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Neonatal Herpes Simplex Infection and the Three Musketeers

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Metaphorically, the Three Musketeers can represent our defenses against viral pathogens. Actually, there were four Musketeers; the hero D'Artagnan was an add-on. In Dumas's novel, the Musketeers' motto, "one for all and all for one," indicated a synergistic approach. Our four antiviral defenses include specific and nonspecific antiviral therapy, passive immunization, and, finally, active immunization, represented by D'Artagnan. We do not have all these defenses for every pathogen. Although active and passive immunization and nonspecific treatment (vitamin A)¹ are available for measles, it would be better if a specific therapy existed, particularly now, when some parents are not vaccinating their children.² Some "Musketeers" are missing for other infections as well: passive immunization is lacking for influenza, and there is no immunization, passive or active, for HIV. All the defenses are available for varicella–zoster virus and many hepatitis viruses. With respect to herpes simplex virus (HSV), passive immunization was never developed, nor is there a vaccine that could be a D'Artagnan to take on this virus.³ Fortunately, there is highly developed specific antiviral therapy for HSV.⁴ In this issue of the *Journal*, Kimberlin and colleagues report an exciting advance in the treatment of babies with neonatal HSV, an unusual but devastating disease.⁵ Medical practice may be changed as a result of these studies.

Neonatal HSV is a dreaded infection that usually occurs in babies who are born to women with primary, asymptomatic HSV.⁶ It comes as a nasty surprise. Affected infants often present only with benign-appearing skin vesicles. Rapid antiviral therapy with parenteral acyclovir, usually for 2 to 3 weeks, is imperative. When the virus is confined to the skin, eye, and mouth at the time of diagnosis, the prognosis is excellent, although neurologic impairments develop in a small proportion of babies.⁷ Among babies with disseminated disease, 20% of survivors have serious neurologic sequelae; if the central nervous system (CNS) is involved, the rate is 70%.⁵ Recurrent skin lesions, from which the virus is transmissible, seem to be a less disconcerting sequel, but they have societal implications and reflect continued viral multiplication.⁵

The article by Kimberlin et al. describes patients enrolled in two studies from the Collaborative Antiviral Study Group of the National Institute of Allergy and Infectious Diseases. Infants who had proven neonatal HSV with CNS involvement or with skin, eye, and mouth involvement only were treated with parenteral acyclovir and were subsequently given either oral acyclovir or placebo three times a day for 6 months. They were evaluated for cognitive development, recurrent skin lesions, and toxic effects of the drug for 1 year. If

an infant had two skin recurrences, the randomly assigned study drug was discontinued, and the infant was given open-label acyclovir. Infants receiving acyclovir had significantly better neurologic outcomes and fewer cutaneous recurrences than did those receiving placebo. The toxic effects were minimal but included some transient neutropenia.

This study presents a practical approach to preventing further CNS damage and decreasing the transmission of HSV from infected babies after the initial treatment with parenteral acyclovir. The number of patients was small (74), and the study lasted 11 years. The statistical analysis was somewhat limited, not only by the loss of patients to follow-up but also by the fact that infants in the placebo group who had two recurrences were treated with open-label acyclovir. Nevertheless, among infants with CNS involvement who had a Bayley Scales of Infant Development assessment at the age of 1 year, mental-development scores (which range from 50 to 150, with a mean of 100 and with higher scores indicating better neurodevelopmental outcomes) were significantly higher in the 16 children who were randomly assigned to the acyclovir group than in the 12 who were randomly assigned to the placebo group (88.24 vs. 68.12, $P = 0.046$). No between-group differences were seen in the cohort of infants with skin, eye, and mouth disease only; they were unlikely to have CNS sequelae, and only 15 had a Bayley Scales of Infant Development mental-development assessment at 12 months.

Because skin recurrences are not related to disease classification, data from all 74 infants were combined for the analysis of the effects of acyclovir on skin recurrences. In this analysis, there was a significant difference between the acyclovir and placebo groups. When only the cohort with skin, eye, and mouth disease was considered, the between-group differences were nonsignificant, probably owing to the small numbers of patients in the cohort (29 in total: 15 randomly assigned to acyclovir and 14 randomly assigned to placebo). It might seem to be more compelling to treat survivors of neonatal HSV who have CNS involvement than to treat those who have skin, eye, and mouth disease only; however, given the limitations of the analysis and considering the potential risks and benefits, it makes sense to treat all survivors of neonatal HSV with oral acyclovir for 6 months. Risks such as toxic effects of the drug, viral resistance to acyclovir, and cost seem to be minimal. Clearly, if an infant's overall development can be improved with 6 months of oral therapy, the benefits are high, given that CNS damage cannot be repaired once it occurs. The prevention of skin lesions is also important. To ensure the best outcomes, attention should be paid to adherence to the medication and to follow-up.

Extended oral acyclovir therapy should improve the lives of babies who have survived neonatal HSV. It is hoped that specific antiviral therapy will be joined by the active immunization "Musketeer" to prevent maternal HSV infections. As with measles, even when there is a vaccine, we need effective specific antiviral therapy. HSV seems unlikely to disappear even with a vaccine. We too need synergy: "one for all and all for one."

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