

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

Programme for the Control of  
Acute Respiratory Infections

World Health Organization  
Geneva



## TABLE OF CONTENTS

1. INTRODUCTION .....	1
2. WHEEZE AND ITS SIGNIFICANCE .....	1
3. BRONCHIOLITIS .....	2
4. ASTHMA .....	3
5. DRUGS USED TO TREAT ASTHMA .....	5
5.1 Beta adrenergic agents .....	5
5.1.1 Mechanisms of action .....	5
5.1.2 Non-selective adrenergic agents .....	6
5.1.3 Non-selective beta-2 adrenergic agents .....	7
5.1.4 Selective beta-2 adrenergic agents .....	7
5.2 Theophylline .....	8
5.3 Anticholinergic agents .....	10
5.3.1 Atropine .....	10
5.3.2 Ipratropium bromide .....	11
5.4 Sodium cromoglycate .....	11
5.5 Corticosteroids .....	12
5.6 Other agents .....	13
6. METHODS OF AEROSOL DELIVERY .....	13
6.1 Nebulization .....	13
6.2 Pressurized metered-dose inhalers with spacer device .....	14
6.3 Dry powder inhalation .....	17
6.4 Preferred method .....	18
7. MANAGEMENT OF ACUTE EPISODES OF WHEEZE .....	18
7.1 Rationale .....	18
7.2 Children 2 months up to 5 years .....	19
7.3 Young infants under 2 months of age .....	22
8. SUMMARY .....	25
REFERENCES .....	27
ANNEX 1 .....	35
ANNEX 2 .....	37



## Acknowledgements

The World Health Organization Programme for the Control of Acute Respiratory Infections expresses its appreciation to the following for their valuable collaboration in the preparation of this document:

Dr Richard Henry  
Professor of Paediatrics  
University of Newcastle  
Newcastle, NSW, Australia,

Dr Steve Berman  
Professor of Paediatrics  
University of Colorado Health Sciences Center  
Denver, Colorado, USA,

and Dr Harry Campbell  
Consultant in Maternal and Child Health  
Fife County Health Board  
Fife County, Scotland, UK.

The Programme also wishes to express its appreciation to:

Dr Steve Abman, University of Colorado Health Sciences Center, Denver, USA  
Dr Allan Adenoff, National Jewish Hospital, Denver, USA  
Professor Peter J. Barnes, National Heart and Lung Institute, London, UK  
Dr Peter Burney, St Thomas's Hospital, London, UK  
Dr Javier Mallol, Paediatric Pulmonologist, La Serena, Chile  
Professor A.D. Milner, St Thomas's Hospital, London, UK  
Dr Frank Shann, Royal Children's Hospital, Melbourne, Australia  
Professor Hamish Simpson, School of Medicine, Leicester, UK  
Dr Peter Sly, Princess Margaret Hospital for Children, Perth, Australia

for their expert comments at different stages in the preparation of this document.



## 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<sup>1</sup>. 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<sup>2</sup>. 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*<sup>3</sup>, or in mixed viral-bacterial lower respiratory infections<sup>4,5</sup>. 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,<sup>7</sup> 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<sup>7</sup>. 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 air flow 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<sup>6,7</sup>. 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%<sup>8</sup>. 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<sup>7</sup>. 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<sup>7</sup>. 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<sup>9</sup>.

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<sup>10-15</sup>. 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<sup>16,17</sup>. 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<sup>18,19</sup>. 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

预览已结束，完整报告链接和二维码如下：

[https://www.yunbaogao.cn/report/index/report?reportId=5\\_30725](https://www.yunbaogao.cn/report/index/report?reportId=5_30725)

