonatal herpes by identifying women infected (seropositive) with genital herpes and offering suppressive antiviral therapy near term. It also may identify susceptible women (seronegative) whose partners could be offered screening, allowing for counseling of at-risk couples about strategies to reduce the possibility of new maternal infection during pregnancy. Several analyses have evaluated the cost-effectiveness of various screening protocols for pregnant patients to reduce the incidence of neonatal HSV infection (55–59). The results from these analyses are highly variable—estimates of the cost to prevent one case of neonatal herpes range from \$200,000 to \$4,000,000.

A number of factors influence these cost estimates, including the costs of testing and counseling, effectiveness of antiviral therapy, the probability of lesions or shedding at delivery in asymptomatic women in whom HSV has been diagnosed only by the screening test, and the likelihood of neonatal herpes with vaginal delivery (54, 55). Currently, there is no evidence of cost-effectiveness of screening strategies from clinical trials or well-designed cohort studies in pregnancy. Whereas screening may be beneficial in particular populations or couples, routine HSV screening of pregnant women is not recommended.

▶ ***When should cesarean delivery be performed to prevent perinatal herpes simplex virus transmissions?***

Cesarean delivery is indicated in women with active genital lesions or prodromal symptoms, such as vulvar pain or burning at delivery, because these symptoms may indicate an impending outbreak. The incidence of neonatal disease is low when there is recurrent maternal disease, but cesarean delivery is recommended because of the potentially serious nature of the disease. In a large cohort study, women who had given birth by cesarean delivery were much less likely to transmit HSV infection to their infants (15). Among women with HSV detected at delivery, neonatal herpes occurred in 1.2% of infants delivered by cesarean delivery compared with 7.7% of infants delivered vaginally (15).

Cesarean delivery does not completely prevent vertical transmission to the neonate. Transmission has been documented in the setting of cesarean delivery performed before membrane rupture (14, 60). Cesarean delivery is not recommended for women with a history of HSV infection but no active genital disease during labor (61).

▶ ***Is cesarean delivery recommended for women with recurrent herpes simplex virus lesions on the back, thigh, or buttock?***

Cesarean delivery is not recommended for women with nongenital lesions. These lesions may be covered with an occlusive dressing, and the patient then can give birth vaginally. However, women with lesions elsewhere also may have cervical lesions and should be examined.

The risk of transmission among women with recurrent HSV at the time of labor is low, estimated to be less than 1% (18, 62). As with other women with recurrent herpes, the low risk is probably related to preexisting maternal type-specific antibodies. Thus, the risk of neonatal HSV associated with vaginal delivery in a woman with recurrent HSV and nongenital lesions would appear to be very low.

▶ ***In a patient with active herpes simplex virus genital infection and ruptured membranes, should cesarean delivery be performed to prevent perinatal transmission?***

In patients with active HSV infection and ruptured membranes at or near term, a cesarean delivery should be performed as soon as the necessary personnel and equipment can be readied. There is no evidence that there is a duration of rupture of membranes beyond which the fetus does not benefit from cesarean delivery (63). At any time after rupture of membranes, cesarean delivery is recommended.

▶ ***How should a woman with active herpes simplex virus and preterm premature rupture of membranes be managed?***

In a patient with preterm premature rupture of membranes and active HSV, the risks of prematurity should be weighed against the risk of neonatal HSV disease in considering expectant management. In pregnancies remote from term, especially in women with recurrent disease, there is increasing support for continuing the pregnancy to gain benefit from time and use of corticosteroids (64, 65). There is no consensus on the gestational age at which the risks of prematurity outweigh the risks of HSV. When expectant management is elected, treatment with an antiviral agent may be considered. The decision to use corticosteroids should be based on the balance between the risk of pulmonary immaturity and the risk of neonatal herpes.

▶ ***Are invasive procedures contraindicated in pregnant women with herpes simplex virus?***

In women with a history of recurrent HSV, transabdominal invasive procedures, such as chorionic villus sampling, amniocentesis, and percutaneous umbilical cord blood sampling, may be performed even when genital lesions are present. Because cervical shedding is associated with genital recurrences, it seems reasonable to delay transcervical procedures until lesions appear to have resolved.

Invasive monitoring, such as fetal scalp electrodes, is a risk factor for transmission of HSV, increasing the risk of neonatal infection approximately six times compared with externally monitored patients (15). However, if there are indications for fetal scalp monitoring, it is reasonable in a woman who has a history of recurrent HSV and no active lesions.

▶ ***Should women with active herpes simplex virus breastfeed or handle their infants?***

Unless there is a lesion on the breast, breastfeeding is not contraindicated. To prevent postnatal transmission,

mothers with herpetic lesions on any part of the body should be advised to take special consideration of hand-washing. Postnatally acquired disease can be as lethal as that acquired during delivery. Oropharyngeal or cutaneous lesions can be an effective source of virus for transmission to the newborn. Because the herpes virus is transmitted through direct contact (eg, hand-to-mouth), neonatal infection may be acquired from family members other than the mother and from sites other than the genital tract (66, 67). Most strains of HSV responsible for nosocomial neonatal disease are HSV-1 rather than HSV-2. Mothers with active lesions should use caution when handling their babies.

Valacyclovir appears to be safe for breastfeeding mothers. Although acyclovir was found in the breast milk in concentrations that were higher than the maternal serum, the amount of acyclovir in the breast milk was only 2% of that used for therapeutic doses in neonates (68).

Summary of Recommendations and Conclusions

The following recommendations and conclusions are based on limited or inconsistent scientific evidence (Level B):

- ▶ Women with active recurrent genital herpes should be offered suppressive viral therapy at or beyond 36 weeks of gestation.
- ▶ Cesarean delivery is indicated in women with active genital lesions or prodromal symptoms, such as vulvar pain or burning at delivery, because these symptoms may indicate an impending outbreak.

The following recommendations and conclusions are based primarily on consensus and expert opinion (Level C):

- ▶ In women with premature rupture of membranes, there is no consensus on the gestational age at which the risks of prematurity outweigh the risks of HSV.
- ▶ Cesarean delivery is not recommended for women with a history of HSV infection but no active genital disease during labor.
- ▶ Routine antepartum genital HSV cultures in asymptomatic patients with recurrent disease are not recommended.
- ▶ Routine HSV screening of pregnant women is not recommended

Proposed Performance Measure

The percentage of pregnant women who have been asked about their history of herpes

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The MEDLINE database, the Cochrane Library, and ACOG's own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1985 and October 2006. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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