

Should acyclovir be used to treat otherwise healthy children with varicella?

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The antiviral agent acyclovir has been used in the treatment of varicella-zoster infections in adults and immunocompromised persons. These groups are known to have a longer duration of disease and a higher incidence of complications. Acyclovir has been shown to decrease the severity of disease in these groups. Some research groups have postulated that acyclovir may be beneficial in treating varicella in otherwise healthy children. To investigate their hypothesis, this paper reviews the clinical course and complications of varicella and the extent to which they are affected by treatment with acyclovir. It was concluded that acyclovir does not result in a clinically significant reduction in the severity of varicella-zoster in otherwise healthy children. As such, it should not be used in the treatment of healthy children with varicella.

Chickenpox is a common contagious disease of childhood caused by primary infection with the varicella-zoster virus. The disease is characterized by a pruritic rash consisting of crops of papules, vesicles and pustules which eventually crust over.

Varicella has long been considered a benign, inevitable disease of childhood. The peak age of occurrence of the disease is five to ten years of age and 90% of children are infected by age 10(1). Complications of varicella are rare, and uneventful recovery is the rule; most cases resolve without treatment.

Varicella can, however, cause prolonged discomfort and serious complications in certain groups: neonates exposed shortly before birth (2,3), adults (1,4), and immunocompromised persons(5-9). Concern about fatal complications in these groups led to the development of a vaccine to prevent varicella and to the testing of antiviral agents in the hope of ameliorating varicella symptoms.

The antiviral drug, acyclovir, has been shown to be effective in the treatment of varicella in immunocompromised patients (10,11,12) and normal adults (13). Some research groups postulated that acy-

clovir may also be beneficial in treating varicella in otherwise healthy children. This paper will review the clinical course and complications of varicella and the extent to which they are affected by treatment with acyclovir.

PATHOGENESIS AND CLINICAL PRESENTATION

Varicella-zoster virus is a member of the herpes virus family. The virus is most likely transmitted by the respiratory route. It replicates in the nasopharynx and seeds the reticuloendothelial system, ultimately leading to viremia and the emergence of skin lesions. The incubation period of varicella is usually between 14 and 17 days.

Clinically, varicella presents as a pruritic rash, low-grade fever, and malaise. Prodromal symptoms (fever, malaise, anorexia) may precede the rash by one or two days. The skin lesions that subsequently appear consist of maculopapules, vesicles and scabs in varying stages of evolution. Successive crops of lesions appear over a two to four day period, at first involving the trunk and face but soon appearing on other areas of the body. There are usually between one and three hundred lesions, but as many as 2000 have been reported. The severity of the rash varies, as do systemic signs and fever, which generally abate after three to four days.

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The most common complication of chickenpox is varicella pneumonia. The complications that are seen with varicella do, however, vary with the age group investigated (Table 1). Among children younger than five, the most common complications seen are lower respiratory tract infections and bacterial infections of the pox lesions. Varicella encephalitis and Reye syndrome are the complications seen most often in children age five through fourteen. Among adolescents, encephalitis and varicella pneumonia are most common. The incidence of varicella pneumonia among adults far exceeds the incidence of any complication seen in the other age groups (4).

Less common complications of varicella include aseptic meningitis, Guillain-Barré syndrome, transverse myelitis, gastritis, appendicitis, glomerulonephritis, vi-

Table 1: Common serious complications among hospitalized varicella patients (adapted from Ref. 4).

Age (years)	Complications	Hospitalizations/ 100 000 Varicella cases
<5	bacterial skin infections	2.6
	Varicella pneumonia	11.3
5-9	Varicella encephalitis	0.9
	Reye syndrome	0.6
10-14	Reye syndrome	1.5
	Varicella encephalitis	0.9
15-19	Varicella encephalitis	2.9
	Varicella pneumonia	2.4
20+	Varicella pneumonia	26.7
	Varicella encephalitis	3.3

ral arthritis, coagulation defects, bullous lesions, and noninfectious gangrene (1, 4- 8, 14, 15).

Most complications of varicella occur only rarely in immunologically normal children but have a greater frequency in adults and immunocompromised children.

Varicella is much more likely to be severe in adults than in children. In persons over twenty-five years of age, the risk of developing a severe case of varicella is twenty-five times greater than the risk in young people (1). Their fever is higher and more prolonged, their constitutional symptoms are more severe, their rash is more profuse, and complications are more frequent. Varicella pneumonia is the most significant complication in adults and accounts for hospitalization in one in every 400 adult varicella cases (4). The estimated risk of death from varicella in adults in 0.031% (15).

Altered immunity, such as that associated with steroid therapy (6,8), radiation, cancer chemotherapy, malignancies (7,9) and AIDS (5) is also associated with a high risk of serious varicella infection. In a report involving sixty children receiving chemotherapy, Feldman

et al. (7) noted that the risk of varicella complications was 36% and the risk of death 7%. The estimated risk of death from varicella in normal children is 0.0014% (15).

ACYCLOVIR IN THE TREATMENT OF VARICELLA

The cost of varicella to society has been investigated in the United States. It is estimated that the mean number of hospitalizations due to varicella is approximately 4000 per year and that the number of physician office visits is 364 000 (4). Most of the costs associated with varicella are not even related to traditional medical costs, but rather to the costs associated with a sick child whose care at home may result in lost time from work (15). It has been estimated that the average number of school and work days lost due to varicella are 8.7 and 0.5 respectively (16).

There are many reports of successful treatment of varicella infections with the antiviral agent acyclovir. Most of these, however, pertain to treatment success in adults and immunocompromised children. Feder (13) describes a series of adults who, when treated with acyclovir within 24 hours of exanthem appearance, developed less than 200 vesicles and had mild cases of disease. This contrasts to patients who were treated 48 hours after appearance of exanthem, or who were not treated at all. These patients developed over 500 vesicles and more commonly experienced minor complications such as prolonged fever and localized secondary infections.

Balfour (10) , Balfour et al. (11) and Prober et al. (12) describe the course of varicella in immunocompromised children treated with acyclovir. All investigators concluded that acyclovir reduces the incidence rate of complications associated with varicella. As noted for adults treated with acyclovir, treatment failure occurs in children in whom treatment is started late (17).

Although adults and immunocompromised children are at significantly higher risk for serious complications from varicella, they account for few varicella-related events. It has been estimated that fewer than 0.1% of all varicella cases occur in immunocompromised patients (15) and fewer than 1.5% occur in adults (4).

Balfour et al. (18) and Dunkle et al. (19) researched the efficacy of acyclovir in healthy children. They claim their findings indicate that acyclovir is safe and effective in reducing the severity of chickenpox. Children treated with the drug within 24 hours of exanthem appearance had fewer varicella lesions, a shorter duration of formation of new lesions, and earlier initial healing of lesions. They also had reduced incidence and duration of fever and systemic symptoms. The clinical relevance of acyclovir treatment, however, remains debatable. As the incidence of varicella complications in otherwise healthy children is so low, the drug does not significantly reduce the number of com-

plications seen. As well, the drug results in only a one-day difference in the duration of fever and in the number of days to onset of cutaneous healing. From a financial point of view, the cost of the drug (\$50- \$80 for a five day course) may not be offset by the decrease in the number of workdays missed by parents caring for their sick children.

Both the Canadian Pediatric Society (20) and the American Academy of Pediatrics (21) do not recommend acyclovir therapy for the routine treatment of uncomplicated varicella in otherwise healthy children. This recommendation is based on the low risk of severe and complicated varicella in immunocompetent children, the marginal therapeutic effect of acyclovir, its cost, and the feasibility of drug delivery in the first 24 hours of illness.

The American Academy of Pediatrics states that it will not recommend the use of acyclovir in uncomplicated varicella due to "the currently unknown and unforeseen possible dangers of treating as many as 4 million children each year" (21). Several cases of resistance to acyclovir have been described in the literature. At least five patients with HIV who received chronic acyclovir therapy for suppression of recurrent varicella-zoster infection developed persistent disseminated hyperkeratotic papules that failed to heal with IV or high-dose oral acyclovir therapy. Varicella-zoster virus resistant to acyclovir in vitro was isolated from skin lesions of all of these patients (22,23). Although no cases of acyclovir resistance have been documented with short course therapy, treatment of millions of children may induce this phenomenon.

There is no question that acyclovir should be used in the treatment of varicella in adults and immunocompromised children. Its benefits for otherwise healthy children are small however. Thus, at the present time, acyclovir should not be used in the treatment of healthy children with varicella.

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