Prim Care Respir J 2012; 21(2): 214-219

Primary Care RESPIRATORY JOURNAL
www.thepcrj.org

DISCUSSION PAPER

Childhood asthma in low income countries: an invisible killer?

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Originally received 6th December 2011; resubmitted 14th February 2012; revised 5th March 2012; accepted 13th March 2012; online 23rd May 2012

Abstract

Bacterial pneumonia has hitherto been considered the key cause of the high respiratory morbidity and mortality in children under five years of age (under-5s) in low-income countries, while asthma has not been stated as a significant reason. This paper explores the definitions and concepts of pneumonia and asthma/wheezing/bronchiolitis and examines whether asthma in under-5s may be confused with pneumonia. Over-diagnosing of bacterial pneumonia can be suspected from the limited association between clinical pneumonia and confirmatory test results such as chest x-ray and microbiological findings and poor treatment results using antibiotics. Moreover, children diagnosed with recurrent pneumonia in infancy were often later diagnosed with asthma. Recent studies showed a 10–15% prevalence of preschool asthma in low-income countries, although under-5s with long-term cough and difficulty breathing remain undiagnosed. New studies demonstrate that approximately 50% of acutely admitted under-5s diagnosed with pneumonia according to Integrated Management of Childhood Illnesses could be re-diagnosed with asthma or wheezing when using re-defined diagnostic criteria and treatment. It is hypothesised that untreated asthma may contribute to respiratory mortality since respiratory syncytial virus (RSV) is an important cause of respiratory death in childhood, and asthma in under-5s is often exacerbated by viral infections, including RSV. Furthermore, acute respiratory treatment failures were predominantly seen in under-5s without fever, which suggests the diagnosis of asthma/wheezing rather than bacterial pneumonia. Ultimately, underlying asthma may have contributed to malnutrition and fatal bacterial pneumonia. In conclusion, preschool asthma in low-income countries may be significantly under-diagnosed and misdiagnosed as pneumonia, and may be the cause of much morbidity and mortality.

MS Østergaard *et al*. *Prim Care Respir J* 2012; **21**(2): 214-219
http://dx.doi.org/10.4104/pcrj.2012.00038

Keywords acute respiratory infections, pneumonia, asthma, under-diagnosis, under-5s, mortality

Introduction

Acute respiratory infections (ARI) are the major cause of morbidity and mortality in children under five years of age (under-5s) in low-income countries[1-7] and account for more than 20% of estimated child deaths annually.[1-6] ARI and pneumonia are often used synonymously although ARI is an umbrella term for several respiratory diseases.[8,9] The case fatality rate from pneumonia in hospitalised under-5s remains at 11–15%,[4,7,10-12] but it can be as high as 30%.[13] Mortality in under-5s is particularly high in Sub-Saharan Africa.[14,15]

The global strategies to reduce mortality from pneumonia aim to improve correct diagnoses and case management using the World Health Organization (WHO) Integrated Management of Childhood Illnesses (IMCI) guidelines[14,16,17] that recommend the use of simple clinical signs and optimal antibiotic treatment. Furthermore, preventive vaccination programmes, strengthening health systems, and improving nutrition are focal points.[6]

Despite much scientific effort since 1980, there has not been a significant reduction in respiratory mortality in under-5s.[6] The reason for the continued high level of respiratory mortality has not been clearly established.[12,18] Lack of diagnostic facilities and trained personnel in under-resourced health centres may contribute to missed diagnoses.[19-22]

Recent studies have brought into question whether strict implementation of the IMCI guidelines may result in an over-diagnosis of bacterial pneumonia and an over-prescription of antibiotics at the expense of an under-diagnosis of asthma or wheezing.[23-27] A re-definition of the WHO IMCI algorithms for pneumonia to include fever along with cough and fast breathing for diagnosing pneumonia has been proposed.[22,28,29]

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This paper explores the definitions and concepts of pneumonia and asthma/wheezing/bronchiolitis and examines whether asthma in the under-5s may be being confused with bacterial pneumonia. It also debates whether the inappropriate management of asthma may be contributing to the current high level of respiratory morbidity and mortality in the under-5s in low-income countries.

Concepts, definitions and overlap of clinical features

Pneumonia is traditionally defined as an acute infection in the alveolar tissue caused by bacteria, virus, or other micro-organisms, and a chest x-ray is the gold standard in the diagnosis of bacterial pneumonia. According to the British Thoracic Society (BTS) pneumonia guidelines,[30,31] bacterial pneumonia should be considered in children with persistent or repetitive fever of >38.5°C together with chest recession and raised respiratory rate.

The WHO IMCI strategy promotes a classification of pneumonia in children in resource-limited settings presenting with 'cough or difficult breathing', while fever was not included in the management guidelines of pneumonia aiming at a high sensitivity at the cost of specificity. The WHO recommends making the diagnosis of pneumonia based on clinical parameters.[16] The clinical features of bacterial pneumonia and asthma in the under-5s, adapted from the WHO IMCI guidelines,[16,17] illustrate an overlap in symptoms and signs (Table 1). However, asthma is only briefly described in the IMCI guidelines, so the severity levels of asthma in Table 1 are adapted from the Global Initiative for Asthma (GINA) guidelines.[32]

Asthma is defined as an inflammatory disorder with hyper-reactive airways resulting in 'chronic or recurrent wheeze, cough and/or breathing difficulties, particularly at night and early morning',[32,33] and is potentially remittent. Major conceptual changes in childhood asthma have been instituted in the last decades with regard to definition, natural history, triggers, and treatment. Epidemiological studies have provided convincing evidence that the symptoms of asthma often start in early childhood.[34] Acute asthma may be exacerbated by viral infections,[32,35-37] often by respiratory syncytial virus (RSV) in children aged <2 years,[32] probably in a bidirectional way since asthma seems to be associated with increased susceptibility to severe RSV disease.[38] Open fire biomass cooking may be an important risk factor for preschool asthma symptoms[39] and respiratory infections.[40]

The terms 'asthma', 'wheezing disorder' and 'bronchiolitis' are often used in parallel[41] and present with similar symptoms,[34,41] triggers,[34,42] and treatment (Table 2).

Wheezing disorder[43] includes 'episodic viral wheeze' to describe children who wheeze intermittently[43] and 'multiple-trigger wheeze' for wheezing triggered by viruses and other

Table 1. Clinical features of bacterial pneumonia adapted from the World Health Organization's Integrated Management of Childhood Illnesses (IMCI) guidelines and asthma adapted from Global Initiative for Asthma (GINA) guidelines

Clinical features	Bacterial pneumonia	Asthma
Natural history	Acute onset, often only one episode	Chronic or recurrent with acute exacerbations often starting in infancy
Triggers	Bacteria, virus	Virus (especially RSV, HRV) allergens
Mild symptoms	Cough, difficult breathing	Cough, difficult breathing and/or wheezing
Severe symptoms	Cough and difficult breathing, fast breathing, chest in-drawing	Cough and difficult breathing, fast breathing, chest in-drawing, +/- wheeze, prolonged expiration
Very severe symptoms	Cough and/or difficult breathing, fast breathing, chest in-drawing, inability to feed, cyanosis, lethargy	Cough and/or difficult breathing, fast breathing, chest in-drawing, inability to feed, cyanosis, lethargy, wheeze loud or +/- absent

HRV=human rhinovirus, RSV=respiratory syncytial virus.

Table 2. Clinical features of asthma, wheezing disorder and bronchiolitis

	Asthma	Wheezing disorder	Bronchiolitis
Natural history	Recurrent or chronic with acute exacerbations, often starting in infancy	Intermittent or chronic often starting in infancy	First manifestation of severe wheezing in children aged <12–24 months
Symptoms as described in IMCI	Cough, difficult breathing and/or wheezing, prolonged expiration, chest in-drawing	Wheezing, prolonged expiration	Cough, difficult breathing and/or wheezing, prolonged expiration, chest in-drawing
Triggers	Viruses (including RSV, HRV), allergens	Viruses (including RSV, HRV), allergens	Viruses including RSV, HRV
Treatment proposal	Steroids and β_2-agonists	Steroids and β_2-agonists and/or montelukast	Steroids, adrenaline, antibiotics, β_2-agonists often used

HRV=human rhinovirus, IMCI=Integrated Management of Childhood Illnesses, RSV=respiratory syncytial virus..

triggers.[43] Recommended treatments are short-acting β_2-agonists, steroids, and/or montelukast.[43]

Bronchiolitis is traditionally described as the first manifestation of severe wheezing in infants.[44,45] It remains a clinical diagnosis without a common international definition.[41] Supportive treatment and antibiotics are recommended;[17] however, adrenaline alone or in combination with prednisolone has been found to be effective,[46] and various treatments such as short-acting β_2-agonists, prednisone, and antibiotics are used in practice.[47]

We have chosen to use the term 'asthma' in the under-5s because asthma is well described[32] and because the term asthma implies well-established treatment, follow-ups, and prophylaxis at discharge. We acknowledge the risk of over-diagnosing asthma. However, as asthma is defined as a recurrent/chronic and potentially remittent disease, it implies regular diagnostic re-evaluations.[32]

Over-diagnosis of bacterial pneumonia

Several studies have brought into question whether strict implementation of the IMCI guidelines may result in an over-diagnosis of bacterial pneumonia.[23-25,48] Herewith several indices which highlight possible over-diagnosis of bacterial pneumonia are listed: In a study of 2,000 young children in six Pakistani hospitals who were suspected to have, and were treated for, non-severe bacterial pneumonia on the basis of fast breathing, fewer than 20% had alveolar consolidation on the chest x-ray.[49] In microbiological studies of under-5s diagnosed with severe pneumonia, virus came out as the predominant pathological agent. In South Africa, pathogens were isolated in 65% of cases and viral pathogens predominated, with RSV being the most common; only 17.7% had bacteraemia and *Streptococcus pneumoniae* and *Haemophilus influenzae* were not isolated.[13] In a sample of Kenyan infants and children admitted with severe pneumonia to a rural hospital, RSV was the predominant viral pathogen and was detected in almost half of the infants.[50]

With regard to antibiotic treatment of pneumonia, the reduction in severe respiratory illness was minor despite frequent contacts with health facilities and early stage antibiotic treatment of children suspected with pneumonia in Uganda.[51] Moreover, several comparative studies showed equivalent treatment results between different types, doses, and administration forms of antibiotics in children with IMCI-defined pneumonia.[52-54] Treatment failures of serious pneumonia were primarily related to infants (3–11 months) with very fast breathing, chest in-drawings and hypoxia[10,11,53] and long-term cough,[10] but were not associated with fever,[10,11,54] raising questions concerning the diagnosis of bacterial pneumonia according to BTS guidelines.[30,31]

Under-diagnosis of asthma

Recent evidence has challenged the perception that asthma is a disease of low prevalence in young children in developing countries compared with industrialised countries. The ISAAC study demonstrated a high prevalence of asthma in schoolchildren in low-income countries;[55] for example, in Mozambique the prevalence of current asthma was 13.3% in schoolchildren aged 6–7 years[56] and the 1-year prevalence among children aged 5–6 years in Bangladesh was 16.1%.[57] Of the few studies reported in under-5s, the prevalence of asthma in 4-year-old children in Tanzania was found to be 14.0 % and the prevalence of current wheezing during infancy was 13.8%.[58] In Brazil the prevalence of wheeze in 6–59-month-old children was 12.5%, of whom 93% were reported with a medical diagnosis of asthma.[59]

With regard to chronic respiratory problems in under-5s, cough and breathing difficulties were highly prevalent in Ugandan children aged <2 years exposed in interviews using 2-week recall; of 3,249 children studied, 10% reported cough, difficult or rapid breathing and/or fever.[60] None of these children had been diagnosed with or treated for asthma or wheeze, although recurrent cough and difficult breathing are core symptoms of asthma. Similarly, ethnographic studies from several regions of Africa, Asia, and Latin America described long-term cough and breathing difficulties in under-5s interpreted as respiratory illness or infections.[61,62] When the symptoms deteriorated and the mothers sought help, the antibiotics given were of limited efficacy.[61,62] Also, infants and toddlers from indigenous populations in Australia, New Zealand, and Canada experienced frequent severe undiagnosed and untreated recurrent wheezing and chronic cough.[63]

Historically, there has been a diagnostic delay in young children with asthma.[64-67] In South Africa, a delay in diagnosis of three years was found in half of the children who were later diagnosed with asthma.[68] The reasons for delayed diagnoses included doctors trivialising the respiratory consultations and overemphasising infectious diagnoses and clinging to outdated asthma concepts.[67] In addition, the diagnostic key symptom such as stetoscopic wheeze may not be present, and audible wheeze is only present in around 30% of children with auscultatory wheeze.[48,69]

Asthma misdiagnosed as pneumonia

A key question is whether the WHO IMCI guidelines may result in over-diagnosis of pneumonia and subsequently over-prescription of antibiotics at the cost of under-diagnosis and under-treatment of asthma or wheezing.[23-27] In Uganda, pneumonia accounted for up to 30% of admissions[11] and only 0.1% of the acutely admitted under-5s were diagnosed with asthma.[70]

Four clinical studies have indicated an over-diagnosis of pneumonia at the expense of under-diagnosis of asthma or wheezing in approximately 50% of cases by using a change in diagnostic and prescription policy when under-5s were admitted and diagnosed with pneumonia,[29,48,54,69] as shown in Table 3. Sachdev *et al*. stated that, on the basis of re-defined IMCI algorithms and subsequently rational use of antibiotics and

Table 3. Over-diagnosis of pneumonia at the cost of under-diagnosis of asthma/wheeze in children admitted with acute respiratory infection and diagnosed with pneumonia

	Age (months)	IMCI-defined pneumonia	Diagnosis when using redefined IMCI criteria and/or responding to bronchodilators	
		Number	Pneumonia	Asthma and/or wheezing
Sachdev (2001)[69]	6–59	200	10%	46–54%
Hazir (2004)[48]	1–59	1622		49%
Addo-Yobo (2004)[54]	3–59	1702		50%
Cardoso (2011)[29]	2–59	410	18%	73%

bronchodilators, acute asthma was the predominant condition.[69]

Epidemiological studies suggest that children diagnosed with recurrent pneumonia in infancy are often later diagnosed with asthma.[25,57,71,72] Heffelfinger *et al*. suggested that children diagnosed with recurrent pneumonia according to IMCI-criteria in Haiti, compared with children never diagnosed with pneumonia, were more likely to get an asthma diagnosis later, and asthma should be considered as an alternatiove diagnosis to recurrent pneumonia.[25]

Asthma in the under-5s: an invisible killer?

Ultimately, it can be hypothesised that untreated asthma contributes to respiratory mortality for the following reasons. Acute respiratory infection treatment failures were predominantly seen in cases with cough of >14 days before admission or prior admissions for acute respiratory infection[10] or cases with very fast breathing, hypoxia, but without fever,[11,54] which are typical features of severe asthma rather than bacterial pneumonia which is characterised by fever >38.5°C.[30,31] Secondly, mortality data from low-income countries showed that RSV is an important cause of respiratory death in childhood.[73,74] Since asthma in young children is often exacerbated by viral infections including RSV[3,35,37,75] and since viral infections are usually self-limiting diseases,[75] it is likely that RSV infections develop severely in children with underlying hyper-reactive airways as in asthma, and that untreated asthma may develop into fatal asthma.[75]

Moreover, long-term cough and untreated asthma may reduce the child's ability to breast feed,[76] which relates to lower weight and height[77,78] and may lead to malnutrition.[79] Malnutrition and acute respiratory infection/pneumonia are interrelated health problems affecting children in developing countries,[80,81] and malnutrition is often an underlying cause of recurrent and fatal pneumonia.[10,11] Underlying asthma causing malnutrition may therefore contribute to fatal pneumonia/respiratory infection.

Short courses of high-dose inhaled corticosteroids (ICS) for wheeze and acute asthma in infants and toddlers[82] have been demonstrated to be effective[83,84] and safe.[83] It is well established that no treatment or under-treatment with ICS is a risk factor for fatal asthma,[85] and that asthma mortality in children in high-income countries declined significantly with adequate acute treatment and prophylaxis with ICS.[32] However, ICS are seldom used to treat under-5s in Africa due to former ignorance of asthma in under-5s and because of non-availability and unaffordability of ICS.[86]

Conclusions

This paper indicates that an overlap in clinical features between bacterial pneumonia and asthma in under-5s using IMCI guidelines, and variability in the terms used for severe cough and wheezing, and a former lack of awareness of asthma in the under-5s, may be contributing to a significant under-diagnosis of asthma which, in turn, may have caused much respiratory morbidity, recurrent admissions, and even mortality. This hypothesis may be directly relevant to the WHO Millennium Development Goal 4 which aims to reduce childhood mortality by two-thirds between 1990 and 2015.[87,88] Moreover, misdiagnosis may cause impoverishment of low-income families spending large sums of money on often inappropriate antibiotics.

The proposed re-definition of the IMCI algorithms for pneumonia to include high fever along with cough and fast breathing for diagnosing pneumonia[22,23,27-29] is supported. One direction for future research is the development of simple valid algorithms based on detailed clinical history including wheeze to improve differentiation between pneumonia and asthma, in line with former proposals. Another direction would be the study of affordable, simple, and cost-effective management strategies for asthma in under-5s in low-income countries.

Handling editor Mike Thomas

Acknowledgements We greatly appreciate the thoughtful comments of Hilary Pinnock, Allergy and Respiratory Research Group, Centre for Population Health Sciences, University of Edinburgh, UK; Rupert Jones, Respiratory Research Unit, Plymouth, UK; and Freddy Karup Pedersen and Anja Poulsen, both from the Paediatric Department, Rigshospitalet, Copenhagen, Denmark.

Conflicts of interest The authors declare that they have no conflicts of interest in relation to this article.

Contributorship MSØ designed and wrote the manuscript. RA, RN and JKT co-authored the manuscript and revised and approved the final version.

Funding The Danish Foreign Offices Development and Research Fund

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