

# Evidence Based Treatment of Bronchiolitis

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Annual epidemics of bronchiolitis fill the pediatric wards in almost all parts of the world. It is not only a considerable cause of morbidity, it also leads to death in severe cases due to respiratory failure. Mortality is higher in children with underlying congenital heart disease, chronic lung disease, or immunodeficiency.

Despite being a common disorder with a known etiology (RSV being the commonest), the treatment has remained almost unchanged for past more than three decades. The only non-controversial part of the treatment is supportive. Children with mild bronchiolitis, which form the large majority of cases, are treated at home. Antipyretics and treatment of nasal block are most often sufficient, as disease may in its natural course remain mild. Parents are however informed about monitoring of features of progressive worsening of respiratory distress and danger signs signaling need for hospitalization. Children with moderate and severe distress are hospitalized.

Treatment of a hospitalized child centers on correction of hypoxia with oxygen, minimal handling and careful noninvasive monitoring for apnea and respiratory failure. Fluid therapy, use of bronchodilators, steroids, Ribavirin, Antibiotics, specific immunoglobulins, vaccines and some other therapies has been through lot of controversies. Final word about most of these is yet to be said. This article will present the current status of these therapies based on evidence.

## Oxygen

Hypoxia due to ventilation perfusion mismatch is an important feature of bronchiolitis. "Oxygen is vitally important in bronchiolitis and there is little evidence that any other treatment is useful".<sup>1</sup> This statement was made in 1960s and almost holds true even today. Maintaining oxygen saturations between 94-96 % would be ideal. In most except with underlying chronic lung disease or CHD, there is very little chance of hypercarbia if child's oxygen saturations are maintained. Pulse oximetry is sufficient to monitor the child; blood gas analysis may be required only in very severely distressed and those with underlying pulmonary or cardiac conditions. Head box is an easier way of delivering oxygen but not necessarily the most acceptable to infants. Moreover a crying child has

higher oxygen requirements. A non-offensive 'blow by' method of oxygenation may be more acceptable while the child is nursed in mother's lap. Nose block and fever must also be treated promptly. An elevation of head end of 15 to 30 degrees probably improves respiratory mechanics and may provide additional comfort to the child.

## Fluid Therapy

Intravenous fluids need to be given to the children with moderate to severe respiratory distress. Inability to accept orally, fever, respiratory distress and cough may lead to dehydration. In addition infants may have a tendency to have post tussive vomiting. This would mean additional fluids. On the other hand negative intrathoracic pressures may add stress to left ventricle and also lead to leak of fluid in the interstitium. There are reports that inappropriate secretion of ADH does take place in children with severe distress in bronchiolitis as in other pulmonary conditions<sup>2,3</sup> resulting in fluid accumulation. A restriction of fluid to two thirds of maintenance is thus advocated. However, a careful balance avoiding both over and under hydration is necessary. It will not be wise to use a preplanned fluid therapy in all cases.

Nasogastric route for fluid and feeds has been advocated by some<sup>4</sup> in those with mild to moderate disease because these children tolerated nasogastric tube very well and felt more comfortable with small frequent feeds. While others prefer to use intravenous fluids in all babies on supplementary oxygen.<sup>5</sup> The argument put forward by them is that there is increased work of breathing due to nasal obstruction and fluid within the stomach when NG tube is used. There will also be increased risk of gastro-esophageal reflux and aspiration. It is therefore necessary to weigh the risks and in severely distressed babies intravenous fluids will avoid sudden deteriorations due to aspirations.

## Bronchodilators

Use of bronchodilators as relievers in asthma has been established but their role in wheeze associated with lower respiratory tract infection has remained controversial, more so in infants with first wheeze which is likely to be an episode of bronchiolitis. That has not hampered the enthusiasm of researcher in experimenting different drugs and dosages in children with bronchiolitis. It is not easy to draw a conclusion from these studies because selection of patients and outcome variables used in different studies

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are not comparable. Moreover multicentric studies with large sample size and similar outcome variable are scarce. Effect of bronchodilators has been studied in preventing hospitalization, improving respiratory scores and oxygen saturations, prevention of need for ventilation or early discharge. Relative efficacy of selective beta 2 agonists, Adrenaline, recemic adrenaline and ipratropium bromide have also been studied.

**Studies on Salbutamol:** A double blind placebo controlled study<sup>6</sup> on 40 children with first wheeze, published in 1990, compared nebulized salbutamol with normal saline. There was significant difference in accessory muscle use and oxygen saturation in two groups. Authors concluded that salbutamol was safe and effective treatment of infants with bronchiolitis. Similar results were shown by other studies.<sup>7,8</sup> However, later studies have disputed these results.<sup>9,10</sup> Oral salbutamol was found to be of no use in mild to moderate illness.<sup>10</sup>

**Studies Comparing Ipratropium and Salbutamol:** A randomized clinical trial<sup>11</sup> conducted on admitted cases of bronchiolitis. Four groups were made and compared. Children receiving salbutamol, ipratropium alone or combined by nebulization were found to be no different from normal saline in clinical scores or length of stay in the hospital.

**Studies on Adrenaline:** Adrenaline has many theoretical advantages over salbutamol. It can decongest mucosa with alpha adrenergic vasoconstrictor action and this may in addition lead to decreased systemic absorption resulting in less tachycardia than salbutamol. With beta 2 adrenergic effect smooth muscle relaxation occurs, and antihistamine effect results in decreased edema and reduced catarrhal secretions. Adrenaline<sup>12</sup> and recemic adrenaline<sup>13</sup> both have resulted in significant improvement in clinical scores as well as oxygen saturations when compared with normal saline. However some recent studies have contradicted the benefits and have found no improvement in oxygen saturation, and clinical scores,<sup>14,15</sup> as compared to normal saline. A recent publication<sup>15</sup> has also found no difference in hospital admission rates between placebo and adrenaline. In a recent multicentric randomized double blind controlled trial<sup>16</sup> neither short-term benefits in clinical scores, oxygen saturation nor long term benefit of reduction in hospital stay were noticed in adrenaline treated group. Interestingly there is no unanimity even on doses. Doses used for adrenaline vary from 0.1 mg/kg to 0.9 mg/kg in different studies. Some workers have used fixed doses.

**Studies comparing Adrenaline and Salbutamol:** Studies<sup>17-20</sup> comparing the two drugs are almost unanimous in showing adrenaline better than salbutamol. Early relief in symptoms, better oxygen saturations and early discharges were seen in adrenaline group. However both the drugs were found to be better than the placebo. Adrenaline was considered better, safe and effective alternative to salbutamol.

Conclusions from these studies are difficult because of

the reasons stated above. Cochrane review<sup>21</sup> on 8 published studies suggested that 46% demonstrated no improved clinical score with bronchodilators compared to 75% with no improvement with placebo (odds ratio for no improvement 0.29, 95% confidence interval 0.19 to 0.45). Bronchodilators recipient did not show improvement in measures of oxygenation, the rate of hospitalization or duration of hospitalization. So a modest short-term improvement did occur in bronchodilator group.

### Steroids

Acute bronchiolitis is an acute inflammatory condition of the respiratory tract. It would appear to be a condition that should get modified by steroid therapy. Based on published material the Committee on drugs for American Academy of Pediatrics concluded in 1970 "there is no scientific basis for routine administration of Corticosteroids in bronchiolitis." An article published in 1997<sup>22</sup> reviewed the studies on role of Corticosteroids in bronchiolitis. Before AAP statement was made, there was only one double blind control trial<sup>23</sup> which showed significant reduction in time of oxygen therapy (25 vs 40 hr.) and more rapid discharge (4.4 vs 7.0 days). Subsequent trials however failed to show that systemic steroids had any effect on natural history of bronchiolitis<sup>24-27</sup> Based on these studies American Academy of Pediatrics issued the above statement. There were very few studies in the following many years. In 1983 a study<sup>28</sup> which included some patients of bronchiolitis, suggested that though beta2 agonist and steroids were ineffective when given alone but combination resulted in early reduction of symptoms. However there were flaws in the design. But three studies<sup>29-31</sup> with large sample size done subsequently failed to show any change in the resolution time of symptoms. A recent study<sup>32</sup> published in 2002 examined the efficacy of oral dexamethasone in 70 children and concluded that outpatients with moderate to severe disease derive benefit as there is reduction in hospitalization rates in dexamethasone group.

Some interest has also been shown in the role of inhaled Corticosteroids. One study<sup>33</sup> has shown that high dose inhaled Budesonide not only leads to more rapid discharge from hospital but also reduces the incidence of subsequent wheezing episodes, the need to visit the general practitioner, and admission to hospital for further respiratory problem. Another study<sup>34</sup> showed similar post bronchiolitis effect of inhaled steroids.

### Ribavirin

Ribavirin is synthetic (purine) nucleoside analogue (first synthesized in 1972) which has broad spectrum antiviral activity including against influenza, respiratory syncytial virus many other DNA and stranded RNA viruses. No viral resistance to Ribavirin has yet been observed. The drug is administered as an aerosol, generated by small particle aerosol generator (SPAG). The aerosol is usually

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delivered into head box for 12 to 18 hours a day. It can be used in ventilator circuits but great care must be taken so that valves do not get blocked due to crystallized drug. Oral bioavailability of Ribavirin is approximately 50%.

In 1991, initial study<sup>35</sup> showed that there was improvement in partial pressures of oxygen, reduced time for mechanical ventilation in patients treated with Ribavirin, compared with controls. American Academy of Pediatrics<sup>36</sup> recommended the use of Ribavirin in certain infants with respiratory syncytial virus infection. The infants included were those with prior diagnosis of congenital heart disease, chronic lung disease, preterm infants, infants younger than 6 weeks old and ventilated patients with respiratory syncytial virus infection. However another multicentric, randomized trial done in previously healthy children who were mechanically ventilated, did not show any benefits of Ribavirin.

There have also been several problems with ribavirin treatment. These include a high expense of treatment, potential toxicity to health care workers, including bronchospasm and potential teratogenic effects. As a result American Academy of Pediatrics<sup>37</sup> changed their earlier recommendations. They now suggest the treatment with Ribavirin on individual basis with specific clinical condition with complicated congenital heart disease, Bronchopulmonary dysplasia, cystic fibrosis or other chronic lung disease. Those children with underlying immunodeficiency, who are severely ill and are younger than 6 weeks of age can also receive ribavirin based on individual clinical situation.

### Antibiotics

Secondary bacterial infections appear uncommon in RSV bronchiolitis.<sup>38</sup> The routine use of the antibiotics has not been shown to influence the course of bronchiolitis, and there is little rationale for their use. Only when there is evidence of secondary infection should antibiotics be considered. Interestingly a study<sup>39</sup> in children under two years of age who were hospitalized with respiratory syncytial virus lower respiratory tract infection reported that those children who were given parental antibiotics for 5 days or longer had 9% incidence of secondary bacterial infection in contrast to overall incidence of 1.2%. However, there may be a case in those who are very ill or have atypical features.

### Herbal Treatment

Shuang huanglian a Chinese herb has been shown to be of some benefit in a randomized single blind trial.<sup>40</sup> The group that received the herb alone or with antibiotics showed improvement in clinical score in children admitted with wheeze associated lower respiratory tract infections. No side effects were noticed.

### Ventilation

A small proportion of bronchiolitis patients may require ventilation despite extremely good care in maintaining

the oxygenation. Recurrent apnea and respiratory failure are the usual indications for intubation. Recurrent apnea with significant desaturations, hypoxia despite high oxygen requirement, persistent acidosis and rising carbon dioxide levels are used as indications in most of the centers.<sup>41,42</sup>

Ventilatory strategy used includes using minimum peak pressures required to achieve acceptable oxygenation. Permissive hypercapnia is preferred over aggressive ventilation. Positive end expiratory pressures though required may be detrimental. Slow rates with long expiratory time are generally required. Heliox<sup>43</sup> and ECMO<sup>44</sup> have been used in certain difficult situations with good results where conventional ventilation was not found to be helpful.

### Prevention

Respiratory Syncytial Virus IVIG, Palivizumab, and Vaccines are some of the potential preventive strategies for preventing morbidity and mortality. The first two are recommended for use in specific conditions. The most recent agent is Palivizumab, a human monoclonal antibody that decrease the disease severity. American Academy of Pediatrics recommends Palivizumab and RSV – IVIG in following situations.<sup>45</sup>

- RSV bronchiolitis in children less than 2 years with chronic lung disease
- Preterm children (32 weeks or less) RSV bronchiolitis may benefit.
- Preterm children 32-35 weeks with additional risk factors may be considered.
- These agents have not been evaluated for immunocompromised.

So far, use of live attenuated, live recombinant and synthetic peptide vaccine for RSV has not provided adequate protection.

## CONCLUSION

Based on the above review of literature and recent published systematic reviews<sup>46,47</sup> following conclusions can be drawn for current treatment practices in bronchiolitis.

- Mild cases form the majority of bronchiolitis and can be treated on domiciliary bases with anti pyretic and nasal clearing. Oral bronchodilators may have no role.
- There is no doubt that oxygen is the mainstay in treating admitted cases of bronchiolitis. Patients should receive oxygen therapy in most non-threatening way. Keeping patient afebrile, in comfortable position with head elevated and nose cleared may reduce oxygen demand.
- Fluids should be used carefully to avoid over as well as under hydration. Nasogastric feed should be avoided in children with severe distress.
- There is still insufficient evidence to support the use

of bronchodilators. Some studies have shown modest effect. Nebulised Epinephrine is better than salbutamol. There is no consensus on dose but higher dose, (0.5 mg/kg, max 5 mg) may be better than lower dose, 0.15 mg/kg. Large multicentric studies are needed.

- Evidence for use of steroids, systemic or inhaled is lacking. Large-scale multicentric trials are necessary to form an opinion.
- There is no place for routine use of antibiotics.
- Ribavirin, RSV IVIG, and Palivizumab can be used in certain high-risk situations only. Palivizumab has been shown as most cost effective in a pharmaco-economic study. (48) Vaccine has no role at present
- Ventilation, ECMO and Heliox can improve outcome in children with respiratory failure if expertise is available.

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