Bronchodilators and other medications for the treatment of wheeze-associated illnesses in young children

Programme for the Control of Acute Respiratory Infections

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1. INTRODUCTION

Acute respiratory infections (ARI) are one of the commonest causes of death in children in developing countries. Almost all ARI deaths in young children in developing countries are due to pneumonia. The WHO Programme for the Control of Acute Respiratory Infections has focused on the case management of pneumonia in an attempt to reduce mortality from acute lower respiratory infections. The WHO Programme also recognizes that the clinical presentation of wheeze (usually due to either bronchiolitis or asthma) has considerable overlap with that of pneumonia. There is a need to identify children with pneumonia, to ensure that they will receive antibiotic therapy and to identify children with wheeze whose drug treatment will include a bronchodilator. In developing countries, wheeze may be common in children with bacterial pneumonia due to Streptococcus pneumoniae or Haemophilus influenzae, or in mixed viral-bacterial lower respiratory infections. Children without a previous history of wheeze who develop a lower respiratory infection with wheeze and tachypnoea may have a bacterial or a mixed viral-bacterial infection and should be treated with antibiotics for suspected bacterial pneumonia. The primary aim in the case management of ARI in young children is the identification and treatment of pneumonia; the identification and treatment of asthma and bronchiolitis are important, but secondary, aims.

This background paper deals with common causes of wheeze, with the pathogenesis and pathophysiology of asthma and bronchiolitis and with the drugs that are available for the treatment of wheeze.

2. WHEEZE AND ITS SIGNIFICANCE

It is difficult to describe a sound and this makes a definition of wheeze imprecise. Wheeze is a soft musical sound heard during expiration. Wheeze refers to the noise heard either with or without a stethoscope.

In a normal situation, a child’s breathing is inaudible without a stethoscope because the velocity of air flow in the airways is too low to produce a sound. When the airways narrow, turbulence occurs. Wheeze may occur when the velocity of air flow increases as a consequence of the airways narrowing. In diseases such as asthma and bronchiolitis, the pathology is in the small airways. This sometimes leads to the erroneous impression that the wheeze is due to air whistling through narrowed small airways. Theoretically, the velocity of air flow in the smaller airways is far too low to cause a wheeze, even when there is significant narrowing. The wheeze is not a result of the small airways obstruction but is generated in the trachea and major bronchi which are made narrower by a secondary compression during expiration. The physiological explanation is that the small airways
obstruction leads to a forced expiration, with positive (rather than the usual negative) intrapleural pressure. This positive intrapleural pressure exceeds the pressure within the lumen of the trachea and other large airways, resulting in compression of these airways during expiration and producing a wheeze in these dynamically narrowed larger airways. In bronchiolitis, the small airways obstruction is due to the inflammation of the bronchiolar epithelium; in asthma the small airways narrowing is due to a combination of mucosal oedema, mucus hypersecretion and bronchial smooth muscle spasm.

Although obstruction in the small airways is the usual reason for wheeze generated in the large airways, obstructive lesions in the trachea or main bronchi can also cause wheeze. In this case the wheeze may be generated by the increase in velocity of airflow at the level of the obstruction. Thus a foreign body in the intrathoracic part of the large airways or large airway compression from a tuberculous lymph node may manifest themselves as wheeze. The inhalation of a foreign body may produce stridor (a harsh noise on breathing in) if the body is lodged in the extrathoracic part of the airway or wheeze if it is lodged within the chest. This paper will be limited to the main causes of wheeze, bronchiolitis and asthma, and to wheeze which may be associated with pneumonia.

3. BRONCHIOLITIS

Bronchiolitis is a common cause of wheeze in the first year of life (infancy). In developed countries between 1% and 2% of infants are admitted to hospital with bronchiolitis. Respiratory syncytial virus (RSV) infections, the most frequent cause of bronchiolitis, are quite common in developing countries. In a series of hospital-based studies in several developing countries sponsored by the Board on Science and Technology for International Development (BOSTID), United States National Research Council, the percentage of all inpatient and outpatient children under 5 years of age with acute lower respiratory infection whose cultured specimens yielded RSV varied from 11% to 37%. The disease occurs mainly in the first year of life and begins as a typical viral illness with coryzal symptoms and mild fever. This progresses to lower respiratory tract infection with a harsh irritating cough, tachypnoea and wheeze. There is hyperexpansion of the chest, chest indrawing, nasal flaring and suprasternal recession. On auscultation, there are widespread wheezes during expiration; showers of fine inspiratory crackles may be heard, especially when the child is resting quietly. The clinical course may be complicated by poor feeding, cyanosis and apnoea.

Although the predominant pathogen in bronchiolitis is the respiratory syncytial virus, other viruses, such as parainfluenza, influenza, adenovirus and rhinovirus are occasionally found, as well as the
organism *Chlamydia trachomatis*. In most countries RSV causes epidemics of infection each winter, with the vast majority of cases of bronchiolitis in a community occurring over a two- to three- month period in any year\(^7\). In tropical climates, the seasonal pattern of activity varies and has no consistent relationship with climatic factors. In temperate climates, RSV infections occur predominantly during winter\(^7\).

RSV colonizes the bronchiolar epithelium, replicates and then produces necrosis and proliferation of the epithelium. T lymphocytes are found in large quantities in the peribronchial tissues and IgE production may also be important in pathogenesis. Oedema and mucus secretion are prominent features of the airway narrowing and the bronchiolar lumen contains thick plugs of necrotic debris.

The airway pathology suggests that bronchodilator therapy is inappropriate and this is supported by considerable clinical and lung function data showing the ineffectiveness of agents such as salbutamol, theophylline, ipratropium bromide and corticosteroids in the management of bronchiolitis\(^16-19\). Those who develop significant respiratory failure need mechanical ventilation and full intensive care. Although some authors believe that bronchodilator therapy is effective in children a few months old with bronchiolitis, the prevailing view is that oxygen remains the main agent that is of benefit\(^16,17\). Ribavirin, an antiviral agent, may have a minor role in the overall management of bronchiolitis and its role is limited to occasional use in intensive care units in large hospitals\(^18,19\). However, the limited benefits of this drug and the high cost preclude its use in less developed countries. Physiotherapy, mist and other physical treatments have not proved beneficial. Of much greater importance in developing countries is the need to be aware of the possibility of secondary bacterial infection, and that some children whose initial illness was viral bronchiolitis will require antibiotics for the superadded bacterial pneumonia.

4. **ASTHMA**

No definition of asthma has received universal acceptance. From a physiological viewpoint the major features of asthma are bronchial hyperreactivity and variable airways obstruction. The bronchial hyperreactivity leads to airway narrowing in response to various stimuli. From a clinical viewpoint the airway obstruction manifests itself as recurrent episodes of cough, wheeze and breathlessness.

The pathological features of asthma include smooth muscle spasm, mucosal oedema and mucus hypersecretion\(^7\). The current view is that airway inflammation is central to these changes\(^20,21\). The inflammatory response mobilizes and activates mast cells, neutrophils, macrophages, platelets and eosinophils with the release of chemical mediators such
as histamine, leukotrienes, prostaglandins, thromboxanes and platelet activating factor\textsuperscript{22-24}.

The common triggers to acute attacks of asthma include acute respiratory infections, exercise, cigarette smoke and other pollutants, specific allergens, drugs (such as aspirin) and emotional factors\textsuperscript{7,25,26}. By far the most important triggers to wheeze are respiratory infections. Classical studies in developed countries have described the association between asthma and viral respiratory infections caused by rhinovirus, respiratory syncytial virus, parainfluenza and other viruses. Although it is also recognized that bacteria such as \textit{Mycoplasma pneumoniae} result in wheezing, the prevailing view has been that bacterial infections are uncommon precipitants of wheeze\textsuperscript{25-27}. By contrast, data from developing countries suggest a high incidence of wheeze among children with bacterial pneumonia due to \textit{Haemophilus influenzae} and \textit{Streptococcus pneumoniae}. In developing countries it must be borne in mind that the presence of wheeze does not decrease the likelihood of a bacterial infection in children\textsuperscript{5}. Even in developed countries a respiratory syncytial virus infection of the respiratory tract may be followed by bacterial infection\textsuperscript{45}.

Estimates of the prevalence of childhood asthma vary from less than 1\% to more than 25\%\textsuperscript{7,28-33}. There seem to be some unexplained and real differences in asthma, with lower rates in a developing country such as Papua New Guinea than developed countries such as Australia and New Zealand\textsuperscript{52}. However, some of the apparent variation in asthma prevalence relates to different definitions of asthma. In particular, some doctors use terms such as "wheezy bronchitis", "wheeze-associated respiratory infections" or "recurrent bronchiolitis" rather than asthma to describe children who have recurrent episodes of cough, wheeze and breathlessness triggered by respiratory infections. There does not seem to be any sound clinical or epidemiological reason for the use of any term other than asthma\textsuperscript{28,34}. In particular, bronchodilator and other anti-asthma therapies are the appropriate drug treatments for these children as well as those whose asthma is triggered by stimuli other than respiratory infections.

Geographical differences in terminology mean that many episodes of wheezing illness which would not be called asthma in some countries are called asthma in this paper\textsuperscript{55}. At present there is no way of resolving the semantic debate — in this paper children with recurrent wheeze are regarded as having asthma. Obviously the incidence of bronchiolitis and asthma in a community will depend on the definitions of each. It should also be acknowledged that in some children it is difficult to decide whether an episode of wheeze is due to bronchiolitis or to the first attack of asthma, triggered by an acute respiratory infection.
To summarize, the terminology used in this paper is that the first attack of wheeze in the first year of life is regarded as bronchiolitis whereas recurrent wheeze at any age is labelled asthma. The first attack of wheeze in a child more than one year of age indicates that the child will probably have further attacks of wheeze (and be diagnosed as asthma) and the label of possible asthma is recommended.

Whatever label is applied to children with recurrent wheeze, the prevalence is high in some communities. For example, in Australia and New Zealand about 25-30% of children have recurrent wheeze in the first five years of life. In children 5 to 10 years of age in these countries approximately 10% experience recurrent wheeze in any one year. These estimates should not be assumed to be average figures for the prevalence of recurrent wheeze internationally.

5. DRUGS USED TO TREAT ASTHMA

There are two main strategies in the drug treatment of asthma. The first is the use of reliever medications to reverse acute airways obstruction — the main groups are bronchodilators (beta adrenergic agents, theophyllines and anticholinergic agents) and corticosteroids. The second strategy is preventive therapy with the aims of decreasing bronchial hyperreactivity and airway inflammation. The main preventive drugs are sodium cromoglycate and corticosteroids.

In order to understand the rationale for the use of these drugs, it is necessary to outline the neural control of airway calibre. The classical view is that the main factors determining airway calibre seem to be a balance between sympathetic bronchodilator activity and parasympathetic bronchoconstrictor activity. The sympathetic (adrenergic) nerves are inhibitory (bronchodilators) and the parasympathetic (cholinergic) nerves are excitatory (bronchoconstrictors). However, neural control of airways is more complex than was realized initially and neural mechanisms which are neither adrenergic nor cholinergic have been described. Nevertheless, the bronchodilator effects of both beta adrenergic and anticholinergic agents are consistent with this model.

5.1 Beta adrenergic agents

5.1.1 Mechanisms of action

The adrenergic nerves are often described as providing the "flight, fright, fight response", since the effects of adrenergic discharge are of considerable value in helping the individual to cope with emergency situations. There are three main types of adrenergic receptors: alpha, beta-1 and beta-2. Alpha receptors mediate effects such as
vasoconstriction, beta-1 receptors mediate actions such as increases in heart rate and increases in cardiac contractility, whereas beta-2 receptors mediate actions such as relaxation of airway smooth muscle, inhibition of release of inflammation mediators, blocking the effect of chemical mediators on airway target cells (such as smooth muscle, mucus-secreting cells and endothelium), and muscle tremor. Adrenergic agents do not decrease bronchial hyperreactivity and this makes them inappropriate as long-term preventive medication.

The ideal adrenergic agents for the treatment of asthma are the agents with specific beta-2 adrenoreceptor (adrenergic) stimulation. Beta-1 receptor stimulant effects are undesirable because of cardiac effects, and alpha receptor stimulant effects are undesirable because of vasoconstriction.

Three groups of sympathomimetic drugs are recognized:

1. those with alpha and non-selective beta adrenoreceptor agonist activity, e.g., epinephrine (adrenalin) and ephedrine;
2. those with non-selective (beta-1 and beta-2) beta adrenoreceptor agonist activity, e.g., isoprenaline (isoproterenol);
3. those with selective beta-2 adrenoreceptor agonist activity, e.g., salbutamol (albuterol), terbutaline, orciprenaline (metaproterenol) and fenoterol.

5.1.2 Non-selective adrenergic agents

a) Epinephrine (adrenaline)

Epinephrine, administered subcutaneously, was described as an effective bronchodilator as far back as 1903. It remains a good bronchodilator but its lack of beta-2 selectivity results in a high incidence of cardiovascular side-effects. If selective beta-2 adrenergic agents are available, they should be used in preference to epinephrine.

In countries where selective beta-2 adrenergic agents are unavailable, epinephrine can be used.

b) Other agents

No other non-selective adrenergic agents are recommended for asthma. In particular, ephedrine has a weak bronchodilator effect when compared to the selective beta-2 adrenergic agents. Both ephedrine and combination preparations (such as those containing barbiturates) are still widely used. Because we have much more effective bronchodilators, it is unnecessary to use ephedrine.
5.1.3 Non-selective beta-2 adrenergic agents

Isoprenaline (isoproterenol)

Isoprenaline has non-selective action on both beta-1 and beta-2 receptors. Both its non-selective activity (with consequent side-effects such as increase in heart rate, myocardial contractility and cardiac output) and its short duration of action (only 1-2 hours) make it unsuitable for the management of asthma.

5.1.4 Selective beta-2 adrenergic agents

The four widely available drugs in this group are terbutaline, salbutamol, fenoterol and orciprenaline (metaproterenol). Many studies have highlighted differences between these four agents. However, in practice they are virtually identical in mode of action, rapidity of onset and duration of action.\(^{36}\)

The oral preparations achieve their maximum effect in 30 to 60 minutes and provide useful bronchodilatation for about four to six hours. The onset of action of the inhaled agents is within five minutes and lasts for approximately four hours.

Annex 1 shows routes of drug delivery and dosages for three selective beta-2 agents: Salbutamol is available as an oral preparation, metered dose inhalation (aerosol), dry powder for inhalation, nebulizer solution and in injectable form for intravenous use; terbutaline has oral, metered dose inhalation (aerosol), dry powder and nebulizer preparations as well as a parenteral form for subcutaneous injection; and orciprenaline has oral, metered dose inhalation (aerosol) and nebulizer solutions. A detailed discussion of the advantages and disadvantages of the different routes of drug delivery can be found in Section 6.

The side-effects of the beta-2 adrenergic agents occur mainly with the oral and parenteral preparations. This is not particularly surprising when one considers that the usual dose of salbutamol via metered inhalation is 200 micrograms (2 doses) which is one-tenth of the 2 mg oral dose administered to a one-year-old child. The most common observed side-effects are muscle tremor (due to the stimulation of beta-2 receptors in skeletal muscle) and hyperactivity. Metabolic effects such as hypokalaemia and hyperglycaemia are rare unless the drugs are being used parenterally.

In the 1960s mortality from asthma increased in certain countries. There was concern that beta agonists might be implicated, particularly the non-selective beta adrenergic agent isoprenaline. Until recently, the general view was that the selective beta-2 adrenergic agents were particularly safe and that the only reports of serious consequence from their overuse had been when they had been used inappropriately as sole
therapy for severe asthma. However, reports from New Zealand suggested that fenoterol (but not salbutamol or terbutaline) had led to an increased risk of death from asthma. In view of this, fenoterol cannot be recommended for use. Other work has suggested that agents such as salbutamol might result in excess mortality. If asthma therapy is required on a regular basis, drugs with anti-inflammatory action should be prescribed. In particular, long-term daily use of beta-2 adrenergic agents without using sodium cromoglycate or inhaled steroids is inappropriate.

Salbutamol is the only selective beta-2 adrenergic agent recommended by WHO in its guidelines for management of acute respiratory infections in children. When WHO protocols were being developed in the early 1980s, salbutamol was the cheapest and most widely available of these four drugs in developing countries, and the only one included in the WHO Model list of Essential Drugs.

5.2 Theophylline

Theophylline is a dimethylated xanthine similar in structure to caffeine and theobromine which are commonly found in coffee, tea, cola drinks and chocolate. In some countries, particularly the USA, theophyllines have been widely used in the management of both acute and chronic asthma. In other countries beta-2 adrenergic agents have been the mainstay of management of acute asthma, with sodium cromoglycate and inhaled corticosteroids the main drugs used for prophylaxis in chronic asthma.

Theophylline is an effective bronchodilator. In spite of extensive research, its mechanism of action in the treatment of wheeze remains to be clarified. Long-term administration of theophylline does not reduce bronchial hyperreactivity.

The principal drugs in this group are theophylline and its ethylenediamine salt aminophylline. Intravenous preparations of aminophylline contain about 80-85% theophylline by weight. Annex 1 shows routes of drug delivery and dosages for theophylline. Oral, rectal and intravenous preparations are available. Some workers are favourably impressed by aminophylline suppositories but others are much more negative: "The absorption of the rectal preparation is erratic, often incomplete and its use should be discouraged" and "rectal suppositories (of aminophylline) are erratically absorbed, are potentially hazardous because of easy overdosage, and therefore are not recommended." The absorption of rectal solutions in childhood has not been adequately studied and its use should be discouraged.

The oral preparations are either in forms that can be rapidly absorbed or that are more slowly absorbed but with a longer duration of action (sustained release). The rapidly absorbed theophylline has an onset of
action within about 30 minutes, maximal effect in two hours and lasts four to six hours. Sustained release preparations take effect within one to two hours and have a duration of action from eight to 24 hours. Unfortunately there is considerable variation in pharmacokinetics among different children; in addition theophylline clearance is slowed by fever and by the concomitant use of drugs such as erythromycin, but not by cotrimoxazole or amoxycillin. The absorption of slow release theophylline which is packaged in beads (sprinkle form) is erratic and is influenced by whether or not it is taken with food. These large variations in absorption and metabolism lead both to the risk of undertreatment (due to inadequate dosage) or to toxicity. In particular, fever is the most practical clinical indication for reducing theophylline dose. The only way to establish the optimum dose of theophylline is by monitoring serum concentrations; however, this is not feasible in developing countries.

Intravenous aminophylline produces bronchodilatation within five to 20 minutes, has a maximal effect within two hours and a duration of six hours. Theophylline half-life and clearance vary with age. Children one to four years of age have a much shorter half-life and higher clearance than younger infants and newborns, who are at greater risk of toxicity.

Inhaled beta-2 adrenergic agents are more effective than theophyllines in relieving acute symptoms of asthma. The real question is whether the addition of theophylline to maximal doses of beta-2 adrenergic agents has any value. The issue remains unresolved but it has proved difficult to demonstrate an additive effect. In spite of the lack of objective data some authors advocate the use of intravenous aminophylline in severe asthma not controlled by beta agonists. If aminophylline is administered intravenously, it is usual to give an initial bolus followed by a continuous infusion or regular boluses. Even when boluses are given, the aminophylline should be diluted and given slowly.

It has been suggested that theophylline could be used on a regular basis to suppress symptoms in persistent asthma. One review of the relative merits of sodium cromoglycate and theophylline suggested similar efficacy in the control of frequent episodic asthma and the view expressed was that the choice between them would usually be made on the basis of personal preference, convenience, cost and freedom from side-effects. However, theophyllines do not decrease bronchial hyperreactivity and in theory would not be expected to have an important role in prophylaxis, nor to have an anti-inflammatory effect. As indicated above, theophylline should not be regarded as preventive medication.

Unfortunately, the frequency of side-effects from theophylline is a limiting factor to their clinical usefulness. Theophylline therapy has a
relatively narrow margin of safety. The marked individual variability in absorption and metabolism of the drug and the multiple factors which can influence its pharmacokinetics increase the risk of toxicity. Common side-effects in the therapeutic range include nausea and vomiting, tachycardia, palpitations and central nervous system stimulation with anxiety and nervousness. Concern has been raised about the effects of chronic theophylline therapy on intellectual functioning and learning, with hyperactivity and poor concentration. Toxic drug overdose causes seizures, cardiac arrhythmias, hyperglycaemia, hypokalaemia, metabolic acidosis, respiratory alkalosis, hypophosphataemia and hypomagnesaemia.

WHO guidelines for the management of asthma refer to aminophylline but not to theophylline\textsuperscript{44}. A number of factors lay behind this decision. First, there is minimal difference in cost between theophylline and aminophylline tablets and only aminophylline is available as a parenteral preparation. Second, it was felt that there was a danger in recommending aminophylline ampoules and theophylline tablets owing to concerns that, despite attempts to teach staff that these were the same class of drug, some children would be poisoned by receiving both together. A third consideration was the possible confusion caused by the 20\% difference in dose between aminophylline and theophylline. Finally, aminophylline, and not theophylline, is included in the WHO Model List of Essential Drugs\textsuperscript{45}.

5.3 Anticholinergic agents

Anticholinergic alkaloids exist in a variety of plants and their use for the relief of respiratory symptoms began in India thousands of years ago\textsuperscript{46}. Experiments in the nineteenth century demonstrated that atropine blocked bronchoconstriction in dogs\textsuperscript{57}. In man, the stimulation of cholinergic parasympathetic nerves produces bronchoconstriction\textsuperscript{58}. The extent to which anticholinergic agents may inhibit bronchoconstriction by blocking the cholinergic receptors on the surface of mast cells and by inhibiting mediator release remains unclear\textsuperscript{49}. Anticholinergic preparations were the treatment of choice for asthma until they were supplanted by the development of adrenaline and ephedrine in the first decades of the twentieth century. In the last 20 years there has been a reawakening of interest in anticholinergic agents.

5.3.1 Atropine

Atropine is an effective bronchodilator but its usefulness is limited by side-effects. These include dry mouth, blurred vision and difficulty in urination. By contrast, quaternary ammonium derivative of atropine, ipratropium bromide, can be inhaled and has minimal side-effects.
5.3.2 Ipratropium bromide

Ipratropium bromide is available as a metered dose inhalation (aerosol) and a nebulizer solution. Dosages are shown in Annex 1. As a single bronchodilator it is inferior to beta-2 adrenergic drugs, with a slower onset of action and a peak effect achieved after about one hour. The amount of bronchodilatation achieved with ipratropium bromide is considered to be less than with the beta-2 adrenergic agents.

The possible therapeutic role for ipratropium bromide is in combination with a beta-2 adrenergic agent during acute attacks of asthma. A number of studies have shown that combination therapy produces more rapid control of acute, severe asthma than either agent used alone. Although it must be acknowledged that there is some dispute about its precise role, it is probably worth giving this combination to the child whose acute attack of asthma is not responding to full therapeutic doses of inhaled beta-2 adrenergic agents and systemic corticosteroids.

Ipratropium bromide has few side-effects. Its major advantage over atropine is that it is basically lipid insoluble so that when it is inhaled less than 1% of the administered dose is absorbed; the drug is relatively free from side-effects and in particular does not present the side-effects of atropine relating to the central nervous system. Ipratropium bromide does not affect respiratory mucociliary clearance, urinary flow or intraocular tension. Cough and bronchoconstriction sometimes occur with the nebulizer solution but whether preservatives or the drug are involved is unresolved.

5.4 Sodium cromoglycate

Sodium cromoglycate was synthesized in 1965. It is not a bronchodilator, and does not provide immediate relief of wheeze; it has purely prophylactic value. The mechanism of action of sodium cromoglycate is unknown. The classical view is that it stabilizes mast cells and prevents the release of the chemical mediators that are involved in the asthmatic reaction; however, other explanations are possible, including a direct effect on receptors. Regular use of sodium cromoglycate leads to a decrease in bronchial hyperreactivity.

Sodium cromoglycate is available as a metered dose inhalation (aerosol), powder inhaler device and nebulizer solution. Dosages are shown in Annex 1. Sodium cromoglycate can be used immediately before exercise to prevent exercise-induced asthma but its main role is as a regularly taken preventive therapy in children with frequent episodic asthma. It is expensive and this limits its usefulness in developing countries.

Sodium cromoglycate is remarkably free from adverse side-effects. Some children complain that the dry powder causes irritation of the
throat. Apart from this, both short- and long-term side-effects seem to be rare, with a very wide therapeutic range and minimal risk of toxicity.

5.5 Corticosteroids

Corticosteroids have been a mainstay in the treatment of asthma for 30 years: the benefits of corticosteroids administered orally and parenterally were obvious but so were the side-effects associated with their prolonged use. This stimulated a search for inhaled corticosteroids in the hope that this mode of drug delivery would be effective without systemic side-effects.

Corticosteroids have an anti-inflammatory action, acting on various components of the inflammatory response. They increase the responsivenes of the beta-2 receptors to exogenous and endogenous drugs, decrease mucosal oedema and reduce the production of mucus. Used on a regular basis they have a prophylactic effect and reduce bronchial hyperreactivity.

Oral corticosteroids are beneficial in short courses during an acute episode of asthma not responding adequately to inhaled beta-2 adrenergic agents. Intravenous corticosteroids are also effective but confer no advantage over oral corticosteroids unless the child is unable to swallow medication. Dosages are shown in Annex 1.

Corticosteroids can also be used as preventive therapy. Inhaled steroids, either via metered dose aerosol or powder inhaler device, are the preferred route of drug delivery for preventive therapy. Their main role is for preventive therapy when sodium cromoglycate has proved ineffective. Preventive therapy will rarely require long-term use of oral corticosteroids.

Inhaled corticosteroids have minor side-effects of which oropharyngeal candidiasis and hoarseness and weakness of the voice (dysphonia) are the most common. Short-term courses of oral corticosteroids (up to two weeks) present minor risks of adverse effects. However, long-term therapy may be associated with important side-effects. These include growth suppression, excessive weight gain, adrenal suppression, hypertension, osteoporosis, cataracts, hyperglycaemia and impairment of the immunological defences against infections.

It must be stated explicitly that oral corticosteroids (e.g., prednisolone 1mg/kg/dose twice a day for up to five days) are often necessary in an acute attack of asthma; by contrast, oral steroids for prevention of asthma should only be prescribed by specialists. The use of steroids should be avoided if the child has HIV infection, or is suspected of having tuberculosis infection, or has been exposed to varicella in the
previous three weeks (because of the risk of disseminated fatal varicella).

5.6 Other agents

Ketotifen, an antihistamine, has been widely promoted, particularly in Europe and developing countries, as a preventive agent for asthma. Controlled trials have not shown that it has an important role in the management of asthma7.

6. METHODS OF AEROSOL DELIVERY

In most circumstances the greatest bronchodilatation is achieved fastest and with fewest side-effects by using the aerosol route of delivery72-74. This allows a higher concentration of active drug to reach the target airway cells with a lower total dose than is possible by other routes of delivery. The three methods of aerosol delivery currently available are nebulization, pressurized metered dose-inhalation (MDI), and dry powder inhalation. If equivalent doses and correct inhalation techniques are used these methods are equally effective for treating children with wheeze. However, most studies have used nebulized treatments for infants and young children because of practical problems in using metered dose inhalers. Unfortunately, it is difficult to obtain objective measurements of improvement in young children due to the difficulty in measuring pulmonary function in these age groups. Consequently, there are only a limited number of studies comparing nebulized and metered inhalation therapy in young children. In theory, when airway obstruction is severe, the reduced air entry may not allow inhaled drugs to reach the peripheral airways; in practice, however, there is no consistent difference in efficacy between inhaled and intravenous bronchodilators, even in acute severe wheezing attacks75.

6.1 Nebulization

Beta-2 adrenergic agents can be given effectively by nebulization using an electric air compressor or continuous flow oxygen at six to eight litres per minute76-78. One end of the oxygen tubing should be attached to a nebulizer and the other to the electric compressor or oxygen regulator. A t-piece or mask is attached to the top of the nebulizer. Infants and young children require the aerosol mask. The bronchodilator and 2-4 mls of normal saline or sterile water are placed in the plastic nebulizer compartment. The patient should be treated until the liquid in the nebulizer has been almost used up, which usually occurs in five to ten minutes. It is unnecessary to nebulize until all the liquid has been used — in practice about 0.25 to 0.5 mls will be left in the nebulizer bowl when a spluttering sound occurs and little of the residual fluid is being nebulized. If normal saline or sterile water is not available for diluting the beta-2 adrenergic agent, drinking water should
be strained with a cloth and boiled for 20 minutes, then allowed to
cool. The tubing and nebulizer should be washed with non-residue soap
(dishwashing detergent) and dried prior to reuse (but not sterilized with
ethylene oxide because of the risk of formation of toxic by-products).
Boiling or autoclaving will destroy the tubing.

Drug delivery from these systems requires careful attention to the
design of the nebulizer\textsuperscript{29}. The respirable output is a single measure of
effective aerosol production. It is defined as the volume of respirable
particles (size less than 5 microns) produced per minute. If the
respirable output is low, the nebulizer system is poor at delivering
bronchodilator to the airways.

Another difficulty occurs when electric compressors, and oxygen
cylinders and regulators are unavailable. In these cases, the best
alternative is the administration of bronchodilators through pressurized
metered-dose inhalers with spacer device (see section 6.2). A second,
but less recommended alternative, is the use of a foot-pump to drive a
nebulizer. The foot-pump must be suitable for this purpose: robust,
durable and easy to operate and maintain. It must also be grease-free,
because grease particles must not be inadvertently mixed with the
bronchodilator and delivered to the airways. Only well-designed and
very efficient nebulizers should be used. They must produce a high
respirable output when driven by the foot-pump at a stroke rate that
can be maintained by the health worker for the time needed to nebulize
about 5 ml of solution. An aerosol mask must be attached to the top of
the nebulizer. The instructions for administration are the same as
described above for electric air compressor or oxygen-driven
nebulizers.

6.2 Pressurized metered-dose inhalers with spacer device

Most children under seven to eight years of age will be unable to
effectively use metered dose inhalation when they are wheezing,
although many young children can manage them when they are free of
symptoms. However, metered dose inhalers can be modified for use by
infants and young children with an appropriate spacer device\textsuperscript{80-85}. Some
of the commercially available spacer devices have a volume of
approximately 750 ml (Figure 1). The spacer allows slowing of the
cloud of spray by air resistance and more time for propellant
evaporation to occur. This results in smaller particles at a lower
velocity and therefore greater potential for penetration into the
peripheral airways. It also allows effective administration which is less
critically dependent on the timing of inspiration with activation of the
aerosol.

Effective, simple, inexpensive spacers can be constructed from (a) large
paper, plastic or wax cups\textsuperscript{86,87} (Figure 2), (b) a one-litre plastic
bottle\textsuperscript{68,69}, or (c) a plastic bag\textsuperscript{90,91}. If the child is able to breathe with a mouthpiece, methods (b) and (c) can be used as follows:

1. the inhaler is inserted into the bag or bottle;
2. it is depressed to generate two doses (for example 200 micrograms of salbutamol);
3. the child is instructed to inhale with the mouth closed around the mouthpiece for five breaths.

A spacer with a mask can be used to treat infants and young children who cannot use a mouthpiece\textsuperscript{63,65} (Figure 3). A less sophisticated system is one in which the open end of a large paper, plastic or wax cup is placed over the child’s nose and mouth, and the metered dose inhaler is placed in the smaller opening made at the base of the cup\textsuperscript{63,65}. A less sophisticated system is one in which the open end of the cup is placed over the child’s nose and mouth, and two to ten doses are delivered while the child breathes in and out. Even if the child is uncooperative, the system ensures drug delivery to the lungs.
Figure 1

Metered dose inhaler attached to a large-volume spacer
(volume 750 ml)

Figure 2

Metered dose inhaler attached to a plastic cup
(volume 150 ml)
6.3 Dry powder inhalation

Devices are available for dry powder inhalation of beta-2 adrenergic agents and sodium cromoglycate. These allow drug delivery without the need to closely coordinate breathing with activation of an inhaler (as with the use of an MDI alone). Various systems exist but all require the child to inhale a powder by sucking on a small device. When properly used, both metered dose and dry powder inhalers have been shown to be as effective in delivering beta-2 agents as nebulized
6.4 Preferred method

All the techniques mentioned above have a role in the management of wheezing. In particular, bronchodilator delivered via a nebulizer driven by an electric compressor pump or gas cylinder is a well-established technique. Small health care facilities in developing countries may not have air compressors, may lack a regular electricity supply and may treat oxygen in cylinders as an expensive resource that is too valuable to be used as a drug delivery system. In terms of ease of administration, availability and effectiveness, metered dose inhaler and spacer devices may be the most appropriate method for administering inhaled medications to young children at home and in outpatient facilities.

7. MANAGEMENT OF ACUTE EPISODES OF WHEEZE

7.1 Rationale

This section is designed to link the material provided in the previous sections with the guidelines for the management of young children with cough or difficult breathing and wheeze that have been published by the WHO ARI Programme\textsuperscript{34,93}.

The management of acute episodes of wheeze in young children in developing countries with high infant mortality rates differs significantly from that in developed countries. In particular, in developed countries the emphasis is on the diagnosis of whether the wheeze is due to asthma, to bronchiolitis, or to pneumonia; the treatment of wheeze is determined in the context of the underlying illness. By contrast in developing countries, as there is a substantial incidence of bacterial pneumonia in children visiting health facilities and as pneumonia is a major cause of death in the first five years of life, the first and most important concern in children who present with wheeze is to recognize and treat pneumonia. Both pneumonia and the other wheeze-associated illnesses can cause chest indrawing and fast breathing. Care must be taken therefore when treating wheeze not to miss treating pneumonia with an antibiotic. This policy has been given further support by recent data from Pakistan showing that a high proportion of children with bacterial pneumonia presented with wheeze\textsuperscript{3}. 

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The WHO guidelines for the management of young children with wheeze should enable effective treatment of most children with wheeze and ensure that due attention is given to the possibility of pneumonia without unnecessary referral to hospital. Separate guidelines are given for children from 2 months up to 5 years of age and for young infants under 2 months of age.

7.2 Children 2 months up to 5 years

In all children with an acute respiratory illness, the priority is to diagnose whether or not pneumonia is present. The protocol presented in Table 1 shows the order of priority when classifying pneumonia. The emphasis is on ensuring that (a) antibiotics are given if pneumonia is present and (b) the severity of illness is classified so that a decision can be made whether or not to refer (or admit) the child to hospital.

The protocol recognizes that some children classified as having very severe disease, severe pneumonia or pneumonia may also have a wheezing condition (such as asthma or bronchiolitis) that requires specific management (for example, a bronchodilator). Each treatment box therefore states: "Treat wheezing, if present". Thus the presence of wheeze leads to further decisions before a final decision is made about treatment. As seen in Table 2, a history is obtained as to whether there have been previous episodes of wheeze and the child is examined for evidence of respiratory distress. "Respiratory distress" is defined as difficult feeding, drinking or talking (child is too breathless to feed, or to drink, or to talk), or the child is uncomfortable and obviously not getting enough air, caused by breathing difficulty.

The first episode of wheeze in an infant under 6 months of age is probably due to bronchiolitis. As the age of onset of the first episode of wheeze increases, the likelihood that the wheeze represents an initial attack of asthma is greater. At 18 months, bronchiolitis is unlikely. Recurrent episodes of wheeze suggest asthma.

Children with a first episode of wheeze who are breathing comfortably and who are not in respiratory distress can be managed with an oral bronchodilator such as salbutamol. Consensus does not exist among paediatricians as to whether or not to treat all children over 2 months of age who have an initial episode of wheeze. The rationale for the use of a bronchodilator in the first episode of wheeze is that a proportion of children will respond. A second advantage is that the management of wheeze is standardized so that the health worker does not have to determine whether the diagnosis is asthma or bronchiolitis.
Table 1: Management of the child with cough or difficult breathing — from the WHO ARI Programme chart for health workers at first-level (outpatient) facilities.

## THE CHILD

**AGE 2 MONTHS UP TO 5 YEARS**

<table>
<thead>
<tr>
<th>SIGNS:</th>
<th>VERY SEVERE DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Not able to drink,</td>
<td></td>
</tr>
<tr>
<td>• Convulsions,</td>
<td></td>
</tr>
<tr>
<td>• Abnormally sleepy or</td>
<td></td>
</tr>
<tr>
<td>difficult to wake,</td>
<td></td>
</tr>
<tr>
<td>• Stridor in calm child, or</td>
<td></td>
</tr>
<tr>
<td>• Severe malnutrition.</td>
<td></td>
</tr>
<tr>
<td>CLASSIFY AS:</td>
<td></td>
</tr>
<tr>
<td>TREATMENT:</td>
<td></td>
</tr>
<tr>
<td>• Refer URGENTLY to hospital.</td>
<td></td>
</tr>
<tr>
<td>• Give first dose of an antibiotic.</td>
<td></td>
</tr>
<tr>
<td>• Treat fever, if present.</td>
<td></td>
</tr>
<tr>
<td>• Treat wheezing, if present.</td>
<td></td>
</tr>
<tr>
<td>• If cerebral malaria is possible, give an antimalarial.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SIGNS:</th>
<th>SEVERE PNEUMONIA</th>
<th>PNEUMONIA</th>
<th>NO PNEUMONIA: COUGH OR COLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Chest indrawing. [If also recurrent wheezing, go directly to Treat Wheezing]</td>
<td>• No chest indrawing, and</td>
<td>• No chest indrawing, and</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Fast breathing (50 per minute or more if child 2 months up to 12 months; 40 per minute or more if child 12 months up to 5 years).</td>
<td>• No fast breathing (Less than 50 per minute if child 2 months up to 12 months; Less than 40 per minute if child 12 months up to 5 years).</td>
<td></td>
</tr>
<tr>
<td>CLASSIFY AS:</td>
<td>SEVERE PNEUMONIA</td>
<td>PNEUMONIA</td>
<td>NO PNEUMONIA: COUGH OR COLD</td>
</tr>
<tr>
<td>TREATMENT:</td>
<td>Refer URGENTLY to hospital.</td>
<td></td>
<td>If coughing more than 30 days, refer for assessment.</td>
</tr>
<tr>
<td></td>
<td>Give first dose of an antibiotic.</td>
<td>• Advise mother to give home care.</td>
<td>• Assess and treat ear problem or sore throat, if present. (see chart).</td>
</tr>
<tr>
<td></td>
<td>Treat fever, if present.</td>
<td>• Give an antibiotic.</td>
<td>• Assess and treat other problems.</td>
</tr>
<tr>
<td></td>
<td>Treat wheezing, if present. (If referral is not feasible, treat with an antibiotic and follow closely.)</td>
<td>• Treat fever, if present.</td>
<td>• Advise mother to give home care.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Treat wheezing, if present.</td>
<td>• Treat fever, if present.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Advise mother to return with child in 2 days for reassessment, or earlier if the child is getting worse.</td>
<td></td>
</tr>
</tbody>
</table>

Reassess in 2 days a child who is taking an antibiotic for pneumonia:

<table>
<thead>
<tr>
<th>SIGNS:</th>
<th>IMPROVING</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Not able to drink.</td>
<td>• Breathing slower.</td>
</tr>
<tr>
<td>• Has chest indrawing.</td>
<td>• Less fever.</td>
</tr>
<tr>
<td>• Has other danger signs.</td>
<td>• Eating better.</td>
</tr>
<tr>
<td>TREATMENT:</td>
<td>THE SAME</td>
</tr>
<tr>
<td>Refer URGENTLY to hospital.</td>
<td>Change antibiotic or Refer.</td>
</tr>
</tbody>
</table>

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Table 2: Guidelines on treatment of wheezing from the WHO/ARI Programme chart for health workers at first-level (outpatient) facilities.

**Treat Wheezing**

### Children with First Episode of Wheezing
- If in respiratory distress ➔ Give a rapid-acting bronchodilator and refer.
- If not in respiratory distress ➔ Give oral salbutamol.

### Children with Recurrent Wheezing (Asthma)
- Give a rapid acting bronchodilator
- Assess the child’s condition 30 minutes later:

**IF:**
- RESPIRATORY DISTRESS OR ANY DANGER SIGN ➔ Treat for SEVERE PNEUMONIA or VERY SEVERE DISEASE (Refer).
- NO RESPIRATORY DISTRESS AND:
  - FAST BREATHING ➔ Treat for PNEUMONIA. Give oral salbutamol.
  - NO FAST BREATHING ➔ Treat for NO PNEUMONIA: COUGH OR COLD. Give oral salbutamol.

### RAPID ACTING BRONCHODILATOR
- Nebulized Salbutamol (5 mg/ml) 0.5 ml Salbutamol plus 2.0 ml sterile water
- Subcutaneous Epinephrine (adrenaline) (1:1000 = 0.1%): 0.01 ml per kg body weight

### ORAL SALBUTAMOL ➔ Three times daily for five days

<table>
<thead>
<tr>
<th>AGE or WEIGHT</th>
<th>2 mg tablet</th>
<th>4 mg tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 months up to 12 months (&lt; 10 kg)</td>
<td>1/2</td>
<td>1/4</td>
</tr>
<tr>
<td>12 months up to 5 years (10-19 kg)</td>
<td>1</td>
<td>1/2</td>
</tr>
</tbody>
</table>
Children who are in respiratory distress or who have a recurrent episode of wheeze should be examined further by assessing the response to rapid-acting bronchodilator (such as nebulized salbutamol). The child’s condition should be assessed soon after and then at least 30 minutes after the administration of the rapid-acting bronchodilator, as the condition of some children will deteriorate after an initial improvement. Signs of improvement include less chest indrawing, less respiratory distress and improved air entry. Usually the wheeze will decrease but if the child had very poor entry before treatment it may actually increase; similarly, the respiratory rate will usually fall but if the asthma was very severe and associated with apnoea and exhaustion, the respiratory rate may increase after treatment.

Table 3 shows the protocol for the management of children with persisting respiratory distress at first referral hospitals. The treatment includes oxygen, rapid acting bronchodilators, antibiotics and supportive care.

Children with bronchiolitis cannot be reliably distinguished clinically from children suffering from wheeze associated with bacterial pneumonia. Antibiotic therapy therefore should be given to those with fast breathing or persistent respiratory distress. However, if at this stage a doctor considers that an episode of recurrent wheeze is due to asthma, an antibiotic is not usually necessary.

7.3 Young infants under 2 months of age

Young infants presenting with wheeze should be classified as having very severe disease, as seen in Table 4. In this age group wheeze is considered to be a danger sign and should lead to the young infant being referred to hospital for further assessment and treatment.

It is recognized that some of the young infants classified as having very severe disease or severe pneumonia may have bronchiolitis (asthma is unlikely in this age group). However, the treatment recommendations shown in Table 4 are appropriate since it is difficult to distinguish clinically bronchiolitis from pneumonia, and the two conditions can often co-exist.

The use of bronchodilators to treat wheeze in the first two months of life is controversial. The protocol that has been developed by WHO is the administration of a rapid-acting bronchodilator (such as inhaled salbutamol) as a therapeutic trial. If inhaled salbutamol is ineffective, further bronchodilators are not administered. Antibiotics, oxygen and supportive therapy should be given as shown in Table 3.
Table 3: Summary of treatment instructions for children with wheeze — from the WHO/ARI Programme guidelines for doctors and other senior health workers at small hospitals.

### Summary of treatment instructions for children with wheezing

If the child is in respiratory distress or if this is a recurrent episode of wheezing:

- give salbutamol by nebulizer or metered-dose inhaler (substitute subcutaneous epinephrine if no salbutamol), then decide on management based on the child’s response at least 30 minutes later.

<table>
<thead>
<tr>
<th>CLINICAL SIGNS</th>
<th>SUMMARY OF TREATMENT INSTRUCTIONS</th>
</tr>
</thead>
</table>
| - Central cyanosis or Not able to drink.  | ADMIT  
Give oxygen.  
Give rapid-acting bronchodilators.  
**Give an antibiotic:** chloramphenicol.  
Treat fever, if present.  
Supportive care. |
| Respiratory distress persists with:  | ADMIT  
Give rapid-acting bronchodilator.  
**Give an antibiotic:** benzylpenicillin.  
Treat fever, if present.  
Supportive care. |
|   - No central cyanosis and Able to drink.  |                                                |
| No respiratory distress and:  | ADVISE MOTHER TO GIVE HOME CARE  
Give oral salbutamol at home.  
**Give an antibiotic** (at home): cotrimoxazole, amoxycillin, ampicillin or procaine penicillin.  |
|   - Fast breathing  |                                                |
|   - No fast breathing  | ADVISE MOTHER TO GIVE HOME CARE  
Give oral salbutamol at home. |

* An antibiotic is usually not necessary if the child has asthma.
* If oxygen supply is ample, also give oxygen to a child with restlessness (if oxygen improves the condition), or severe chest indrawing, or a breathing rate of 70 breaths per minute or more.
* Fast breathing is: 50 breaths per minute or more in a child age 2 months up to 12 months; 40 breaths per minute or more in a child age 12 months up to 5 years.
Table 4: Management of the young infant with cough or difficult breathing — from the WHO/ARI Programme chart for health workers at first-level (outpatient) facilities.

## THE YOUNG INFANT
**(AGE LESS THAN 2 MONTHS)**

<table>
<thead>
<tr>
<th>SIGNS:</th>
<th>VERY SEVERE DISEASE</th>
<th>SEVERE PNEUMONIA</th>
<th>NO PNEUMONIA: COUGH OR COLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Stopped feeding well,</td>
<td>• Refer URGENTLY to hospital.</td>
<td>• Severe chest indrawing, or</td>
<td>• Advise mother to give the following home care:</td>
</tr>
<tr>
<td>• Convulsions,</td>
<td>• Keep young infant warm.</td>
<td>• Fast breathing (60 per minute or MORE).</td>
<td>• Keep young infant warm.</td>
</tr>
<tr>
<td>• Abnormally sleepy or</td>
<td>• Give first dose of an antibiotic.</td>
<td>• No severe chest indrawing, and</td>
<td>• Breast-feed frequently.</td>
</tr>
<tr>
<td>difficult to wake.</td>
<td>(If referral is not feasible, treat with an antibiotic and follow closely.)</td>
<td>• No fast breathing (LESS than 60 per minute).</td>
<td>• Clear nose if it interferes with feeding.</td>
</tr>
<tr>
<td>• Stridor in calm child,</td>
<td></td>
<td></td>
<td>• Return quickly if:</td>
</tr>
<tr>
<td>• Wheezing, or</td>
<td></td>
<td></td>
<td>• Breathing becomes difficult.</td>
</tr>
<tr>
<td>• Fever or low body temperature.</td>
<td></td>
<td></td>
<td>• Breathing becomes fast.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Feeding becomes a problem.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• The young infant becomes sicker.</td>
</tr>
</tbody>
</table>

TREATMENT:
8. SUMMARY

The management of wheeze in children must be viewed in the context that bacterial pneumonia is the main cause of respiratory mortality in young children in developing countries. Doctors in developed countries often believe that wheeze is associated with viral but not bacterial infections. However, some studies showing a high frequency of combined viral and bacterial infections have indicated that up to half of outpatient cases with documented *H. influenzae* and *S. pneumoniae* bacteraemic pneumonia had wheeze. This means that the diagnosis and treatment of bacterial pneumonia remains the priority.

The first-line bronchodilator for the management of acute episodes of wheeze is a beta-2 adrenergic agent such as salbutamol.

Financial restraints will limit the feasibility of long-term preventive therapy of acute episodes of wheeze due to asthma. Sodium cromoglycate and inhaled corticosteroids are the best therapeutic options. All these possible therapies need to be considered in the light of the WHO Essential Drugs List of therapies for asthma (Annex 2).

The main therapeutic drugs used in acute asthma are an inhaled beta-2 adrenergic agent with oral corticosteroids added if necessary. This will achieve bronchodilatation and reversal of the airway narrowing caused by mucosal oedema, by mucus hypersecretion, and by smooth muscle spasm. The prevention of recurrent wheeze should focus on the use of sodium cromoglycate or of inhaled corticosteroids. The use of long-term beta agonist therapy on its own is inappropriate, as it will not decrease airway inflammation. In addition to drug prevention, allergen avoidance has a role in some cases.

This review paper has focused on the management of wheezing illnesses in young children in countries in which there is a high infant mortality rate and in which bacterial pneumonia is a significant public health problem. Detailed guidelines for the assessment and treatment of childhood asthma in industrialized countries have recently been published by an international expert group. It is important that these guidelines be considered together with the issues raised in this review paper in developing country settings.
REFERENCES


## ANNEX 1 Presentation and dosage of bronchodilators and other drugs for the treatment of wheeze

These dosages are guidelines for children up to five years old. Other treatment regimens may be appropriate. All drug dosages should be considered with regard to manufacturers’ recommendations. Packaging and strength of formulations vary in some countries.

<table>
<thead>
<tr>
<th>DRUG BY ROUTE OF DELIVERY</th>
<th>DOSING INTERVALS</th>
<th>ACUTE EPISODE</th>
<th>MAINTENANCE</th>
<th>PRODUCTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SALBUTAMOL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>oral</td>
<td>2-11 months 1 mg/dose</td>
<td>6-8 hourly</td>
<td>8-hourly</td>
<td>Syrup: 2mg/5ml Tablets: 2 and 4 mg</td>
</tr>
<tr>
<td></td>
<td>1-4 years 2 mg/dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>metered dose inhalation (aerosol) with spacer</td>
<td>200 mcg/2 doses</td>
<td>4-hourly</td>
<td>6-8 hourly</td>
<td>200 doses per inhaler</td>
</tr>
<tr>
<td>nebulized *</td>
<td>2.5 mg/dose</td>
<td>4-hourly</td>
<td>6-8 hourly</td>
<td>5mg/ml solution 2.5mg in 2.5ml single dose units</td>
</tr>
<tr>
<td>dry powder **</td>
<td>200 mcg</td>
<td>4-hourly</td>
<td>6-8 hourly</td>
<td>200 mcg/capsule</td>
</tr>
<tr>
<td>parenteral intravenous</td>
<td>10 mcg/kg over 10 mins followed by continuous infusion 0.2 mcg/kg/min to max 2 mcg/kg/min</td>
<td></td>
<td></td>
<td>0.05 mg/ml in 5 ml ampoules</td>
</tr>
<tr>
<td><strong>TERBRUTALINE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>oral</td>
<td>0.075mg/kg/dose</td>
<td>6-6 hourly</td>
<td>8 hourly</td>
<td>Tablet: 2.5, 5 mg Syrup: 3mg/10ml</td>
</tr>
<tr>
<td>metered dose inhalation (aerosol)</td>
<td>500 mcg/2 doses</td>
<td>4-hourly</td>
<td>6-8 hourly</td>
<td>200 doses per inhaler</td>
</tr>
<tr>
<td>nebulized *</td>
<td>5mg/dose</td>
<td>4-hourly</td>
<td>6-8 hourly</td>
<td>10mg/ml solution 5mg in 2.5ml single dose units</td>
</tr>
<tr>
<td>dry powder **</td>
<td>500mcg</td>
<td>4-hourly</td>
<td>6-8 hourly</td>
<td>200 doses per turbuhaler</td>
</tr>
<tr>
<td>parenteral subcutaneous injection</td>
<td>0.005mg/kg/dose</td>
<td>4-hourly</td>
<td></td>
<td>0.1mg/ml 0.5mg/ml</td>
</tr>
<tr>
<td><strong>ORCIPRENAINE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>oral</td>
<td>0.4 mg/kg/dose</td>
<td>6-6 hourly</td>
<td>8 hourly</td>
<td>Syrup: 10mg/5ml Tablets: 10 and 20 mg</td>
</tr>
<tr>
<td>metered dose inhalation (aerosol)</td>
<td>1500 mcg/2 doses</td>
<td>4-hourly</td>
<td>6-8 hourly</td>
<td>200 doses per inhaler</td>
</tr>
<tr>
<td>nebulized **</td>
<td>0.8 ml/dose</td>
<td>4-hourly</td>
<td>6-8 hourly</td>
<td></td>
</tr>
<tr>
<td><strong>EPINEPHRINE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>parenteral subcutaneous injection</td>
<td>0.01ml/kg/dose (max 0.3ml)</td>
<td>4-hourly</td>
<td></td>
<td>1:1000 sol (1mg/ml)</td>
</tr>
</tbody>
</table>

35
<table>
<thead>
<tr>
<th>THEOPHYLLINE</th>
<th>5mg/kg/dose</th>
<th>6-hourly</th>
<th>12-hourly</th>
<th>Liquid: 105 mg/5ml sustained release preparation: 50, 75, 100, 125, 200, 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>oral</td>
<td>sustained release theophylline twice the above dosages</td>
<td></td>
<td>12-hourly</td>
<td></td>
</tr>
<tr>
<td>AMINOPHYLLINE</td>
<td>6mg/kg/dose</td>
<td>6-hourly</td>
<td></td>
<td>Tablet 100mg, 200mg</td>
</tr>
<tr>
<td>oral</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>parenteral intravenous</td>
<td>Initial dose 5-6 mg/kg/dose (max 300mg) if patient has not taken aminophylline theophylline within 24 hours and maintenance 5 mg/kg/dose OR continuous infusion 0.9 mg/kg/hr</td>
<td></td>
<td></td>
<td>250 mg/10 ml ampoule</td>
</tr>
<tr>
<td>CORTICOSTEROIDS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>oral</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>prednisolone</td>
<td>0.5-1.0 mg/kg/dose</td>
<td>12-hourly</td>
<td></td>
<td>Syrup: 5mg/5ml Tablets: 1.5,25 mg</td>
</tr>
<tr>
<td>parenteral intravenous</td>
<td>4 mg/kg/dose</td>
<td>6-hourly</td>
<td></td>
<td>Vials: 100, 250, 500, 1000 mg</td>
</tr>
<tr>
<td>hydrocortisone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sodium succinate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>parenteral intravenous</td>
<td>1 mg/kg/dose</td>
<td>6-hourly</td>
<td></td>
<td>Vials: 40, 125, 500, 1000 mg</td>
</tr>
<tr>
<td>methylprednisolone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Na succinate)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>parenteral</td>
<td>0.2 mg/kg</td>
<td>24-hourly</td>
<td></td>
<td>Vials: 4 mg</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>BECLOMETASONE</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>PROPIONATE</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>metered dose</td>
<td>50-250mcg</td>
<td>12-hourly</td>
<td></td>
<td>50mcg/dose, 100mcg/dose, 250mcg/dose inhalers All 200 doses</td>
</tr>
<tr>
<td>inhalation (aerosol)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dry powder **</td>
<td>100-200 mcg</td>
<td>12-hourly</td>
<td></td>
<td>100 mcg caps, rotahaler</td>
</tr>
<tr>
<td>BUDESONIDE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>metered dose</td>
<td>50-200mcg</td>
<td>12-hourly</td>
<td></td>
<td>50mcg,100mcg,200mcg/dose 200 doses per inhaler</td>
</tr>
<tr>
<td>inhalation (aerosol)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dry powder **</td>
<td>100-400mcg</td>
<td>12-hourly</td>
<td></td>
<td>100mcg,200mcg,400mcg/dose turbuhaler</td>
</tr>
<tr>
<td>nebulized *</td>
<td>0.5mg/2mls</td>
<td>12-hourly</td>
<td></td>
<td>0.5mg/2ml single dose units</td>
</tr>
<tr>
<td>IPRATROPIUM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BROMIDE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>metered dose</td>
<td>40mcg/2 doses</td>
<td>6-hourly</td>
<td></td>
<td>200 doses per inhaler</td>
</tr>
<tr>
<td>inhalation (aerosol)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nebulized *</td>
<td>250 mcg/dose</td>
<td>6-hourly</td>
<td></td>
<td>250 mcg/2mls</td>
</tr>
<tr>
<td>SODIUM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CROMOGLYCLATE</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>metered dose</td>
<td>2 mg/2 doses</td>
<td>6-8 hourly</td>
<td></td>
<td>200 doses per inhaler</td>
</tr>
<tr>
<td>inhalation (aerosol)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nebulized *</td>
<td>20 mg/dose</td>
<td>6-8 hourly</td>
<td></td>
<td>20 mg/2 ml sol</td>
</tr>
<tr>
<td>dry powder **</td>
<td>20 mg</td>
<td>6-8 hourly</td>
<td></td>
<td>Capsule: 20 mg</td>
</tr>
</tbody>
</table>

* Diluted in 2-4 ml of normal saline. ** Used in rotahaler, spinhaler or turbuhaler.
ANNEX 2  Bronchodilators and other drugs for the treatment of wheeze included in the WHO list of essential drugs

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>UNICEF STOCK NO</th>
<th>UNIT</th>
<th>PRICE US$</th>
</tr>
</thead>
<tbody>
<tr>
<td>SELECTIVE BETA-2 ADRENERGICS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salbutamol Tablet 2mg</td>
<td>Not included</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salbutamol Tablet 4mg</td>
<td>1562015</td>
<td>1000 tab/pack</td>
<td>3.91/pack</td>
</tr>
<tr>
<td>Salbutamol Tablet 4mg</td>
<td>1562030</td>
<td>100 tab/pack</td>
<td>0.49/pack</td>
</tr>
<tr>
<td>Salbutamol Oral inhaler 0.1mg/dose — 200 doses</td>
<td>1562020</td>
<td>200 dose/inhaler</td>
<td>2.80/inhaler</td>
</tr>
<tr>
<td>Salbutamol Syrup 2mg/5ml</td>
<td>Not included</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salbutamol Injection 0.08mg/ml in 5ml ampoule</td>
<td>Not included</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salbutamol Solution for use in nebulizers 5mg/ml</td>
<td>Not included</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NON-SELECTIVE ADRENERGICS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine injection 1mg/1ml amps</td>
<td>1501000</td>
<td>10 amps/box</td>
<td>1.10/box</td>
</tr>
<tr>
<td>AMINOPHYLLINE (86% THEOPHYLLINE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminophylline Tablet 200 mg</td>
<td>1505010</td>
<td>100 tab/pack</td>
<td>0.77/pack</td>
</tr>
<tr>
<td>Aminophylline Tablet 100 mg</td>
<td>1505025</td>
<td>1000 tab/pack</td>
<td>4.17/pack</td>
</tr>
<tr>
<td>Aminophylline Injection 250 mg/10ml amp</td>
<td>1505015</td>
<td>10 amps/box</td>
<td>1.45/box</td>
</tr>
<tr>
<td>CORTICOSTEROIDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beclomethasone Oral inhaler 0.05mg/dose — 200 doses</td>
<td>1511500</td>
<td>200 dose/inhaler</td>
<td>3.22/inhaler</td>
</tr>
<tr>
<td>Hydrocortisone Powder for injection 100mg/vial</td>
<td>1552610</td>
<td>10 vials/box</td>
<td>5.48/box</td>
</tr>
</tbody>
</table>

References:


(b) UNICEF. Essential drugs price list, Copenhagen, January-June 1993.