

Pediatric Pharmacotherapy

A Monthly Newsletter for Health Care Professionals
Children's Medical Center at the University of Virginia

Volume 3 Number 10

October 1997

Prevention and Treatment of Respiratory Syncytial Virus The Search for a Cost-Effective Strategy Marcia L. Buck, Pharm.D.

Respiratory syncytial virus (RSV) is one of the most common viral pathogens known to man. Nearly all children have been infected by the age of two years. Infection with RSV typically results in symptoms associated with a common cold. However, RSV may be a significant cause of morbidity and mortality in infants with underlying respiratory or cardiovascular disease, premature infants, immunocompromised patients, and the elderly. There are more than 90,000 annual hospitalizations in children for RSV lower respiratory tract infection.^{1,2}

Two therapies for RSV are available in the United States. Ribavirin (Virazole®; ICN Pharmaceuticals) was approved in 1986 as a treatment for patients with RSV. Respiratory syncytial virus immune globulin (RespiGam®; MedImmune, Inc.) was released in 1996 for prophylaxis against RSV infections in susceptible patients. This newsletter will briefly review these therapies and the controversies surrounding their use.

Ribavirin

Ribavirin, a synthetic nucleoside analog resembling guanosine, has antiviral activity against RSV as well as influenza, parainfluenza, adenovirus, and herpes simplex viruses. Although its exact mechanism of action remains unknown, ribavirin appears to interfere with messenger RNA expression, resulting in inhibition of viral protein synthesis. Ribavirin is administered by inhalation using a special small particle generator (SPAG-2). The standard treatment regimen is to administer an aerosol solution of 20 mg/ml over a 12 to 18 hour period for three to seven days via tent, oxygen mask, hood, or through a ventilator circuit.^{3,4} An alternative method using a more concentrated solution of 60 mg/ml administered over a two

hour period three times daily provides similar results without requiring constant exposure to the medication.^{5,6}

The effectiveness of ribavirin treatment remains controversial. Initial studies demonstrated significant benefit with ribavirin use as measured by improvement in arterial blood oxygenation, pulmonary function testing, and clinical assessment scores. In some of the trials, ribavirin use was also associated with a reduction in the need for mechanical ventilation and a decreased length of stay in the intensive care unit.^{3-5,7,8}

Adverse effects during these clinical trials were relatively rare and consisted of bronchospasm, rash, conjunctivitis, and reticulocytosis. A serious problem, however, was also discovered. In patients on mechanical ventilation, ribavirin particles were being deposited into the equipment, or "raining out," resulting in ventilator malfunction. This problem has been remedied by the use of one-way inspiratory valves and more frequent suctioning and filter changes in the ventilatory circuit.⁹

Based on these trials, the American Academy of Pediatrics (AAP) issued recommendations for ribavirin use in 1993.¹⁰ These guidelines recommended the use of ribavirin in all patients requiring mechanical ventilation for RSV infection and in infants with complicating factors placing them at high risk for severe disease, including underlying cardiovascular or pulmonary disease.

The results from some of the initial studies upon which the guidelines were based have been subsequently questioned.¹¹ Most relied only on short term outcome measures and several did not have adequate controls. In addition, the use of water as a placebo has been questioned.

Inhalation of water, while useful for maintaining blinding of the investigators, may induce bronchospasm and worsen clinical scores. Studies using a water “placebo” may have, in fact, biased the results to show improvement in the ribavirin treatment group.

More recent studies have failed to demonstrate a significant improvement in patients treated with ribavirin.¹²⁻¹⁴ In a retrospective review of patients at two hospitals, Wheeler¹² and colleagues found that measurement of long-term outcomes, such as length of hospital stay, number of days receiving oxygen therapy, and the need for mechanical ventilation were no different in ribavirin-treated patients than in infants treated with appropriate supportive care. Meert¹³ and colleagues found similar results in a prospective study comparing ribavirin versus a saline placebo.

An additional concern identified during this period was the potential for ribavirin-induced teratogenicity. In several of the animal species studied, ribavirin demonstrated teratogenic or embryocidal characteristics. Studies in primates, however, have found no teratogenicity. The risk to humans is not known; but to date, there have been no reports of birth defects of infants exposed to ribavirin *in utero*. It is still recommended that pregnant health care providers or family members not be involved in the direct care of patients during ribavirin treatment or in medication preparation.¹⁰

As a result of these concerns and the high cost of treatment, subsequent revision in 1996 of the AAP recommendations for ribavirin use replaced the phrase “should be used” to “may be considered” in those populations previously described.¹¹

The final decision on the role of ribavirin in infants with RSV is yet to be made. Retrospective data from the manufacturer suggests that ribavirin use may reduce the severity of subsequent RSV exposure and the incidence of wheezing in the months following administration. Large scale, prospective studies are needed to clarify the long-term benefits of treatment.

Ribavirin is also being studied in other patient populations at risk for severe disease. Investigators from Baylor have shown clinical improvement with the use of ribavirin, with or without immunoglobulin, in patients who

develop RSV after having recently undergone bone marrow transplantation.^{15,16}

RSVIG

In the early 1990's, an attempt was made to prevent RSV infections by administering standard immune globulin on a monthly basis to infants and children at greatest risk of severe disease. While this method failed to show significant benefit, most likely due to the relatively low RSV antibody titer of standard preparations, it formed the foundation for further work with passive immunization.¹⁷

Development of a hyperimmune globulin product, RSVIG, made it possible to provide the necessary antibody titers. RSVIG is administered once a month during the RSV season. The recommended dosage is 750 mg/kg (15 ml/kg) infused at a rate of 1.5 ml/kg/hr for the first 15 minutes, then 3 ml/kg/hr for the next 15 minutes. If tolerated, the rate may then be increased to 6 ml/kg/hr for the remainder of the infusion.

The first two trials of RSVIG use, the National Institute of Allergy and Infectious Disease (NIAID) trial¹⁸ and the Prophylaxis of RSV in Elevated Risk Neonates (PREVENT) trial¹⁹, formed the basis for FDA approval. These trials documented a significant reduction in RSV hospitalizations and length of hospital stay in RSVIG treated infants compared to controls. They also documented an additional benefit: treated patients had significantly fewer cases of otitis media.

Adverse reactions in the NIAID and PREVENT trials were similar to those experienced with standard immune globulin administration: fever, allergic reactions, vomiting, diarrhea, hypertension, tachycardia, fluid overload, and respiratory distress. These latter two adverse effects were particularly concerning. In the NIAID trial, five of the six patient deaths were in infants with congenital cardiac defects. No causal relationship was found between treatment and mortality, but the potential for fluid overload should be anticipated.²⁰

Earlier this year, the AAP published recommendations for RSVIG use.²¹ These guidelines mirror the FDA-approved indications. Use of RSVIG prophylaxis is suggested for those infants and children less than two years of age with bronchopulmonary dysplasia who currently require or have recently required oxygen therapy and for infants born at 32 weeks gestation or less.

Readers should refer to the AAP statement for more details on patient selection and information on administration.

At this time, much more work needs to be done in order to establish the usefulness of RSVIG in infants. It should be noted that RSVIG appears to be effective only as prophylaxis. It is not useful as treatment in infants and children with documented RSV infections.²²

Cost of Therapy

Clearly, the primary drawback of these therapies is their cost (Table). A single treatment course of ribavirin would utilize 3 to 7 vials. Treatment of a single patient with RSVIG through one RSV season would typically require 5 to 7 grams of drug.

Table. Cost of RSV Therapies

Medication	Average Wholesale Price (AWP)
Ribavirin 6 gram vial	\$ 1,319.85
RSVIG 1 gram vial	\$ 385.84
RSVIG 2.5 gram vial	\$ 661.53

Several authors have attempted to perform cost analyses of these therapies.^{23,24} The results have been mixed. In most cases, the benefit of treatment depends on the methodology used for comparison, i.e. the cost of no treatment or prophylaxis.

The expense of these drugs will have a major impact on hospital budgets. In a recent paper, the Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) estimated the annual cost of treating children under the age of four at nearly \$ 20 million. In their data review, 71% of the pharmacy costs during the previous year were for ribavirin alone, which was used in only 7% of the patients.²

Future Directions

The next advancement in RSV prevention will likely be the release of monoclonal RSVIG. This product will reduce the risks associated with the administration of antibody derived from human serum. In addition, it should prevent a shortage of drug as experienced during the previous year. Another shortage is expected for the 1997-1998 RSV season. The manufacturer of RespiGam[®] has already cut all planned shipments by 40% in response to increased demand.

In addition, work continues on the development of a safe and effective vaccine for RSV. Previous attempts to develop a vaccine have

failed. Administration of a formalin-inactivated vaccine in the early 1960's resulted in high levels of antibody production. Unfortunately, once treated patients were exposed to natural RSV, they developed severe disease.¹

A new vaccine, a purified fusion protein product, appears more promising. At this time, it has only been studied in a small number of patients, but provides a significant antibody response.^{25,26} It is unlikely that a vaccine will be approved for widespread use within the next five years.

Summary

The prevention and treatment of RSV remain controversial. At this time, the success of available therapies has not been clearly established. Ribavirin use will likely remain as an option for children with the greatest risk of significant illness. The widespread adoption of RSVIG awaits further clinical trials documenting its efficacy in preventing illness.

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Pharmacology Literature Review

Meropenem Review

Meropenem is a carbapenem antibiotic similar to imipenem. It has a broad spectrum of activity, particularly against Gram negative bacteria. This thorough review discusses the spectrum of meropenem as well as clinical trials documenting its use, pharmacokinetics, and adverse effects. The dosing section includes a discussion of use in pediatric patients. Meropenem was recently placed on the formulary at UVA. This article

will be a useful review for those planning on using this antibiotic in their practice. Fish DN, Singletary TJ. Meropenem, a new carbapenem antibiotic. ***Pharmacotherapy* 1997;17:644-69.**

Phenobarbital and Peritoneal Dialysis

The authors describe the case of a 2 year old child on continuous cycling peritoneal dialysis who developed generalized seizures. His treatment with phenobarbital and the resultant serum concentrations are presented in order to highlight the significant variability in clearance of drug by this method of dialysis. Porto I, John EG, Heilliczer J. Removal of phenobarbital during continuous cycling peritoneal dialysis in a child. ***Pharmacotherapy* 1997;17:832-5.**

Safety Issues with Methylphenidate

This brief review focuses on issues related to the safe use of methylphenidate for the treatment of attention deficit/hyperactivity disorder. Adverse effects are discussed, as well as drug interactions and the potential for substance abuse. Rappley MD. Safety issues in the use of methylphenidate: An American perspective. ***Drug Safety* 1997;17:143-8.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 9/26/97:

Carvedilol (Coreg[®]; SmithKline Beecham) was added to the formulary. This agent blocks both alpha and beta adrenergic receptors. The recommended starting dose for adults is 3.125 mg PO given twice daily. Carvedilol use is restricted to patients with moderate to severe congestive heart failure (NYHA class II or III) refractory to other treatment measures.

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