

Finally, the study by Rodenhuis et al., which was designed in 1993, and the investigation by Tallman et al., which began accrual in 1991, may provide proof of a principle, but neither is representative of current high-dose chemotherapy. Relapse after primary therapy remains the most important problem to overcome in high-risk breast cancer. High-dose chemotherapy should best be viewed as a launching pad from which to explore new methods of post-transplantation therapy to reduce the probability of relapse.^{9,10}

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Treatment of Acute Bronchiolitis

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In this issue of the *Journal*, Wainwright et al.¹ provide data from a clinical trial in which 194 infants hospitalized with bronchiolitis were treated with inhaled epinephrine or placebo. In this age of commercial support for clinical trials, funding is available only when commercial sponsors stand to make a profit from the manufacture of a drug. Thus, Wainwright et al. are to be congratulated for having tackled an important question using a multicenter, randomized, blinded clinical trial that does not involve a new drug. The authors' findings overturn the popular notion that treatment of bronchiolitis with inhaled epinephrine, as compared with placebo, shortens the hospital stay or the time until the infant is ready for discharge from the hospital. In fact, there are no data showing that the treatment of bronchiolitis with any bronchodilator, including albuterol, significantly shortens the hospital stay.²

These investigators chose appropriate end points for a clinical trial addressing an important issue, since estimated admissions of children under one year of age for bronchiolitis increased from 1.3 percent in 1980 to 3.1 percent in 1996, and during the same time period, the number of hospitalized children with bronchiolitis who were under six months of age increased by 239 percent.³ These increases may reflect an attempt to improve care through

access to measurements of oxygen saturation and a readily available supply of oxygen. Such care is important, since small increases in the imbalance between ventilation and perfusion can have a profoundly negative influence on oxygen saturation at the so-called knee of the oxygen-saturation curve, a common situation in many of these sick infants.

The rationale for the treatment of acute bronchiolitis with bronchodilators is limited. Respiratory syncytial virus infection, the most common cause of bronchiolitis, results in loss of epithelial cilia and sloughing of epithelial cells in the airway. The pathological features of bronchiolitis include collections of desquamated airway epithelial cells, polymorphonuclear cells, and lymphocytes within the airway and cellular infiltration and edema around the airway, with very little alveolar infiltration with inflammatory cells. Desquamation of airway epithelial cells and inflammation are more extensive in bronchiolitis than in asthma, a condition known to be responsive to inhaled adrenergic agents. In acute bronchiolitis, sloughed epithelial cells, neutrophils, and lymphocytes appear to be the major contributors to airway obstruction. The complete plugging of some airways and partial plugging of others may lead to localized atelectasis of some units of lung parenchyma and overdistention of other units. This

patchwork of overdistention and underdistention is a common finding on chest radiographs in infants with bronchiolitis. The imbalance of ventilation and perfusion results in hypoxemia that is generally relieved by the administration of oxygen,⁴ an observation made before the establishment of blood-gas machines as we know them today and certainly before oxygen-saturation meters were available in every emergency facility.

Some 20 years ago, we suggested that epinephrine might be a better bronchodilator for use in patients with bronchiolitis than the increasingly selective β -adrenergic bronchodilators under development at that time.⁵ This may still be true. To our knowledge, no study comparing selective β -adrenergic agents with placebo in which the length of the hospital stay was used as an outcome measure has demonstrated improvement of any magnitude.² Some clinical trials comparing albuterol with placebo have shown a deterioration of oxygen saturation with albuterol.² Some of the trials comparing albuterol with placebo that have used clinical scores as the outcome measure included older infants, who may have had asthma.²

A study measuring combined pulmonary and upper-airway resistance in infants with bronchiolitis who were treated with epinephrine or albuterol showed that resistance to breathing was reduced by one third in the infants treated with epinephrine but that there was no reduction in infants treated with albuterol.⁶ These measurements of resistance included the nose and upper airway. Measurements of resistance in sicker, intubated infants (in whom the upper airway was bypassed), carried out later in the course of their disease, showed that treatment with epinephrine reduced resistance to breathing in some infants without any indication of improved gas exchange.⁷ These findings suggest that once plugging of the airway has occurred, no treatment is effective except respiratory support, oxygen, and time. Since the upper airway accounts for such a large fraction of the combined upper-airway and pulmonary resistance and since a number of infants with bronchiolitis have nasal coryza and edema, some of the demonstrated effects of treatment with nebulized epinephrine early in the course of bronchiolitis might be observed with the use of nose drops, a cheaper alternative than the equipment required for nebulized therapy. The notion is consis-

tent with the finding that infants with bronchiolitis who are treated with inhaled epinephrine in the emergency room are discharged home more rapidly and have a lower rate of hospitalization than do those treated with albuterol.⁸

Perhaps physicians must recognize that no treatment of bronchiolitis, not even corticosteroid therapy,⁹ will reduce the length of stay in the hospital. Infants with bronchiolitis are admitted to the hospital because their respiratory status is of concern and because there are no reliable tools to predict which of these infants will have apnea or respiratory failure. The goals of care for hospitalized infants may be to ensure adequate fluid intake, to provide a suitable thermal environment in which oxygen consumption will be minimized, and to administer oxygen in order to maintain adequate gas exchange. Since no bronchodilator reduces the length of stay, treatment of hospitalized infants with either albuterol or epinephrine cannot be recommended. However, epinephrine does reduce airway resistance and improves the clinical score as compared with albuterol. We speculate that the same benefits might be achieved by the administration of α -adrenergic nose drops, particularly before feeding. How simple.

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