

Original Article

# Prophylactic Valacyclovir to Prevent Outbreaks of Primary Herpes Gladiatorum at a 28-Day Wrestling Camp

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**SUMMARY:** Herpes gladiatorum (HG) plagues the sport of wrestling, especially in high school wrestlers and summer camps they attend. This study evaluated the usage of valacyclovir to prevent acquisition of primary HG, due to herpes simplex virus type 1 (HSV-1), in high school wrestlers at a 28-day wrestling camp. At the beginning and end of camp, IgM and IgG anti-HSV-1 antibodies were collected. Out of 332 male wrestlers, aged 13-20, who entered camp, 94 elected to participate in blood sampling. Sixty-four were on antiviral medication. Among the 94 wrestlers, 28 (29.8%) had positive IgG anti-HSV-1 titers. Of this group, 66 of 94, were HSV-1 IgG seronegative. At the end of camp, 55 of these original seronegative individuals elected to participate in blood sampling and none had detectable IgM anti-HSV-1 and -2 antibodies. Compared to previous years without antiviral usage, introducing prophylactic valacyclovir reduced clinical HG outbreaks by 87% at this 28-day wrestling camp. Due to the high prevalence of this virus in high school wrestlers, serological testing should be done at the beginning of each season. HSV-1 seropositive individuals should consider being on antiviral medication throughout the season to minimize the risk of transmitting the virus to other wrestlers.

## INTRODUCTION

Since 1989, several outbreaks of herpes gladiatorum (HG) have been documented at a 28-day wrestling camp in Minneapolis, Minnesota, USA (1,2). Each summer 300 male wrestlers, 13-18 years of age, participate in this intensive wrestling camp. Upon entering camp they are divided into wrestling groups based on weight, and for the duration of the camp they only wrestle campers within their own group. Each day the athletes take part in a 5-10 mile run and three 2-h wrestling sessions and conditioning drills. To prevent HG outbreaks, individuals with a history of recurrent herpes gladiatorum (RHG) are required to take suppressive antiviral medication, daily skin checks are routinely performed on all wrestlers to monitor outbreaks, and individuals with outbreaks are not permitted to participate in direct wrestling contact with other campers until considered non-infectious.

Even with this protocol, 15-20 outbreaks occur each camp session. Consideration of alternative means of prevention was prompted by an outbreak in 2001 in which 57 individuals contracted the virus (2). In 2002, the camp director took a different approach after reading an article by Kuzushima et al. (3) describing a 1992 outbreak of herpes stomatitis caused by herpes simplex virus type 1 (HSV-1), in which acyclovir was given prophylactically to exposed children in a daycare setting to prevent acquisition of virus once it had been detected.

Upon implementing this protocol at the 2002 wrestling camp, the occurrence of HG was reduced by 78% compared to that 3 years previously,  $P < 0.01$  (Figure 1). This served as the impetus to perform a prospective study using prophylactic valacyclovir to prevent outbreaks of primary HG at this 28-day wrestling camp.

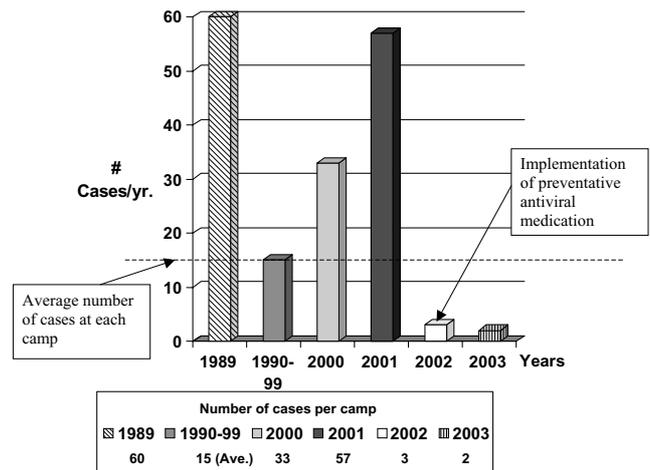


Fig. 1. Occurrence of HG at 28-day wrestling camp from 1989 to 2003. Comparison of HG developing in the camp, before and after introduction of antiviral medication usage in all participants. Comparison of 2002 to 1990-1999, showed a 78% reduction in cases ( $P < 0.01$ ). 2003 an 87% reduction ( $P < 0.01$ ). Calculations showed statistical significance using Fisher's exact test.

## METHODS

The study was a prospective evaluation of a protocol to control HSV outbreaks among participants at a Minnesota wrestling camp that started June 28, 2003 and ended July 25, 2003. The study protocol was approved by an Investigational Review Board affiliated with the University of Minnesota before the camp opened. Study activities that were not part of a routine monitoring protocol, such as phlebotomy for antibody screening, were voluntary and required written consent from the wrestlers and their guardians.

Information about the study was sent to all camp participants and their guardians before the camp began. Camp participants were asked to seek the advice of their health care provider, and if there was no contraindications, to initiate

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prophylactic therapy with valacyclovir 1 g per day to be started 1 week before entering camp. Physicians were at liberty to substitute other antivirals (such as famciclovir or acyclovir) for valacyclovir.

Before the camp began, the investigator contacted each guardian and wrestler to request permission to draw blood samples on the first and last days of camp for evaluation of serum IgM and IgG for anti-HSV titers. IgM antibody is a marker of acute HSV infection and can appear as early as 21 - 25 days after exposure (4). IgG antibody develops 6 - 8 weeks after a primary outbreak or exposure and serves as a marker of latent infection. Participants who were negative for anti-HSV antibodies were rechecked for IgM antibody at the end of camp. Antibody titers were analyzed at the Minnesota Public Health Department (Minneapolis, Minn., USA). Wrestlers and guardians were notified of these results 2 weeks after conclusion of the camp.

Certified athletic trainers performed skin checks on each camp participant daily before they engaged in any physical activities. To maintain consistency in care and expertise in evaluating skin lesions, the same trainers had been used over the past three camp seasons. Any wrestler with a presumed outbreak was evaluated by a physician, and vesicular fluid was cultured for HSV at Fairview University Hospital Laboratories, Minneapolis, Minn. Cultures positive for HSV were further subtyped for HSV-1 and -2 using monoclonal antibodies. Wrestlers were not permitted to participate in wrestling practice or competition for 120 h, in conformity with the guidelines established by the National Federation of State High School Association (NFHS).

## RESULTS

A total of 332 male wrestlers, aged 13-20 entered camp, and were assigned to one of 5 wrestling groups based on weight. Ninety-four of these wrestlers elected to participate in the study and allow blood draws to assess anti-HSV antibody titers (Table 1). When asked, all participants stated they were compliant with antiviral medication. Age distribution of this group accurately reflects that of the whole camp. Sixty-four of these wrestlers were on prophylactic therapy, with 58 (90.5%) on valacyclovir, 5 (7.9%) on acyclovir and 1 (1.6%) on famciclovir. The remaining 30 wrestlers had elected not to be on prophylactic antiviral therapy. Of the remaining 238 wrestlers who did not participate in blood sampling, 179 were on prophylactic antiviral medication. Among them, 96.7% were on oral valacyclovir 1 g per day.

Although only 11 wrestlers had a history of RHG, 28 of the camp participants who volunteered for assessment of anti-HSV antibody titers (28/94 = 29.8%) had positive IgG anti-HSV-1 titers. None of them had positive IgM titers. The remaining 66 volunteers had negative IgM and IgG anti-HSV titers. Six of the wrestlers who were positive for IgG

anti-HSV-1 antibody were also positive for IgG anti-HSV-2 antibody. No one was positive for IgM or IgG anti-HSV-2 antibody alone. Distribution was as follows (Table 1).

We observed three outbreaks considered likely to be HG. The first outbreak occurred on the 5th day of camp in an athlete with no known history of HG who was not on prophylactic antiviral medication. However, tests performed at camp entry showed the presence of anti-HSV-1 IgG antibodies in this individual. The lesion was cultured and was positive for HSV-1. Twenty-two other wrestlers in this weight group had participated in the antibody determination. Of these individuals, 13 were IgG-seronegative to HSV-1 and five were not on antiviral medication.

The second outbreak occurred with a camper in another group who also had no known history of HG, although he was compliant on his recommended dosing of valacyclovir. The outbreak occurred on Day 10 of camp, and surface cultures were positive for HSV-1. The wrestler had not participated in the initial blood draw testing for anti-HSV antibodies and refused them at this time. The lesions were localized in a smaller area on the forehead region, indicative of a possible recurrent outbreak. In this group, 18 wrestlers had participated in the initial antibody determination, and three of the 12 who were shown to be IgG-seronegative to HSV-1 were not on antiviral medication.

A third likely outbreak occurred on Day 19 of camp in an individual on prophylactic acyclovir. At the beginning of camp, this wrestler was seronegative for both HSV-1 and -2. Surface cultures from the questionable lesion were negative for both HSV-1 and -2, and follow-up tests performed 8 weeks after camp were negative for anti-HSV antibodies. In this group, 13 wrestlers had participated in the initial antibody determination and five of the 11 wrestlers who were shown to be IgG-seronegative to HSV-1 were not on antiviral medication. On Day 27 of camp, 55 of the 66 individuals who were HSV-1-seronegative at the beginning of camp elected to have a second blood draw. All 55 remained IgM-seronegative to both HSV-1 and -2. Only one wrestler elected to recheck blood titers for IgG antibody to HSV at a follow-up visit 2 months after camp, and test results were negative.

Due to the unique nature of this camp, fatigue and dehydration were common during the first 2 weeks. Several wrestlers in the study succumbed to these conditions, yet were evaluated in the clinic and found metabolically stable. They were able to continue with the camp and study. No adverse events were recorded due to the usage of antiviral medication.

Implementation of camp wide usage of antiviral medication showed a significant reduction in the number of outbreaks of HG. The 2003 camp had two diagnostically confirmed HG outbreaks, compared to an average of 15-20 seen in previous years, according to camp records, and a significant reduction compared to the 57 outbreaks seen in 2001 (Figure 1). Prophylactic treatment with 1 g daily of valacyclovir reduced HG outbreaks by 78% in 2002,  $P < 0.01$  and by 87% in 2003,  $P < 0.01$  (Figure 1). This was in contrast to the 15-20 average in each camp before the drug prophylaxis was implemented.

The health records of each wrestler were reviewed at camp entry and showed that 3.3% (11/332) of the participants entered the camp with a known history of RHG or herpes labialis. Anti-HSV antibody titers at camp initiation showed that 29.8% (28/94) of the participants between the ages of 13-18 were IgG-seropositive for HSV-1 and that 6.4% (6/94) were IgG-seropositive for HSV-2.

Table 1. Initial blood sampling measuring anti-HSV IgG ( $n = 94$ )

Age	Participants	HSV-1 (+)	HSV-2 (+)
13	2	0	0
14	7	3	1
15	20	4	2
16	37	12	2
17	25	7	1
18	3	2	0
Total	94	28 (29.8%)	6 (6.4%)

## DISCUSSION

Estimates of HSV-1 seroprevalence in non-wrestling males, in the age group of the wrestling camp participants, range from 25-31% (5). Although only 11 wrestlers in the camp ( $n = 332$ ) were aware that they were infected with HSV-1, 28 of 94 wrestlers (29.8%) in the group that underwent serology testing were positive for anti-HSV-1 IgG antibody.

In the non-wrestler, HSV-1 outbreaks typically occur around the oral-nasal region. By contrast, analysis of HSV outbreaks in a summer wrestling camp showed that greater than 70% of the outbreaks occurred on the face and periorbital region (2). An athlete with RHG may be at a greater risk for eye involvement, with infections potentially leading to corneal scarring or even retinal necrosis and blindness. Although such severe consequences are rare, HSV-1 infection is the leading cause of blindness from an infectious disease in the US (6,7).

Six individuals were seropositive for both anti-HSV-2 and anti-HSV-1 IgG antibodies. It has been reported that 3-6% of herpes labialis (8-11) is due to HSV-2. Herpes labialis or HG can be due to either virus, but due to this sport and location in the facial region favors HSV-1. The complicating factor for either type has both short and long term consequences. Sexual behavior patterns may be changing due to social pressure and media coverage of the HIV epidemic. Alternative forms of sexual pleasure maybe leading to increasing incidence of oral-genital contact, due to fear of HIV contraction and unprotected oral sex considered a low risk sexual activity (12). Recently HSV-1 has shown a dramatic increase in ano-genital herpes simplex outbreaks in females. Since socially privileged Western cultures have shown primary HSV-1 outbreaks to be acquired at a later age (13), first time acquisition could be at a time where reproduction is an issue. Consequences are well documented with primary genital HSV outbreaks where in the past 20 years it has led to increased incidence of neonatal herpes (14). With wrestlers and coaches who suffer from HG, the risk of transmission to a female partner and potential spread through oral sexual contact is not only a potential, but documented event. Combining that with the fact that HSV-2 genital herpes increases the risk of acquiring (15,16) and transmitting HIV-1 supports the issue of prevention and prophylaxis for HG.

With recurrent HSV-1 or -2 infections, viral shedding can occur in the absence of apparent clinical signs or symptoms (17) and infectious virus can then be transmitted by direct skin-to-skin contact. A prospective study of new HSV infections found that one-third of all newly acquired HSV-1 infections were asymptomatic (18). In a landmark study Corey et al. showed that suppressive therapy with valacyclovir was effective in reducing the transmission of HSV-2 in discordant couples (19). Suppressive antiviral therapies in HSV-1 seropositive individuals reduce the likelihood of RHG outbreaks (20) and could reduce asymptomatic shedding.

With respect to our second outbreak, it occurred in an individual who was on prophylactic dosing. Of interest is that he had no knowledge of acquiring this virus, yet it appeared as a smaller outbreak, cleared within 4-5 days while on valacyclovir and was representative of a recurrent process. While antiviral medication is not infallible in preventing RHG, the lesions did clear quickly. HSV-1 resistance does exist against acyclovir and valacyclovir, but this athlete had no risk factors for being immunosuppressed (21).

In light of this, our study does strengthen the point that

this virus is unknowingly present in a higher number of participants, 29.8% in this age group, than previously estimated by Becker et al. (22), 2.6%. With such a high prevalence of HSV-1 in this age group, means of decreasing asymptomatic sloughing would be very crucial yet has never been investigated in this activity. Animal models have shown valacyclovir to reduce HSV-1 shedding in a dose-dependent manner (23). In our study the use of prophylactic valacyclovir reduced clinical HG outbreaks by 87%, compared to previous years. We did not have sufficient data to evaluate whether or not the incidence of HSV acquisition was reduced. Exposure to the virus late in camp was a concern and would not be detected with anti-HSV-1 IgM antibodies drawn at its closure. Follow up blood analysis for this antibody was recommended to all 55 participants at 4-8 weeks post-camp, but only one followed through and had a negative IgM/IgG antibody to HSV-1.

For participants in the summer wrestling camp, whether or not to use prophylactic antiviral medication was a decision made by the wrestler, his parent or legal guardian, and his primary care provider. Reasons for choosing not to use prophylactic therapy included the following: (i) the recommended medication was not covered by the health insurance plan; (ii) the primary care provider was unfamiliar with the medication; (iii) the primary care provider was unaware that RHG is a problem in the sport of wrestling. These findings underscore the importance of educating primary care providers and wrestlers about HSV and disease etiology, treatment, and prevention.

Due to the seriousness of RHG in this sport and the risk of viral transmission, we recommend serology testing at the beginning of each wrestling season to confirm the seronegative status of wrestlers not already known to be infected. Individuals who are HSV-1 seropositive should be on suppressive antiviral medication throughout the wrestling season.

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