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DEBATE

Current pharmacological treatments for bronchiolitis are useless
The case for the pro's

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Acute bronchiolitis is probably the commonest cause for hospitalisation in infancy. It has been known for nearly 50 years that the commonest organism responsible for this clinical entity is the respiratory syncytial virus. However it is not unique in it ability to cause acute bronchiolitis which may be due to many 'traditional' respiratory viruses such as rhinovirus, more recently described viruses such as pneumovirus and almost certainly, other viruses still to be described. While few would disagree about this broad statement there are still important ongoing debates in this area such as does RSV infection cause asthma? is there a specific immunopathology that is responsible for acute brocnhiolits? do pharmacological therapies have a role to play in acute bronchiolitis? and perhaps, most importantly, what is acute bronchiolitis.

Understanding this later issue is perhaps critical in trying to unravel the very confusing and often apparently contradictory publications in this area. In the UK, Australia and parts of Europe the term acute bronchiolitis is applied to a clinical phenotyped characterised by evidence of upper respiratoy tract infection with coryza accompanied by evidence of lower respiratory tract infection characterised by tacypnoea, hyperinflation of the chest *and widespread crepitation on auscultation*. Wheeze may be present at time both audibly and on auscultation but is variable and, in the majority, absent. Such patients may frequently be labelled as having 'pneumonia' in the USA because they frequently have right upper or middle lobe collapse/consolidation on chest X-ray. The recognition that such an appearance is common and of no significance in infants with RSV bronciolitis has led most authorities in the UK and Australia to recommend not undertaking CXRs in this group of patients. In North America the term 'acute bronchiolitis' is apparently used to describe an infant with evidence of an upper respiratory tract infection and their first episode of wheeze, a group who in the UK would be described as having their first episode of wheezy bronchitis[viral associated wheeze]. Why one patient experiencing their first episode of wheeze associated with a viral respiratory infection should be separated out from those experiencing their second or subsequent episode by labelling them as having 'bronchiolitis' is unclear. These differences in definitions are very important if one is to interpret the results from both epidemiological and therapeutic studies.

In 1964 Reynolds and Cook wrote an Editorial in J Paediatrics which would accurately sum up our knowledge and treatment of this condition in 2006. They display a clarity of thought that has been conspicuously absent in so many contributions to the field since. They stated that acute bronchiolitis was the commonest acute LRI in infancy, was due to one or more viruses, had a mortality of approx 1% and that there was no indication for routine antibiotics. Perceptively they concluded that there were probably 2 groups of patients, those with oedema and secretions and those with a predisposition to asthma, that these groups cannot be easily distinguished and most are in former group. They also noted that good supportive care by correction of hypoxia with oxygen and provision of fluids are the comer stone of therapy and that there is no evidence any other therapy is consistently or even occasionally useful.

A key observation was the suggestion that while clinically similar there were probably two groups of patients. Those

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in whom airways secretions and oedema predominated probably accounting for those with widespread crepitations and those with a 'tendency to asthma' in whom wheeze is likely to predominate. We now know that the majority of infants and very young children who wheeze with viruses do not develop typical asthma irrespective of the virus but a significant cohort 20–40% will exhibit asthmatic symptoms during the later part of the first decade of life and beyond indicating that their 'viral induced wheeze' was the first overt exacerbation of asthma.

A number of studies have now indicated that the long term follow up of those with British bronchiolitis is significantly different to those with North American bronchiolitis. There is a transient excess of respiratory symptoms in the formed group that wanes rapidly with time while a significant proportion of the later group do have asthma at 10 and 20 years of age. However they are still a minority of the total group. More over it is now clear that RSV induced viral wheeze does not precipitate asthma and indeed it appears that patients with viral associated wheeze are more likely to have asthma if their episode is triggered by rhinovirus. The frequency of RSV bronchioliotis, irrespective of definition is appears attributable to the poor 'herd immunity' resulting from its ability to avoid the host immune system and therefore young infants are at risk because of the magnitude of the annual epidemics and the poor passive protection they receive from their mother.

While many appear to have devoted their lives to trying to prove that RSV infections in early infancy causes/induces asthma the overwhelming evidence would suggest that this is not the case as outlines above. The majority of work involving rodents should be ignored as rats do not experience bronchiolitic symptoms when infected with human RSV and in order to get an 'allergic response' with eosinophils and a 'Th2' response the models need to be extensively manipulated. Bronchiolitis is a neutrophil dominated disease and indeed PMN influx with subsequent induction of mucus production coughing and sneezing appear to characterise respiratory viral infections.

The vast majority of a infants with 'bronchiolitis' irrespective of definition are not admitted to hospital. As noted above, good supportive care remains the cornerstone of management for those who are and the observation some 40 years ago that 'Oxygen is vitally important and there is little evidence that any other intervention is helpful' still holds today. The routine use of oxygen had reduced mortality amongst admitted infants down from approximately 20% in the 1940s to 1% by the early 1960's. The mortality expressed as a percentage of those admitted has probably not changes significantly between then and now but this is because although the quality of intensive care for those who are most severely ill has improved considerably we are now dealing with far more compromised patient group such as those with severe chronic lung disease of prematurity who did not exist in 1964.

A large number of studies have been undertaken with a variety of pharmacological agents including bronchodiltators [anticholinergis and sympathomimetic agents] anti-inflammatory agents and anti-viral agents without convincing evidence that any have any impact on outcomes such as admission to hospital, duration of oxygen therapy, need for intensive care of duration o hospitalisation. There have been some studies suggesting that adrenaline/epinephrine may be valuable but this was not bourn out in a recent study. It seems clear that none of the bronchodilators will have much effect in a condition that is characterised by airways oedema and airways secretion [British bronchiolitis] and equally there is no evidence that bronchodilators or steroid therapy has a significant impact in viral induced wheeze. However amongst a cohort of infants with North American bronchiolitis a significant cohort, perhaps 20–30%, may be destined to have asthma and therefore may potentially benefit from one or more therapies traditionally used for 'asthma'. However since we cannot identify these infants any benefit in this subgroup would probably be obscured due to the lack of response in the large cohort of infants with simple viral induced wheeze. Until we can accurately identify the different phenotypes of wheezing infants this suggestion cannot be confirmed and 'evidence based' guidelines from around the world consistently recommend that pharmacological agents are not used to treat 'bronciolitis'. Despite this these agents are extensively used particularly in North America. Another potential criticism of these recommendations is that the studies utilise the wrong end point. While they may not reduce hospitalisation or result in more rapid discharge it is possible that these agents may lead to small but desirable improvements in symptoms in at least a subgroup of those with 'bronchiolitis'. The analogy would be in the treatment of acute exacerbations of asthma where β agonists may not lead to more rapid discharge but they certainly help the patients distress, if only transiently and poorly, while the steroids take effect. As we cannot ask our infants if they feel better after a nebuliser some other marker of distress should be built into any studies utilising 'reliever' therapy.

It can be anticipated that anti-viral will not work from an understanding of the disease process. By the time infants develop significant lower respiratory tract symptoms the viral replication has probably peaked and started to wane. The symptoms are almost certainly driven not by the virus but the host response and by neutrophi influx in particular. There is increasing interest in manipulating this response as a means of alleviating symptoms [though clearly preventative strategies would be preferable] The only concern with this approach is that the neutrophils do appear to be important in clearing virus from the airway as well as having a major role in inducing symptoms. Experimental evidence has indicated that agents such as corticosteroids are unable to switch off the production of key cytokines such as IL-8 after infection of cells has occurred and so would not be expected to have any significant impact.

In conclusion interpreting the epidemiological and therapeutic studies related to acute bronchiolitis is challenging due to the failure to include comparable phenotypes of disease. Irrespective of phenotype there is still little to support the use of pharmacological agents and good supportive care remains vital. In those with phenotype characterised by evidence of viral infection and wheeze a minority will be experiencing their first exacerbation of asthma and if we could more reliably identify this group we may be able to design studies that would support the use of agents such as bronchodilators but until this such studies evidence based guideline will continue to support the position that pharmacological agents do not have a role in the treatment of acute bronciolitis.

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