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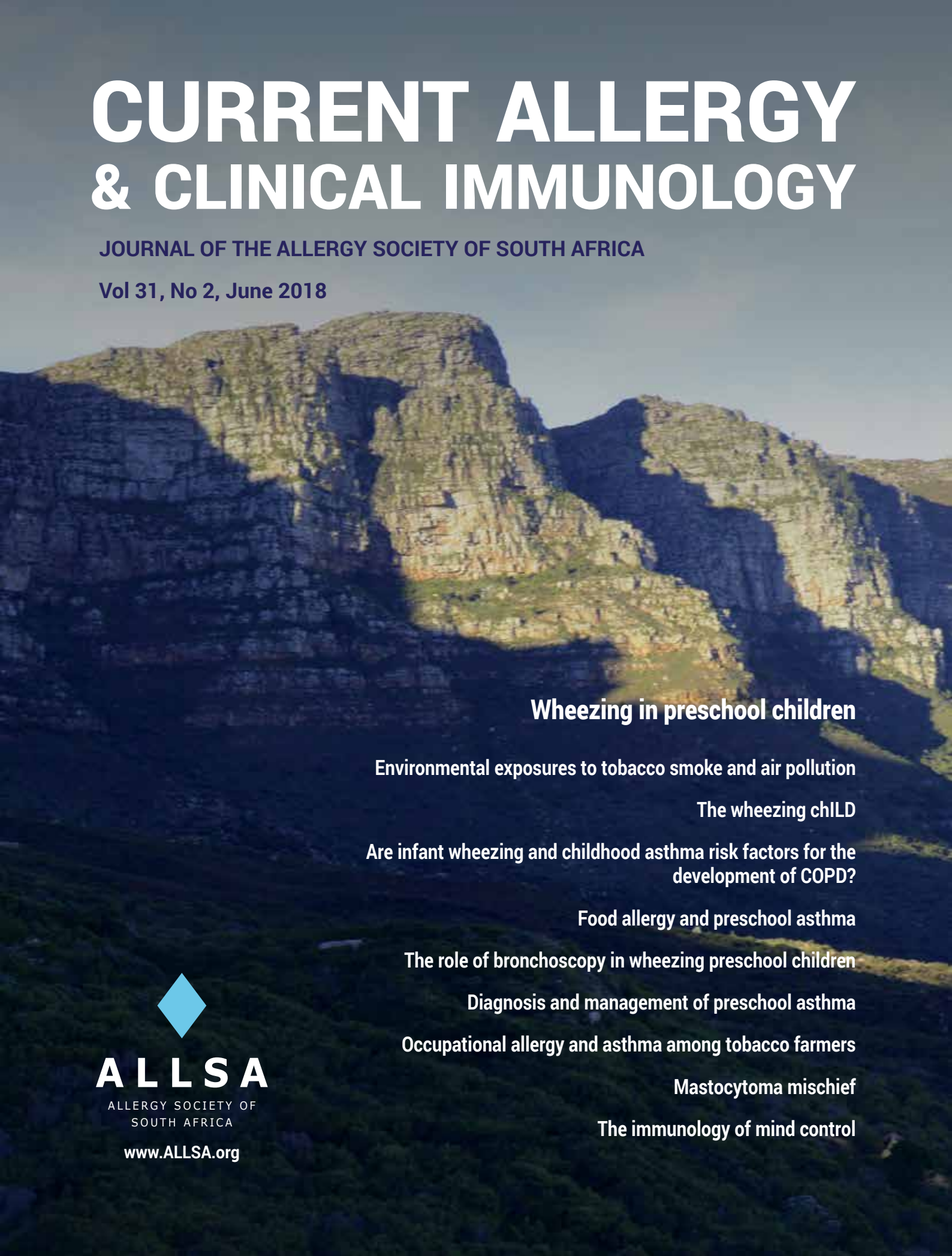

Wheezing in preschool children

Environmental exposures to tobacco smoke and air pollution

The wheezing chILD

Are infant wheezing and childhood asthma risk factors for the development of COPD?

Food allergy and preschool asthma

The role of bronchoscopy in wheezing preschool children

Diagnosis and management of preschool asthma

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SUBMISSIONS
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GUEST EDITORIAL

PRESCHOOL WHEEZING

Preschool wheezing remains an important topic as it is, firstly, very common, with almost 50% of children reported to have wheezing in the first year of life and 20% with continued wheezing symptoms in later childhood.[1] Secondly, it is also an important topic as, despite ongoing research, we still struggle to define all the aetiological factors/interactions in order to differentiate between preschool asthma and other wheezing phenotypes, and to offer preventative strategies or successful therapies. Lastly, it is important as it can be a presenting sign of serious, congenital or other chronic respiratory disease and it has far-reaching implications for lung health throughout life. For this edition, I aimed to explore some of these points.

Dr Aneesa Vanker from the Department of Paediatrics at the University of Cape Town, contributed an important article on the impact of environmental exposures such as tobacco-smoke exposure and air pollution on preschool wheezing. Her recently published data from an African birth cohort have highlighted the importance of this topic, as well as the urgent need to institute public-health interventions to prevent not just preschool wheezing but also the possible long-term impact on chronic obstructive pulmonary disease (COPD).[2]

In their article entitled *The wheezing chILD*, Drs Julia Carlens and Nicolaus Schwerk from the Hannover Medical School, Germany and Dr Melinda Solomon from the Division of Paediatric Respiratory Medicine of the Hospital of Sick Children in Toronto, focus on a rare but important cause of persistent preschool wheeze, namely, Children's Interstitial Lung Disease (chILD). This article also suggests a very helpful diagnostic approach to the child with persistent wheeze and suspected diffuse lung disease.

Over the past decade it has become clear that the root of adult chronic obstructive lung disease is most likely found in early-life events. In their article, Dr Julie Morrison and Prof Robert Gie from the Department of Paediatrics of Stellenbosch University have provided valuable answers to the burning question: Are infant wheezing and childhood asthma risk factors for the development of COPD?

Asthma is the most common chronic disease in childhood, affecting up to 15% of preschool-aged children.[3,4] The incidence of asthma as well as food allergy continues to increase.[5] The current understanding of the interaction between asthma and food allergy is explored by Dr Andrew Mazzanti of the Department of Immunology, University of Toronto, and Dr Thomas Eiwegger from the Division of Immunology & Allergy at the Hospital for Sick Children, Toronto, in their excellent review.

Prof Pierre Goussard from the Department of Paediatrics at Stellenbosch University is an exceptional interventional paediatric pulmonologist and has published important data on the role of bronchoscopy in the diagnosis and management of respiratory diseases in childhood.[6,7] In this article he focuses on the role of bronchoscopy in the management of preschool wheezing children in particular.

Despite many publications on the diagnosis and management of preschool asthma, clinicians still find it difficult to distinguish between preschool asthma and other common or serious lung conditions that present with wheezing. Drs Marie-Helene Maisonneuve and Prof Hartmut Grasemann from the Division of Respiratory Medicine at the Hospital for Sick Children in Toronto, provide an excellent overview of the diagnostic complexities in and treatment options available to the preschool asthmatic.

Lastly, we have the regular contributions on ethics and occupational health from Prof Sharon Kling and the authors from the Occupational Medicine Division of the School of Public Health and Family Medicine at the University of Cape Town.

It has been a wonderful privilege and enriching experience to edit this edition of *Current Allergy and Clinical Immunology*. Thank you to all my colleagues, local and international, for their outstanding and insightful contributions to the journal. Thank you also to Prof Weinberg and Ms Robyn Marais for the opportunity as well as your guidance. May you all enjoy reading this edition.

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ERRATUM:
The editors which to apologise for the exclusion of page 2 of the PID123 from the Vol 31 No 1 March (2018) issue of the *Current Allergy and Clinical Immunology Journal.* The full PID123 is published in this issue on page 101-102.

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Review Article

ENVIRONMENTAL EXPOSURES TO TOBACCO SMOKE AND AIR POLLUTION: THEIR IMPACT ON PRESCHOOL WHEEZING

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ABSTRACT
Wheezing in preschool children is common. An interplay of genetic and environmental factors may play a role in the development of wheezing disorders. Environmental exposure to tobacco smoke and air pollution are important risk factors for preschool wheezing with the antenatal and early-life period being a critical exposure period. Minimising exposure to tobacco smoke and indoor air pollution may be important in reducing preschool wheezing and improving lifelong respiratory health.

Keywords: preschool wheezing, environmental exposure, air pollution

BACKGROUND

Preschool wheezing is common with approximately one-third of children diagnosed with a wheeze in the first three years of life.[1] Preschool wheezing is most simply classified as either episodic viral wheeze or multi-trigger wheeze.[2] Children with multi-trigger wheeze often pose the greater challenge due to the multifactorial aetiology. Furthermore, children with multi-trigger wheeze are more likely to develop asthma. Children are exposed to a myriad environmental insults from the antenatal period through childhood with an interplay of genetic and environmental factors influencing individual susceptibilities.[3]

Environmental exposures are vast and can include biologic agents that may be found in the home, for example house-dust mite (HDM), or may be the result of outdoor or indoor air pollution including tobacco smoke. Air pollution comprises numerous particles and chemicals that once inhaled disrupt host defences against respiratory infections through a number of complex mechanisms.[4] These include impairing mucociliary clearance, affecting humoral and cellular defence mechanisms, causing respiratory inflammation, impairing bronchoalveolar permeability and impairing macrophage functions.[4] The most common compounds studied and implicated in respiratory illnesses include particulate matter (PM), nitrogen dioxide (NO_2), carbon monoxide (CO), ozone (O_3) and volatile organic compounds.[5–8] However, many more may also play a role in this. Tobacco smoke contributes to air pollution and despite anti-tobacco campaigns and legislation, maternal smoking and household smoke exposure may be significant and often under reported, particularly in low and middle-income countries (LMIC).[9,10] In this article, the impact of environmental exposures from air pollution and tobacco smoke on preschool wheezing are explored.

'GOOD VS BAD' EXPOSURES AND THEIR IMPACT ON WHEEZE

Conflicting evidence has led to the concept of 'good' versus 'bad' exposures and their impact on wheezing.[3] This was illustrated by the effect of HDM, where exposing an infant to an environment with no HDM exposure, decreased airway resistance ('good') but increased HDM sensitisation ('bad').[11] This is further demonstrated by the effect of lipopolysaccharide (LPS) – found in mattresses – on wheeze prevalence. In children with atopic wheeze, LPS had a protective effect, however, in non-atopic wheeze LPS exposure increased the risk.[12] These examples highlight the complexities in understanding the impact of the environment on wheeze. However, certain exposures, including tobacco-smoke exposure, are always 'bad'.[3]

TIMING OF EXPOSURE AND THE DEVELOPMENT OF WHEEZING DISORDERS

Preschool wheezing, and the subsequent development of asthma can be considered a developmental disease in which environmental exposures act on an underlying genetic predisposition and alter the normal development of the respiratory and immune system.[13] The embryonic development of the lung begins at 4–7 weeks of gestation with alveolarisation continuing until adolescence.[14] In utero environmental exposures affect lung growth and development by way of a number of mechanisms. Tobacco smoke, for example, contains a large number of chemicals and carcinogens which may affect the developing respiratory system.[15] Nicotine, in particular, has been shown to affect the embryologic development of the lung as well as impact on collagen deposition.[16,17] Furthermore, tobacco smoke alters early-life immune function resulting in an imbalance in Th1 and Th2 responses thereby increasing the susceptibility to allergic diseases.[18,19]

The pathogenesis of in utero air-pollution exposure on respiratory disease is also multifactorial. Air-pollution exposure induces maternal systemic inflammation which results in oxidative stress and placental insufficiency impacting on foetal lung development. Pollutant nanoparticles also have a direct effect on foetal development. Furthermore, pollutants induce epigenetic changes in the foetus.[20] These antenatal factors may therefore increase the susceptibility of wheezing in infants and young children.

The mechanisms involved in postnatal environmental exposure and wheezing are from direct inhalation of toxic particles impairing natural lung defences. This results in increased epithelial permeability, decreased mucociliary clearance and impaired macrophage function.[7] Environmental exposures may impact on the development of wheezing disorders, play a role in exacerbations in those with wheezing disorders or may be particularly harmful to individuals with an increased susceptibility to these exposures.[7]

ENVIRONMENTAL EXPOSURE AND PRESCHOOL WHEEZING

TOBACCO-SMOKE EXPOSURE

Both antenatal and postnatal tobacco-smoke exposure have been implicated in wheezing in young children. A meta-analysis comparing antenatal and postnatal tobacco-smoke exposure on wheeze incidence found that exposure to either conditions increased the risk of wheeze development by 30–80%.[21] However, postnatal tobacco-smoke exposure was the strongest risk factor (OR 1.70, 95% CI 1.24–2.35) for wheezing in children younger than two years of age.[21] In contrast, a large population-based prospective cohort study of tobacco-smoke exposure and wheeze development found that continued maternal smoking during pregnancy increased the risk of early and persistent wheezing (OR 1.24, 95% CI 1.01–1.52; OR 1.48, 95% CI 1.13–1.95) and asthma (OR 1.65, 95% CI 1.07–2.55). However, postnatal smoking was not associated with increased wheezing.[22] A meta-analysis of smoke exposure on the development of wheezing and asthma in unselected cohorts also confirmed this, with antenatal maternal smoking associated with a 36% increased risk of early-life wheezing, but no postnatal effect was found.[23] The association between maternal smoke exposure (in non-smoking mothers) and the subsequent development of wheezing and asthma was also significant, (adjusted HR 1.34 [95% CI, 1.01–1.76]).[24] This was also noted in a South African birth-cohort study which assessed the impact of environmental exposures on wheezing in infancy. Wheezing illness was associated with both antenatal (incidence rate ratio 2.09, 95% CI 1.54–2.84; p = <0.0001) and postnatal (1.27, 95% CI 1.03–1.56; p = 0.024) maternal smoking.

Antenatally, wheezing was associated with maternal passive smoke exposure (1.70, 1.25–2.31; p = 0.001) and, postnatally, with any household member smoking (1.55, 1.17–2.06; p = 0.002). This highlights the impact of not just maternal smoking but also household smokers and other sources of tobacco-smoke exposure on wheezing in infancy.[25]

AIR POLLUTION

Air pollution – from both indoor and outdoor sources – comprises a large number of particles, compounds and toxins which may have an effect on the development of wheezing illnesses or play a role in exacerbations.[7] The risks associated with exposure can begin in the antenatal period with maternal exposure to both PM and polycyclic aromatic hydrocarbons (PAHs) having been found to increase the frequency of wheezing episodes in the first two years of life.[26]

Another large study of more than 3 000 children diagnosed with asthma found that in utero and early-life exposure to NO_2, sulphur dioxide (SO_2), PM, CO and black carbon (C) from outdoor air pollution was associated with a significantly increased risk of asthma.[27] When considering the effects of air pollution not just on preschool asthma but also other allergic symptoms, children of mothers exposed to NO_2 from traffic-related pollution had an increased incidence of asthma (6.8%), allergic rhinitis (7.3%) and eczema (28.6%).[28] These associations were confirmed in a recent systematic review assessing the association between prenatal air pollution exposure on childhood wheezing and asthma, which found statistically significant associations between prenatal exposures to NO_2 [OR 1.04 (95% CI 1.01–1.07)], SO_2 [OR 1.02 (95% 0.98–1.070)] and PM 2.5 [OR 1.4 (95% CI 0.97–2.03)] and the risk of wheezing and asthma development in childhood.[29]

Air pollution comprising NO_2, O_3 and PM, mainly from traffic sources, has also been implicated in wheezing exacerbations and susceptibility.[7]

GENE–ENVIRONMENT INTERACTIONS AND WHEEZING

Polymorphisms in genes and environmental exposures are individually associated with asthma risk. An interaction between genetic susceptibility and environmental exposures therefore further increases the risk of asthma and wheezing.[30] Epigenetic phenomena are heritable changes in gene expression from non-structural and non-coding changes in DNA.[31] Of all the airborne pollutants, tobacco smoke is most associated with epigenetic changes.[31] However, particulate pollutants from traffic-related sources, have also been implicated in DNA methylation changes.[32] There is also evidence of a trans-generational effect of smoke exposure, with a child whose grandmother smoked having a doubled chance of developing asthma than one whose grandmother did not.[31] In addition, if the grandmother smoked during her pregnancy with the child's mother, it impacted on the subsequent risk of asthma in the grandchild regardless of the mother's smoking status.[32]

There is increasing evidence that the roots of adult obstructive lung diseases, such as chronic obstructive pulmonary disease (COPD), lie in early childhood.[33] Studies have reported the impact of environmental exposures, in particular from tobacco smoke, on genetic programming that subsequently controls life-long lung development and aging.[34] Furthermore, COPD genes whose expression may be influenced by in utero tobacco exposure have been identified.[35,36]

PREVENTION OF EXPOSURE TO TOBACCO SMOKE AND AIR POLLUTION

Despite global tobacco control initiatives, including legislation on smoking in public places,[37,38] household smoking and its subsequent exposure to children remains unregulated.

Public-health initiatives targeting vulnerable groups including adolescents and women of childbearing age are required. Children need to be protected from tobacco-smoke exposure from the time of conception.[39] While smoking cessation is the best intervention, in those mothers unable to terminate smoking, vitamin C supplementation during pregnancy has been shown to decrease wheezing in children in the first year of life and improve pulmonary function at birth.[40]

Addressing air-pollution exposure may be more difficult. However, awareness of potential sources of indoor air pollutants and simple interventions to reduce exposures including improving household ventilation by installing chimneys or opening windows during cooking, may decrease exposure.[41] Managing air pollution needs to be a national and international priority with a multi-sectoral approach required.[42]

CONCLUSION

Wheezing in preschool children is common and a complex interplay of environmental and genetic factors may play a role in both the development of wheezing disorders and exacerbations. The antenatal and early-life period is a critical exposure period during which lifelong lung trajectories are set. Addressing early-life environmental exposures, particularly from tobacco smoke, is important in managing wheezing disorders in children.

DECLARATION OF CONFLICT OF INTEREST

The author declares no conflict of interests.

This article has been peer reviewed.

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*Platelet Activating Factor (PAF) is one of the most important mediators for induction of oedema/nasal obstruction, as well as increasing vascular permeability and causing rhinorrhoea, whereas histamine is responsible for itching and sneezing[6]

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Review Article

THE WHEEZING chILD: CHILDREN'S INTERSTITIAL LUNG DISEASE – A RARE BUT IMPORTANT DIFFERENTIAL DIAGNOSIS IN CHILDREN WITH SEVERE WHEEZE

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ABSTRACT

'Children's interstitial lung disease' (chILD) is an umbrella term for disorders that mainly affect the lung parenchyma and lead to impaired alveolar gas exchange. The main symptoms are tachypnoea, hypoxaemia, retractions, crackles and failure to thrive. Even though wheeze is not a common symptom of chILD, there are various disorders which also affect the conducting airways, leading to bronchial obstruction in some children. Therefore, chILD has to be considered, especially in children with severe persistent wheeze refractory to asthma treatment and after the exclusion of more common causes. The aim of this article is to give an overview of the clinical symptoms, present the current classification scheme of chILD and describe examples of selected disorders which can present with wheeze. Furthermore, suggestions for diagnostic approaches for children with persistent bronchial obstruction and suspected diffuse lung disease are given.

Keywords: children's interstitial lung disease, chILD, diffuse lung disease, diffuse parenchymal lung disease, wheeze, asthma

INTRODUCTION

'Children's interstitial lung disease' (chILD) is an umbrella term for more than 200 different rare lung diseases with significant morbidity and mortality.[1–3] Only limited data on the frequency of chILD are available; previous studies have reported an incidence of 0.1–16.0 per 100 000 children per year and a prevalence of 3.6 per million children. It seems likely, however, that the frequency of chILD is underestimated, owing to difficult diagnosis and a very low awareness among treating physicians.[4–6]

The term 'chILD' is misleading as the diseases mostly do not solely affect the interstitium but often involve other pulmonary compartments such as the conducting airways, alveolar spaces, pulmonary vessels, lymphatic vessels and pleural spaces. Therefore, some authors prefer the term 'diffuse parenchymal lung disease' (DPLD). Independent of the different aetiologies, chILD commonly causes an impaired alveolar gas exchange that leads to tachypnoea, dyspnoea and even hypoxaemia and respiratory failure in more severe cases.[4,6,7] Additional clinical findings can be persistent cough, retractions, crackles, failure to thrive, pulmonary hypertension and also wheeze in up to 15% of cases when conducting airways are involved.[4–9] For decades, no consistent classification scheme for chILD existed. This made comparisons between clinical observations and case studies very difficult. In 2007, the chILD Research Co-operative proposed a classification system based on 187 histological confirmed DPLD cases in children less than two years of age[7] (see Table I). Subsequently, this classification has been widely used and over the past several years has been expanded to include both older children and novel sub-categories.[6,10–14] On this basis, in 2013 an official clinical practice guideline for the classification, evaluation and management of chILD was published by the Committee on Childhood Interstitial Lung Disease and the chILD Research Network on behalf of the American Thoracic Society (ATS).[10] This was followed in 2015 by a proposal for the diagnosis (see Figure 1) and initial treatment of interstitial lung disease in children by the chILD–EU collaboration.[13]

TABLE I: PROPOSED CLASSIFICATION SCHEME FOR chILD (ADAPTED FROM DEUTSCH ET AL[7])

	DISORDERS MORE PREVALENT IN INFANCY	DISORDERS NOT SPECIFIC TO INFANCY	
A	**Diffuse development disorders** • Acinar dysplasia • Congenital alveolar dysplasia • Alveolar-capillary dysplasia with misalignment of pulmonary veins	**Disorder of the normal host** • Infectious and post-infectious processes • Disorders related to environmental agents • Aspiration syndromes • Eosinophilic pneumonia	A
B	**Growth abnormalities** • Pulmonary hypoplasia • Chronic neonatal lung disease • Structural pulmonary changes with chromosomal abnormalities • Associated with congenital heart diseases	**Disorders related to systemic disease processes** • Immune-related disorders • Storage disease • Sarcoidosis • Langerhans cell histiocytosis • Malignant infiltrates	B
C	**Specific conditions of undefined aetiology** • Neuroendocrine cell hyperplasia • Pulmonary interstitial glycogenosis	**Disorders of the immunocompromised host** • Opportunistic infection • Disorders related to therapeutic intervention • Disorders related to transplantation and rejection syndromes • Diffuse alveolar damage of unknown origin	C
D	**Surfactant mutations and related disorders** • SPFTB genetic mutations • SPFTC genetic mutations • ABCA3 genetic mutations • NKX2.1 genetic mutations • GMCSFA-R genetic mutations	**Disorders masquerading as interstitial diseases** • Arterial hypertensive vasculopathy • Congestive vasculopathy • Lymphatic disorders • Congestive changes related to cardiac dysfunction	D
E	**Unclassified**		E

WHEN DO I HAVE TO SUSPECT CHILD IN A WHEEZING CHILD?

STEP 1: IS IT REALLY ASTHMA? WHEN DO I HAVE TO RECONSIDER THE DIAGNOSIS?

All children with suspected asthma should, in addition to a detailed history, undergo a basic diagnostic workup, including spirometry and bronchodilator responsiveness (BDR) testing, a chest radiograph, allergy diagnostics and a sweat chloride test in case of any signs suspicious for cystic fibrosis. The first important step is to realise that not all who wheeze have asthma. Even if asthma is the most common chronic lung disease in children, numerous other diseases can cause bronchial obstruction and wheeze in children. Therefore, the diagnosis of asthma can be made only after exclusion of other causes, especially when:

- Wheeze starts very early during the first months of life.
- Symptoms are very severe, leading to recurrent hospitalisations.

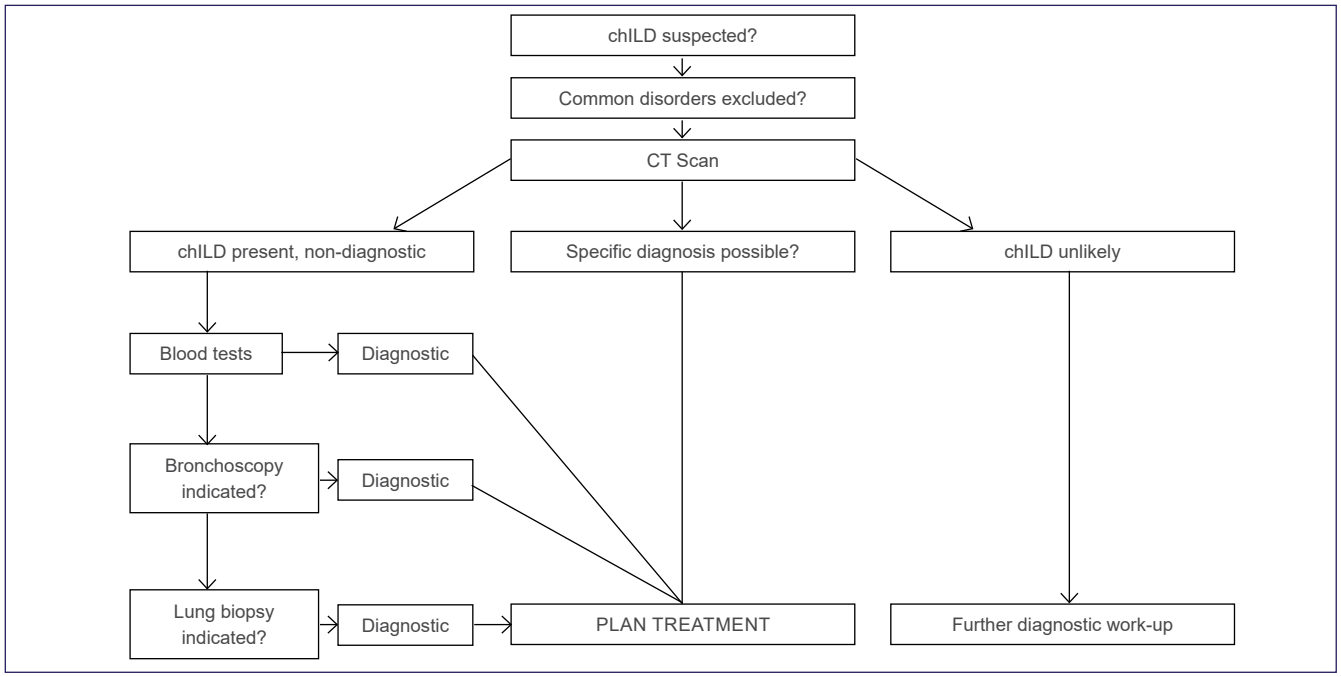

Figure 1: Diagnostic algorithm for children with suspected chILD (adapted from Bush et al[13])

- Symptoms start rapidly without any sign of infection or allergy in a previously healthy child.
- Wheeze persists continuously, especially after a preceding lower respiratory tract infection.
- Wheeze is refractory to asthma-specific treatment.
- Symptoms are consistent with other pulmonary complaints that are not typical for asthma (e.g. chronic wet cough, persistent tachypnoea, recurrent or persistent cyanosis).
- Clinical findings are not typical for asthma (e.g. persistent unilateral obstruction, crackles, clubbing and failure to thrive).
- Chest radiography shows abnormal findings, inconsistent with asthma.
- Lung-function testing is not typical for asthma (e.g. fixed obstruction without reversibility to short-acting beta-agonists, additional or solely restrictive pattern; impaired diffusion capacity).

Significantly, the earlier respiratory symptoms start in life and the more severe they are, the less likely the diagnosis of asthma is correct. In these circumstances differential diagnoses have to be considered and appropriate diagnostic investigations initiated.

STEP 2: IF IT IS NOT ASTHMA, CAN MORE COMMON CAUSES FOR WHEEZE THAN CHILD BE EXCLUDED?

In all wheezing children with suspected diffuse lung disease, more common causes than chILD should be considered first.[10,13] These include congenital or acquired diseases of the airways (e.g. laryngeal or subglottic stenosis, bronchomalacia, bronchial stenosis, mucus plugging), congenital thoracic malformations (e.g. congenital hyperlucent lobe, congenital pulmonary airway malformations, congenital bronchus atresia), cystic fibrosis, primary ciliary dyskinesia, congenital or acquired heart diseases, congenital or acquired immunodeficiency, chronic lung diseases, respectively bronchopulmonary dysplasia, pulmonary infections (e.g. protracted bacterial bronchitis, TB) and recurrent aspiration (see Table II). Since asthma has a high prevalence in childhood, one should keep in mind that patients with a proven asthma diagnosis can simultaneously suffer from additional diffuse lung diseases, and especially young children with interstitial lung disease might show additional bronchial hyper-responsiveness and wheezing, among other symptoms.[7] Patients with asthma are notably even at increased risk of some diffuse lung disorders such as allergic bronchopulmonary aspergillosis (APBA).[15] Decisions about the kind and invasiveness of diagnostic investigations have to be made per individual and should depend on age and the severity at the onset of symptoms, the patient's history, the nature of the symptoms and the presence or absence of extra-pulmonary findings.

STEP 3: IF IT IS chILD, WHICH ENTITIES ARE MORE LIKELY TO PRESENT WITH WHEEZE?

Wheeze is not a typical symptom of chILD but can be present in up to 13–15% of cases.[7,8] Even within one disease group, some children may wheeze whereas others do not. Therefore, there is no 'classical' disorder within the chILD umbrella that has the leading symptom of wheeze. In the following section, some examples of the chILD sub-categories that potentially present with wheeze are discussed in more detail.

Growth anomalies reflecting deficient alveolarisation

Deficient alveolarisation can be secondary, as in children with lung hypoplasia related to diaphragmatic hernia or diaphragmatic relaxation, impaired alveolarisation related to long-term ventilation or to congenital heart disease; or primarily related to chromosomal disorders.[7]

Histologic examination of lung biopsies does not show the 'classical' picture of interstitial lung disease but reflects a rarefication of alveoli and pulmonary vessels as well as dysplastic alveoli with relevant heterogeneity with respect to size and form.[11,16] In some cases the interstitium can also be thickened, often described as 'immature' by the pathologist, which aggravates diffusion impairment. The distal airways are also often involved, leading to peripheral ventilation inhomogeneity with a mixture of atelectatic and hyperinflated areas of the lung that can also be seen on a chest X-ray or CT-scan.[17] Furthermore, in children with congenital heart disease, large airways (mostly the left main bronchus) can be compressed by enlarged vessels (mostly the left pulmonary artery) leading to relevant obstruction with consecutive wheeze. In some children with trisomy 21 a combination of all these pathologies can be seen, which explains why they frequently suffer from recurrent or chronic bronchial obstruction that is often aggravated by viral infections.[18] When children with chILD related to growth anomalies are able to perform lung-function tests, obstruction can be seen in nearly all patients, usually without any response to bronchodilators.

In summary, even if these patients can develop asthma-like symptoms, the pathophysiology leading to airway obstruction is completely different. This explains why anti-inflammatory inhalation therapy is not helpful in most cases. Moreover, chronic inhalation of glucocorticosteroids might harm these children as steroids have a negative impact on post-natal alveolar maturation. Therefore, asthma therapy should be avoided or its efficacy should at least be critically re-evaluated in these patients.

Specific conditions of undefined aetiology

This category encompasses two diseases, namely, neuro-endocrine cell hyperplasia (NEHI) and pulmonary interstitial glycogenosis (PIG).[7,14] The aetiology of both diseases is not completely understood. Some experts postulate that NEHI is a progenitor cell/stem cell disease caused by misregulated progenitor cell growth.[19] For NEHI, familial cases have been described which might point out a hereditary component, and recently an association with a mutation in the NKX2.1 gene (encoding the thyroid transcription factor 1) has been described.[20,21] Formally, NEHI is not an interstitial lung disease but is a form of small airway disease, characterised by increased numbers of neuroendocrine cells within the airways of infants and toddlers.[22,23] Neuroendocrine cells play an important role in lung development and are also present in healthy individuals

TABLE II: RELEVANT DIFFERENTIAL DIAGNOSIS IN CHILDREN WITH WHEEZE AND SUSPECTIVE DIFFUSE LUNG DISEASE

DIAGNOSIS	SYMPTOMS	TYPICAL AGE OF ONSET	DIAGNOSTIC APPROACH
Congenital or acquired airway diseases	Stridor, wheeze, cough, dyspnoea	After birth (if congenital), at any age (if acquired)	Bronchoscopy
Congenital thoracic malformations	Dyspnoea, retractions, hypoxaemia, unilateral attenuated breathing sounds	After birth	Chest X-ray, prenatal ultrasound (if available), CT in case of high suspicion
Cystic fibrosis	Chronic cough, recurrent pneumonia, failure to thrive, chronic diarrhoea	First year of age	Seat test, genetics
Primary ciliary dyskinesia	Respiratory distress of term neonate, persistent wet cough, situs anomalies, chronic rhinitis	After birth (persistent wet cough in nearly all children)	Nasal nitric oxide, ciliary function, electron microscopy, genetics
Congenital or acquired heart disease	Feeding difficulties, failure to thrive, tachycardia, tachypnoea cyanosis, fatigue, impaired exercise tolerance	First four weeks (if critical), up to any age (if not critical or acquired)	Echocardiography
Congenital or acquired immunodeficiency	Recurrent (not only but often opportunistic) severe infections	Any age	Differential blood count, serum immunoglobulins, vaccination antibodies
Protracted bacterial bronchitis	Chronic wet cough. In addition, chronic or recurrent wheeze in a relevant proportion of patients	Preschool age	Induced sputum (if possible), bronchoalveolar lavage (optional), 'diagnostic' antibiotic treatment
Other infections	Chronic wet cough, recurrent pneumonias, wheeze in a relevant proportion of patients	Any age	Chest X-ray, CT (optional), tuberculin skin test, interferon-gamma-release assay, induced sputum, bronchoalveolar lavage
Recurrent aspiration	Chronic cough, recurrent pneumonias, wheeze, halitosis, bad dental status	Any age	24-h-pH-metry, impendance, ultrasound, chest X-ray, barium swallow
ABPA	Deterioration of previously controlled asthma, chronic/ recurrent cough, brownish mucus plugs	Adolescence	Chest X-ray, CT, total IgE, specific IgE to recombinant Aspergillus antigens (Aspf2,4,6) specific IgG to Aspergillus antigen, exclude cystic fibrosis
Bronchiectasis	Chronic wet cough (especially in the morning), recurrent lower respiratory tract infections, wheeze, decreased exercise capacity	Any age but very rarely in infants and toddlers	CT, consider underlying causes
Bronchopulmonary dysplasia	Preterm, post-long-term ventilation/oxygen supplementation, recurrent/ persistent wheeze, difficult breathing	First weeks of age	Oxygen titration at age 28 days, chest X-ray, exclusion of other causes than prematurity
Foreign-body aspiration (FBA)	Sudden onset of cough, unilateral decreased breathing sounds, recurrent/ chronic infiltrates/ pneumonias localised on the same side	Toddlers and preschool children	Bronchoscopy
Intrathoracic tumours	Often only mild symptoms, cough, dyspnoea, haemoptysis, localised abnormal breathing sounds	Any age	Chest X-ray, ultrasound, CT, MRI

after birth.[23] Therefore it is unclear whether these cells cause the disease per se or represent a secondary phenomenon of an unknown disease process. NEHI is probably the most common chILD-form in infants and is probably highly underdiagnosed. The typical clinical sign is persistent tachypnoea with or without hypoxaemia and failure to thrive, typically manifesting between 1–3 months of age.[22,24] On auscultation, 'bronchiolitis-like' crackles are present in most but not all cases. In addition, as a result of peripheral bronchial obstruction, wheeze is present in some patients.[25] Therefore, most of them are initially misdiagnosed with viral bronchiolitis and later sometimes as severe asthma.

A chest X-ray is not diagnostic but a chest CT shows typical abnormalities with central localised ground-glass opacities, especially in the middle lobe and the lingula, together with peripheral hyperinflation (see Figure 2). These findings are so specific that a lung biopsy is not necessary to prove the diagnosis if typical symptoms are present.[26] Prognosis is excellent and no deaths related to NEHI have been described to date.[24] Most children become symptom-free by the age seven years, but some continue to have chronic bronchial obstruction, which can lead to the incorrect diagnosis of asthma.[25] NEHI is not responsive to steroids. Children with NEHI should therefore not be treated like children with asthma, even if their symptoms can be similar.

The histological picture of PIG is shaped by an interstitial accumulation of PAS-positive immature mesenchymal cells.[16] Affected children often have concomitant disorders and are mostly symptomatic directly after birth with difficulty breathing, tachypnoea and hypoxaemia. Radiography is non-specific but shows diffuse ground-glass opacities in most cases. PIG does not cause bronchial obstruction and therefore misdiagnosis of asthma is very unlikely. A relevant proportion of children with PIG also have critical congenital heart defects.[27,28]

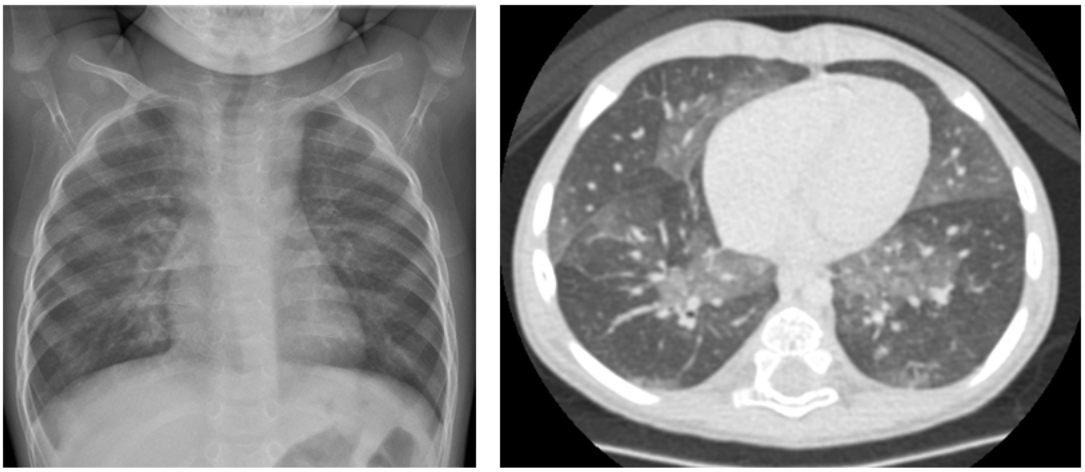

Figure 2: Chest X-ray and CT of a four-month-old infant with typical appearance of NEHI. The chest X-ray is not specific, showing discrete central ground-glass opacities and peripheral hyperinflation. An inspiratory high-resolution CT scan show sharply defined areas of ground-glass opacification along mediastinal borders, most prominently in the right middle lobe and lingual.

Surfactant dysfunction disorders

Surfactant dysfunction disorders mostly cause severe lung diseases. Children with homozygous surfactant protein B- and ABCA3-gene mutations usually present in early infancy and show high morbidity and mortality.[29] In patients with NKX2.1 and SPC-mutations, the onset and severity of disease is more variable and symptoms may not present until adulthood.[30,31] Surfactant dysfunction disorders are typically not associated with bronchial obstruction or wheeze and a misdiagnosis of asthma is therefore unlikely.

Disorders related to systemic disease processes

This category contains a large group of different rare diseases, including immune-mediated disorders, storage diseases, sickle-cell anaemia, sarcoidosis or Langerhans cell histiocytosis.[7,10,14] Some of them can accompany bronchial obstruction and wheeze, for example follicular bronchiolitis. This very rare disease affects mainly children with autoimmune disorders or patients with AIDS.[32,33] Langerhans cell histiocytosis is also characterised by severe bronchial obstruction, air trapping and secondary pneumothoraces. However, chest X-ray findings are quite characteristic (see Figure 3) and are unlikely to be misdiagnosed as asthma.[34] Lung involvement is relatively often seen in immune-mediated disorders such as juvenile idiopathic arthritis (JIA), systemic lupus erythematosus (SLE), granulomatosis with polyangiitis or eosinophilic granulomatosis.[12,35] These lung diseases do not typically cause airway obstruction but manifest typically with pulmonary haemorrhage, non-specific interstitial pneumonia, bronchiolitis obliterans organising pneumonia, pleuritis and pleural effusions or shrinking lung syndrome and therefore they do not resemble asthma.

Disorders of the normal host

Most of these diseases are caused by infections or environmental agents. It is still a matter of controversial debate whether post-infectious bronchiolitis obliterans (BO) belongs to chILD or not. The disease is caused by a dysfunctional repair process after an infectious insult, for example with adenoviruses or Mycoplasma

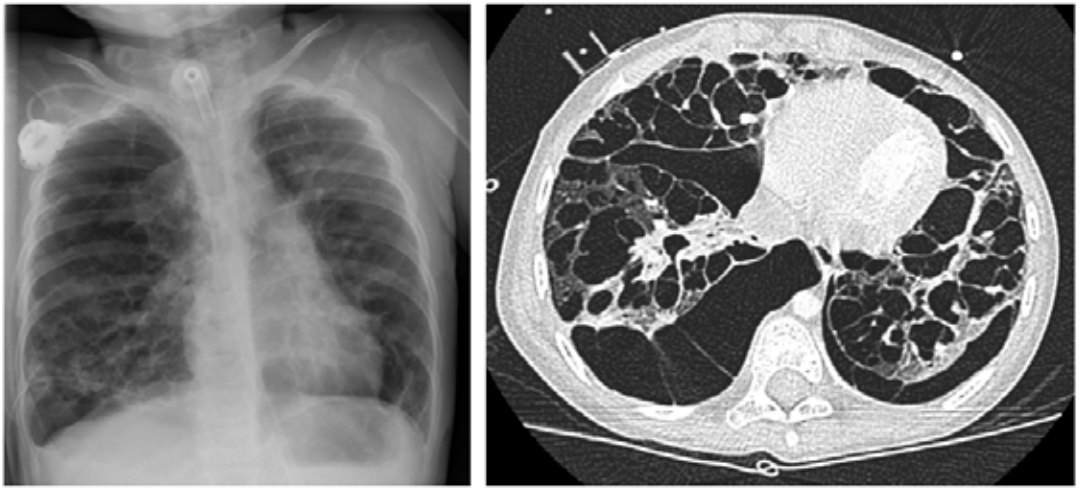

Figure 3: Chest X-ray and CT LCH of a nine-year-old boy with pulmonary Langerhans cell histiocytosis. The chest X-ray shows a mixture of air-filled cystic lesions, consolidation and hyperinflation. Notice the right-sided chest tube which was inserted. The high-resolution CT scan shows multiple bilateral cystic lesions of different size.

pneumonia, leading to partial or complete occlusion of small airways by fibrinous scar formations.[36] Neither the interstitium nor the alveolar space is affected, therefore BO is not an interstitial lung disease as such. Post-infectious BO affects mostly infants and preschool children after a preceding severe and prolonged infection with severe bronchial obstruction and respiratory insufficiency in most cases.[36] In contrast to patients with common viral bronchiolitis, these children do not recover and suffer from persistent, severe obstruction, and a relevant proportion of patients are oxygen-dependent for weeks or even months or years. They usually respond neither to inhaled nor to systemic glucocorticosteroids or bronchodilators which is not surprising bearing in mind the histological changes of scar tissue formation. In contrast to asthma, lung-function measurements of BO patients show a non-reversible severe obstruction with pseudorestriction due to hyperinflation.

Another example of chILD related to the normal host is hypersensitivity pneumonitis, which is caused by type-3 and type-4 allergic reactions mainly to organic antigens.[37–39] It can occur at any age but mostly in older children and adults. In the initial phase, bronchial obstruction can be the leading symptom and it can therefore be misdiagnosed as asthma. In the later phases, interstitial inflammation and fibrosis is predominant, leading to diffuse changes in chest X-ray and a restrictive pattern in lung function.[40] As the disease causes irreversible lung damage and even terminal respiratory failure, if untreated, it is very important to make the diagnosis at an early stage. A detailed patient history (e.g. association between the acquisition of a feather bed and onset of symptoms in a previously healthy child) is the most important diagnostic test, followed by radiographic examinations and the detection of precipitants against organic antigens. A lung biopsy can be helpful in the case of inconclusive findings but is usually not necessary. The most important treatment is allergen avoidance. Systemic steroids can accelerate recovery.

Disorders of the immunocompromised host

Diseases in this category affect mostly children beyond two years of age and adolescents.[12] They are related to opportunistic infections, therapeutic interventions or to transplantation and rejection. In contrast to post-infectious BO, BO following bone-marrow transplantation or lung transplantation has a much poorer prognosis, with a continuous decline of lung function refractory to medical treatment leading to end-stage lung disease in a relevant proportion of patients. In such cases, lung transplantation or re-transplantation is the only treatment option. As most of these patients have a long medical history and are already being treated in tertiary centres where any complications are monitored, they are unlikely to be misdiagnosed as having asthma.

CONCLUSION

Wheeze is not a typical sign of chILD but it should be considered in patients with early-onset or severe persistent wheeze refractory to asthma medication and other signs of pulmonary or extrapulmonary involvement not typical of asthma after the exclusion of more common causes. It is important to increase the awareness of chILD among treating physicians, as these disorders often accompany relevant morbidity and mortality. Every child with suspected chILD should be referred to a specialised centre because the diagnosis, care and treatment of these patients necessitate great expertise. Further international collaboration on these orphan diseases has to elucidate the proportion of children presenting with wheeze in different sub-categories and age groups.

DECLARATION OF CONFLICT OF INTEREST

The authors state that they do not have any conflict of interest to declare.

This article has been peer reviewed.

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Review Article

ARE INFANT WHEEZING AND CHILDHOOD ASTHMA RISK FACTORS FOR THE DEVELOPMENT OF COPD?

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ABSTRACT

Wheezing in childhood and chronic obstructive pulmonary disease (COPD) in adults are both common clinical problems associated with tobacco smoking. This therefore raises the question whether childhood wheezing is also a risk factor for the development of COPD. The programming of lung development occurs in utero, with foetal exposure to maternal smoking resulting in decreased lung function at birth. Decreased lung function at birth tracks through life, resulting in decreased lung function in adulthood. Not only tobacco smoking and exposure but also indoor and outdoor atmospheric pollution influence foetal lung development. Adults with decreased lung function are at risk of developing COPD in the fourth and fifth decades of life. The data from cohorts followed up from childhood have confirmed that viral associated wheezing (wheezy bronchitis) and severe asthma in childhood are risk factors for developing COPD. These risk factors are independent of tobacco smoking during adulthood. Although many factors other than tobacco smoke influence the development of COPD, it is estimated that 33 per cent of South African mothers smoke during pregnancy. This results in decreased lung function in early life and an increased risk of COPD. Maternal smoke cessation programmes are urgently needed in South Africa.

Keywords: infant wheezing; childhood factors; COPD; risk factors; lung function tracking

INTRODUCTION

In 2016 chronic obstructive pulmonary disease (COPD) was the sixth leading cause of death globally, with approximately 250 million people suffering from the disease worldwide.[1] With childhood wheezing being a common clinical problem, it is understandable that parents are concerned that their children will develop COPD as adults. Previously, the opinion was that their concerns were misplaced as there was the misconception that COPD was attributable solely to tobacco smoking in adulthood. COPD diagnosis is based on spirometric criteria, where the FEV_1 : FVC ratio is less than 0.7 post bronchodilator.

The limitation of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition is that it takes into account neither the spirometric changes related to age and sex nor the different phenotypes of COPD and early-life events contributing to the disease. Recently, it has estimated that the percentage of COPD cases attributable to smoking is approximately 54% of male and 24% of female patients.[2] In industrialised countries the association is higher than in developing countries.[2] Although COPD becomes clinically evident at around 40–50 years of age, it is clear that in many patients it has its origins early in life. There is now sufficient evidence that antenatal exposures result in decreased lung growth. Infants born with decreased lung function have an increased risk of developing COPD as an adult.[3] The magnitude of this effect is so large that it has been suggested that certain exposures in childhood pose a risk for developing COPD that is as high as heavy smoking during adulthood.[4] The aim of this article is to consider the available evidence that early-life insults and exposures which contribute to wheezing in early childhood increase the risk of developing COPD in later life.

SEARCH STRATEGY

This article is based on publications in the English scientific literature over the past 20 years. It is not a comprehensive review or a meta-analysis article. The literature was searched using Pubmed and Google Scholar. The search words and terms used were COPD, infant wheezing, early origins of COPD, early-onset COPD, lung development and COPD, childhood environmental exposures and COPD, foetal tobacco exposure and COPD, risk factor for development of COPD. From the articles recovered, the references were used to identify additional articles. Articles found to be relevant to the subject were included.

LUNG GROWTH AND COPD

The interaction of lung growth and the development of COPD is complex. An individual's lung function is programmed in early life. To be able to understand the interaction between lung growth and the development of COPD one needs to understand the factors that influence development. Three phases are identified in lung development: lung growth, lung plateau and lung decline.

LUNG GROWTH

Lung growth is best divided into airway and alveolar development. Previously, it was thought that alveolar development continued until two years of age and after this no new alveoli developed. This concept has recently been challenged and it is now thought that alveoli develop throughout somatic growth.[5] In contrast, more is known about lung-function (airway) development. Lung function increases, reaching a maximum at approximately 22 years of age,[3] with the lung volumes increasing approximately thirty-fold from infancy. Most of the structural changes in lung development occur in utero and the first years of life.[3]

Risk factors that influence the in utero lung development include maternal smoking, maternal asthma and atopy, a low birth weight, prematurity, diet, environmental factors including indoor pollution and genetics.[6] These factors result in decreased lung function early in life (see Figure 1).

In a sentinel study, it was demonstrated that decreased lung function at birth was associated with wheezing during infancy.[7] In this study, the main risk factors for decreased lung development were antenatal maternal smoking and being born small for gestational age. Data from this cohort demonstrate that approximately 10% of healthy individuals have decreased lung function at birth which tracks its centile into adulthood, resulting in decreased lung function in the third decade of life.[8] Many studies following birth or childhood cohorts have demonstrated similar findings. An interesting hypothesis suggested that 40% of airway bronchial hyperactivity (ABH) is acquired in utero and 60% in early childhood.[9]

Epidemiological studies demonstrate that antenatal factors (maternal smoking, genetics, intrauterine growth restriction, maternal atopy, etc) lead to a modification in airway and alveolar development and maladaptive response in the newborn lung. In early childhood, exposure to tobacco smoke and environmental pollution are risk factors for asthma and recurrent lower airway tract.

In the period after birth, lung growth continues to be negatively influenced by maternal and environmental tobacco exposure in addition to respiratory viral infections, indoor and outdoor pollution, malnutrition, asthma and multiple atopic sensitisations; all of these exposures are associated with a decrease in lung growth.[10]

The COPDGene study showed that childhood pneumonia was associated with increased chronic bronchitis, more frequent and severe COPD exacerbations and an increased frequency of cardiovascular disease.[11] In a cohort recruited in Hertfordshire a reduction in adult FEV_1 after bronchitis or pneumonia in infancy was reported, with an increased odds ratio of wheezing and persistent sputum production in adult life independent of birth weight, smoking habit and social class.[12] Whooping cough in infancy was associated with a 0–2.2 L (0.02–0.42 L) reduction in adult FEV_1.[12] In addition to the above, the development of bronchopulmonary dysplasia (BPD) in premature babies – defined as oxygen dependency at 36 weeks' gestational age – is also associated with decreased lung function. Survivors of BPD have been shown to have increased airway wall thickening that is compatible with airway obstruction.[3]

LUNG FUNCTION PLATEAU

Between 20 and 25 years of age the lung growth reaches a plateau, after which there is no further growth or decline in lung function. Lower lung function in childhood leads to lower peak lung function in early adulthood; this is known as 'tracking': lung function tracks the percentile from early childhood into adulthood; decreased lung growth in childhood results in a lower lung-function plateau. The factors that influence the lung-function plateau are largely unknown, although tobacco smoking shortens the plateau phase.[13]

LUNG FUNCTION DECLINE

After the plateau phase, lung function steadily decreases, with the forced vital capacity in 1 second (FEV_1) decreasing at approximately 20 mL/year in non-smokers. Smokers lose lung function at approximately twice the rate (40 mL/year) of non-smokers.[13] This decrease continues throughout life, probably as a result of a loss of lung elastance.[2] Tobacco smoking results in an increased loss of lung function annually, with approximately 50% of smokers reaching the lung function threshold when they become symptomatic, usually in the fourth or fifth decade.[13] Whereas tobacco smoking is the most important cause of accelerated lung function loss, other causes include indoor and outdoor pollution, occupational exposures and acute exacerbations of bacterial infections.

EARLY CHILDHOOD WHEEZING AND COPD

Children who have transient wheezing in the first three years of life have decreased lung function, recorded soon after birth; the decreased lung function manifests prior to developing wheezing, which tracks over the first three decades of life. There is some evidence that three connecting genes present in patients with transient wheezing are also present in patients with COPD.[14] It is postulated that maternal tobacco smoking interferes with these genes, which are needed for normal lung development in utero and are also responsible for airway inflammation later in life.[14]

Because both viral associated wheezing (VAW) and wheezy bronchitis (WB) are closely associated with decreased lung function early in life, it is not surprising that these children have an increased risk of developing COPD.[15,16] Data supporting this observation comes from cohorts in Australia and Scotland who have been followed up on for more than 50 years. In both cohorts, the participants were recruited as children and followed up on for decades, with their lung function measured at regular

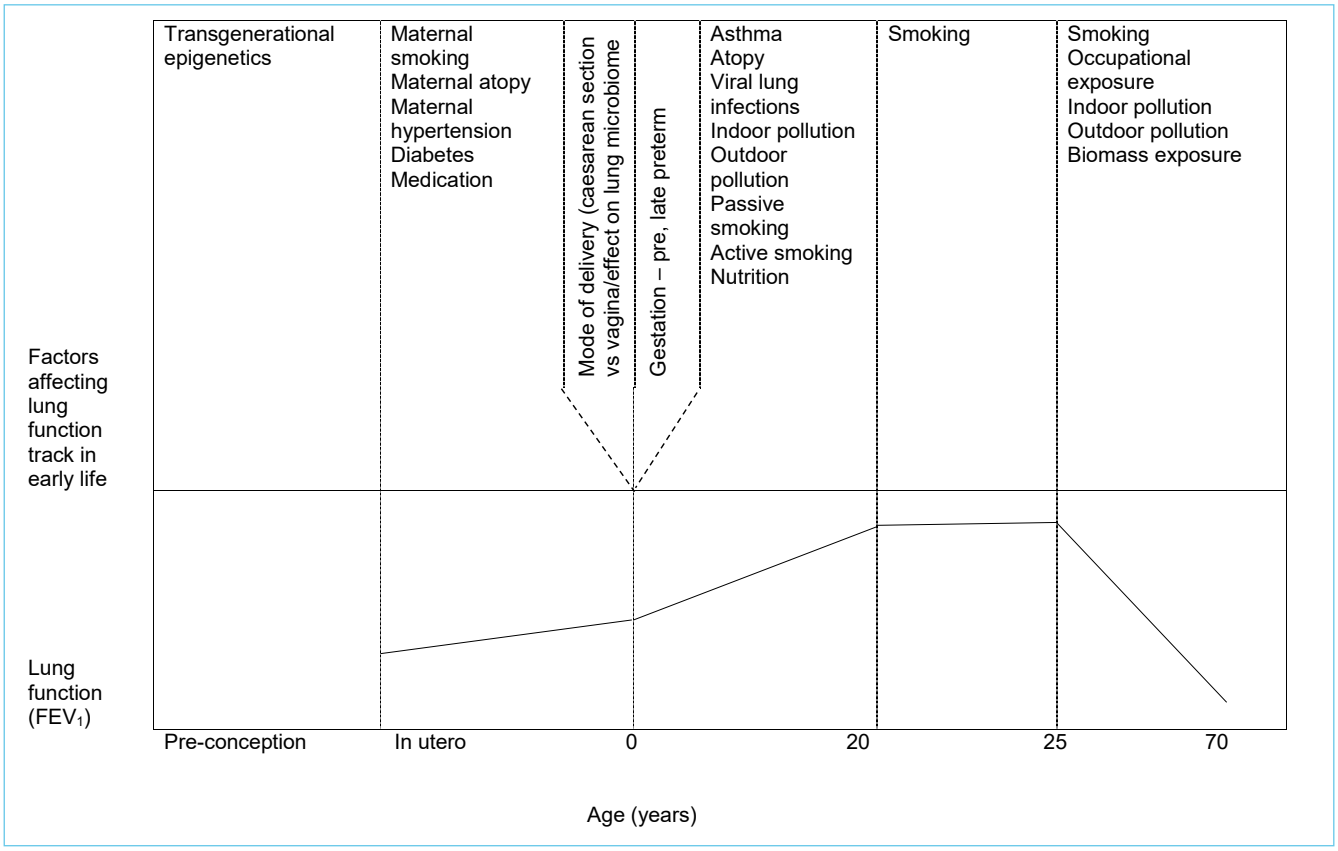

Figure 1: Factors affecting lung function track throughout life

intervals. In both studies the participants with WB/VAW had an increased risk of developing COPD (OR 181 95th CI 1.12–2.91 and OR 3.5 95th CI 0.4–35.2 respectively).[15,16] The diagnosis of COPD (GOLD criteria) became evident only from the fifth decade of life onwards.[15] Of interest was that those at risk of developing COPD had a lower lung function (FEV_1) in early life, which tracked with time and was not the result of an accelerated loss of lung function as seen in smokers.[15] This emphasises the fact that decreased lung function in childhood is an important risk factor for the development of COPD.

Adults who develop wheezing later in life have increased lung function loss that results in their developing COPD.[15] These two different mechanisms of developing COPD suggest that there might be different phenotypes of COPD.

CHILDHOOD ASTHMA AND COPD

Numerous studies demonstrate that severe asthma is associated with the development of COPD. It is estimated that the history of asthma increases the risk of developing COPD by 10–30-fold.[17] There are, however, not many cohorts that have been followed up from childhood into the sixth and seventh decades of life.[17] This long-term follow-up is essential because COPD usually becomes evident only later in life, as has been demonstrated in long-term follow-up trials.[15,16] From these studies it is evident that children suffering from severe asthma have a 32-fold (95th CI 3.4–269) increased risk of developing COPD by the sixth decade of life.[18] Asthmatic children with an increased risk of developing COPD are characterised by a low baseline FEV_1, early onset of symptoms and persistent wheezing.[2] In contrast, children with intermittent and persistent non-severe asthma do not have an increased risk of developing COPD.[18]

Similarly, in the Scotland cohort referred to above, childhood asthma was associated with an increased risk of developing COPD (OR = 6.37 95th CI 3.73–10.94). In this study, asthmatic children between the ages of 10 and 15 years with obstructive spirometry were more likely to develop COPD in the fourth decade of life.[18] In a US study of 1 041 asthmatic children (5–14 years of age) 11% of them had developed COPD by 30 years of age. The diagnosis of COPD was based on spirometric criteria that demonstrated a post-bronchodilator response, which indicated irreversible or partially reversible airway obstruction (FEV_1/FVC <0.70). Those most likely to develop COPD had low FEV_1 lung-function measurements and/or an early decline in their FEV_1.[19]

The development of decreased lung function that increases the risk of developing childhood asthma is programmed in utero. In a meta-analysis of 24 938 children, reported in 24 birth cohorts, gestational age and decreased weight for gestational age (small for gestational age) were associated with decreased lung function and increased risk of developing childhood asthma.[20] In this article, median analysis suggests that the decrease in lung function might explain between 7% (2–10%) and 45% (15–81%) of the association between early growth characteristics

and childhood asthma.[20] This once more suggests that in utero programming increases the risk of developing childhood asthma and COPD in later life.

It has been suggested that the diagnosis of chronic childhood asthma adds 20 years to the lung age or the equivalent of 60 pack years of smoking, suggesting that chronic childhood asthma might be as large a risk factor for the development of COPD as is adult tobacco smoking.[21]

LIMITATIONS IN THE STUDIES

The first limitation concerns the diagnosis of COPD. The GOLD guidelines for the diagnosis of COPD suggest that COPD is characterised by partially irreversible airway obstruction. COPD is diagnosed when the forced vital capacity in 1 sec (FEV_1) to forced vital capacity (FVC) ratio (FEV_1/FVC) is less than 0.7 following an inhaled bronchodilator. Unfortunately, the FEV_1/FVC is influenced by age and sex. In younger adults, the ratio would underdiagnose COPD, whereas in older patients it could lead to an overdiagnosis.[5]

The second limitation is that the diagnosis of COPD is based on spirometric criteria and does not necessarily reflect the different phenotypical forms of COPD. Will the outcome of COPD associated with decreased lung function in childhood be similar to COPD which develops in adults who have an accelerated decrease in lung function and become symptomatic at an earlier age?

Another uncertainty is whether the COPD that follows WB/VAW in childhood has the same pathogenesis that follows severe childhood asthma where ongoing airway inflammation is present.

Furthermore, these studies all indicate that the known risk factors in childhood for the development of COPD apply to the group of children or adults investigated and not to the individual patient. If a clinician is discussing the risk of developing COPD with a parent, this weakness needs to be borne in mind.

RELEVANCE TO THE SOUTH AFRICAN CONTEXT

The prevalence of COPD in two suburbs of Cape Town has been reported to be higher than in 11 other large cities in the world.[22] This was true for both men and women.[22] With maternal tobacco smoking being associated with a decrease of in utero foetal lung growth, a sobering report, recently published by Vanker et al, is worth bearing in mind.[23] In this study of more than 1 000 mother–infant pairs conducted in two suburbs (Drakenstein) in the Western Cape, they report that 77% of pregnant mothers either actively smoked or were exposed to tobacco smoke during pregnancy.[23] Of even greater concern was that at birth 18% of the babies had urine cotinine levels equivalent to those of an active smoker and 38% had cotinine levels that indicated recent exposure to tobacco smoke.[24] In addition, these two studies indicated that antenatal exposures to maternal tobacco smoking and other indoor pollutants had a far greater impact on their infants' lung health than postnatal exposures.[23,24] We would postulate that if this is true for other regions of South Africa, the country will experience an unprecedented increase in the prevalence of COPD in the future.

Furthermore, the effect of maternal tobacco smoking has been shown also to have a transgenerational effect. If a grandmother smokes, her grandchild has an increased risk of developing childhood asthma, even if the child's mother does not smoke.[5] This epigenetic effect is thought to be the result of gene methylation.[5] This suggests that the effects of maternal smoking on infant lung health are going to be present in future generations even if smoking cessation programmes are successfully introduced. In southern Africa, there are other important risk factors for the development of COPD that require attention. These include pulmonary tuberculosis, HIV infecton and poverty.[25]

CONCLUSION

Dozens of studies demonstrate that in utero and early-life lung development are influenced by many risk factors, of which maternal smoking is the most important. Infants with decreased lung development have a greater risk of developing VAW and childhood asthma. Moreover, the decreased lung-function centile tracks into adulthood, resulting in a reduced lung-function centile in adulthood that is associated with the development of COPD. Smoke-cessation programmes, especially those that focus on pregnant women, need urgent attention if the long-lasting effects of smoking on the lung health of children and adults are to be prevented.

DECLARATION OF CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

This article has been peer reviewed.

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Review Article

FOOD ALLERGY AND PRESCHOOL ASTHMA

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ABSTRACT

Asthma is a chronic disease that affects many children worldwide. Atopic march suggests that asthma is preceded by other atopic events such as transient or persistent food allergy and atopic dermatitis. A growing number of large cohort studies has supported a greater appreciation for the heterogeneity of asthma, especially with regard to its diverse aetiologies. It is critical to monitor asthma in food-allergic preschool-aged children. Several studies have begun to reveal connections between food allergy and the eventual development of allergic asthma that appear to verify the atopic march. As the incidence of both food allergy and asthma increases, it is critical to understand the genetic and environmental factors that predispose children to atopic disease, and to understand how early clinical manifestations such as food allergy can increase the risk for chronic allergic diseases such as asthma.

Keywords: food allergy, preschool asthma

INTRODUCTION

Asthma is the most common chronic disease in childhood,[1] affecting approximately 11.6% of children ages 6–7[2] and up to 15% of preschool-aged children.[3] According to the World Health Organisation (WHO), the incidence of asthma continues to increase and is responsible for approximately 250 000 deaths per year.[1] The incidence of food allergy similarly continues to increase.[4] Beyond its impact on patient health, it significantly reduces quality of life and contributes to financial burdens on patients and health systems. Our current understanding of asthma is that it represents a syndrome that is more complex than a specific mono-causal disease entity.[5]

ENDOTYPES VS PHENOTYPES

Recent efforts have been made to sub-classify further the distinct phenotypes and aetiologies of asthma into 'endotypes' defined by unique functional or pathobiological mechanisms. This approach is complicated by the fact that the diagnosis of asthma in preschool age can be very challenging because of the restricted number of validated tests. Accordingly, each distinct endotype responds differently to a variety of treatments. Two endotypes are specifically relevant to preschool-aged children. The first is the 'Asthma Predictive Index (API)-positive preschool wheezer': more than three prolonged episodes of wheezing, provided that a major criterion – parental asthma, atopic dermatitis or sensitisation to an aeroallergen – or two minor criteria – more than 4% peripheral eosinophils, wheezing outside of cold, and sensitisation to a food allergen – are also satisfied. The second is "allergic asthma (adults)".[6] Although this PRACTALL consensus article describes 'allergic asthma' as affecting adults only, the authors also associate it with a history of asthma and eczema in childhood. Therefore, it is relevant to consider allergic disease in the preschool years and its association with adult asthma. Preschool-aged patients with variable presentations, aetiologies and phenotypes of asthma respond variably to current treatments.[7,8]

A key concept of clinical trajectories in childhood allergic disease is called 'atopic march'. This sequence of disease phenotypes has traditionally been understood to move from atopic dermatitis (AD) to food allergy, allergic rhinitis (AR) and, ultimately, to persistent allergic asthma. Recent large-scale population studies have revealed a multitude of connections between early childhood atopic disease and more severe allergic disease later in life. These datasets suggested a better response rate to inhaled steroids in cases of Th2 inflammation (eosinophilia, aeroallergen sensitisation).[7,8] Notably, both the 'API-positive' and the 'allergic asthma' endotypes are characterised by a Th2 predominance. Therefore, irrespective of the diagnostic and treatment-related limitations present in preschool asthma,[9] atopy represents a significant risk factor. Children with asthma also commonly suffer from a number of atopic diseases.

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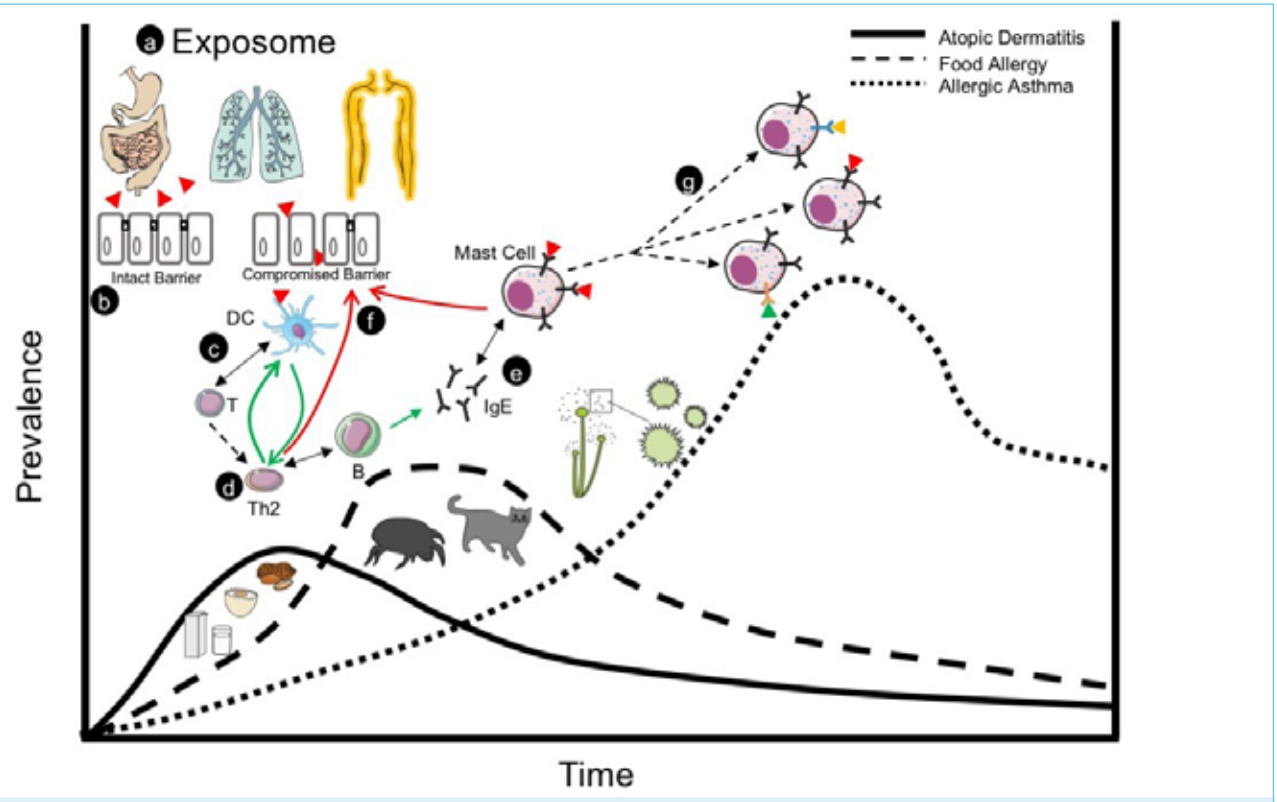
BARRIER DYSFUNCTION AND ALLERGIC SENSITISATION

AD is the first disease in the atopic march. The current understanding of AD embraces the fact that skin-barrier defects are instrumental in driving disease and facilitate the high percentage of allergic sensitisations, particularly in patients with severe AD. This predisposition to become sensitised to a number of environmental allergens in the context of an atopic predisposition forms the starting point of the so-called 'atopic march'. Once sensitised to the respective allergen, IgE binds to the high-affinity IgE receptor on the surface of basophils and mast cells in tissues. Subsequent exposure to the allergen triggers the release of mediators that cause an allergic reaction.[10]

In line with the barrier-defect hypothesis, consistent exposure of the immune system to environmental allergens via antigen-presenting cells such as dendritic cells or B cells via CD23, the low-affinity IgE receptor, increases the allergen-specific IgE repertoire to different allergen families. It also permits slightly altered antigens with a lower binding affinity to trigger the production of new IgEs. In this way, one allergic epitope can give rise to a variety of allergies. This phenomenon is known as 'epitope spreading';[11] it is a molecular mechanism potentially at the root of atopic march. Therefore, a singular clinical manifestation (AD) spirals into multiple clinical conditions (food allergy, AR, asthma). Biological barriers maintain integrity and regulate the interactions between environmental antigen and the immune system. The skin, the airway epithelium and the gastrointestinal tract are constantly exposed to antigens and allergens, yet not all people develop allergy. Several longitudinal studies have begun to shed light on factors that predispose individuals to atopy, among them a loss-of-function (LOF) mutation in the filaggrin (FLG)[12,13] gene, which has been linked to allergic disease[14] and AD.[15,16] Such an association clearly establishes the importance of epithelial barrier integrity and implicates its loss in inflammation.

FOOD ALLERGY AND ASTHMA

Of special concern when considering preschool-asthmatic children and allergic sensitisation is food allergy. Most importantly, children with food allergies who suffer from asthma are particularly at risk of having severe, potentially life-



Allergy to foods such as milk, egg and peanut has been associated with later atopic disease, including allergy to aeroallergens from dust mites, pets and pollen, and with allergic asthma. The exposome includes environmental allergens and antigens (red triangles) that come into contact with biological barriers, including the GI tract, airway epithelium and skin (a). Barrier defects, such as in LOF FLG mutations, can result in a loss of tight junctions, compromising barrier integrity (b). Antigen presenting cells, such as dendritic cells (DC), can pick up and present antigen (c), initiating the differentiation of T lymphocytes into subsets such as Th2.

Th2 cells promote further antigen processing and presentation (d), and stimulate B cells to produce allergen-specific IgE (e), which can then prime the surface of mast cells. Mast cells and Th2 cells further compromise barriers by secreting inflammatory molecules (f). The phenomenon of epitope spreading increases the diversity of IgE on mast cells, which also increases the risk of allergic inflammation at biological barriers (g).

Figure 1: IgE-mediated immune response to allergens and progression of atopic march. (Partially adapted from Servier Medical Art under Creative Commons License CC BY.)

threatening events in response to an allergic reaction.[17,18] The functional link between loss-of-function (LOF) mutations in FLG and food allergy is not as clear as that in AD; however, patients with the mutation and AD are more prone to developing food allergy. FLG is not expressed in the bronchial airways or in the gastrointestinal tract beyond the oral mucosa,[19] but linkages between primary and secondary barrier dysfunction, on the one hand, and asthma[20] and food allergy,[21] on the other, are established. Therefore, factors other than FLG mutations must also be relevant to barrier function and asthma.[16] The skin as a sensitising organ to food and inhalant allergens has to date been largely under-appreciated, and food allergy and respiratory allergy have not been given due consideration as key steps in the atopic march. In line with this argumentation, the German Multicentre Allergy Study (MAS) reported that sensitisation to egg at the age of 12 months is predictive for sensitisation to airborne indoor and outdoor allergens.[22] Another interesting theory suggests that type 2 inflammation has a significant impact on tight junction integrity in the lung and as a result facilitates respiratory sensitisation.[23,24]

LESSONS FROM COHORT STUDIES

Several large cohort studies support this progression of the atopic march. The MAS study followed more than a thousand participants from 1990 until adulthood and revealed that those with two allergic parents were three times more likely to have allergies than those with two healthy parents. In addition, they found that asthma was more likely to occur with another allergic condition (such as AR or AD) than to occur on its own.[22] Significantly, children in the MAS cohort with long-lasting sensitisation to food allergens in the first two years of life had a 3.4-fold higher risk for AR and a 5.5-fold higher risk for asthma when compared to children with only transient sensitisation.[25]

The Canadian Healthy Infant Longitudinal Development (CHILD) Study was launched in 2008 and recruited 3 500 pregnant women with the aim of better understanding genetic and environmental contributors to atopic disease. It was found that children at three years of age with AD but without allergic sensitisation were not at increased risk of food allergy and were also not at increased risk of asthma. Children with both AD and allergic sensitisation were found to have seven times the risk of developing asthma. Importantly, food sensitisation was found to be more responsible for this effect than environmental allergen sensitisation, and increased risk occurred even with no AD.[26]

Similar findings were reported by Alduraywish et al, who investigated two birth cohorts (MACS and LISAplus). The sensitisation to food at ages 6, 12 and 24 months resulted in a significantly higher risk of developing asthma at the age of 10–12 years. This risk was further increased if children displayed co-sensitisation with aeroallergens.[27,28]

In the HealthNuts cohort from Melbourne, asthma, eczema and food allergy were assessed at 12 months and four years of age. Approximately 11% of children at 12 months had a food allergy, but by age four only 3.8% had food allergy.[21] Subsequent analysis of the dataset revealed that children with one food allergy confirmed by oral challenge at 12 months were 1.69 times as likely to have asthma than those with no food allergy; those with two or more food allergies were 2.76 times as likely to have asthma.[29] Asthma risk was further increased by eczema and by persistent rather than transient food allergy, at least in the case of egg. This cohort in particular draws a clear connection between food allergy, eczema and risk for asthma.

The CDC has reported that asthma affects 4.7% of children aged 0–4 years and affects 9.8% of children aged 5–14 years.[30] They have also reported that 4.7% of 0–5-year-old children have food allergy, whereas 3.7% of 5–17-year-old children have food allergy.[31] Examining the connection between the two variables is difficult as there is no gold-standard test for asthma, given its diverse endotypes; moreover, the gold-standard test for food allergy – a double-blind placebo-controlled food challenge – is time-consuming and the data are impractical to collect on the scale of a cohort study.

However, serological data from the National Health and Nutrition Examination Survey (NHANES) cohort suggests that of those with diagnosed asthma 27.5% have a food sensitisation and, of those, 1.9% have 'likely food allergy'; conversely, of those without asthma, 14.9% have a food sensitisation and, of those, only 0.9% have 'likely food allergy'.[32]

CLINICAL IMPLICATIONS

This significant body of evidence linking sensitisation to food allergens, which is a surrogate marker of food allergy, implies that children with polysensitisations early in life are at high risk of developing persistent asthma. In addition, AD has been identified as an independent risk factor that contributes significantly to asthma risk. As such, these patients may be identified, and their parents may be informed about that risk and followed up with in order to guarantee a timely and accurate diagnosis and treatment of asthma. Moreover, food allergens should also be considered as a potential trigger factor of severe intermittent asthma in the absence of environmental triggers.

CONCLUSIONS

Food allergy is a significant co-morbidity of preschool asthma and vice versa. The management of preschool asthma may significantly improve upon characterisation of its underlying mechanisms. This will allow risk factors to be elucidated for discrete asthma endotypes linked to severe anaphylaxis in asthmatic patients and could result in novel preventive and therapeutic concepts of allergic diseases such as AD, asthma and food allergy.

DECLARATION OF CONFLICT OF INTEREST
The authors declare no conflict of interest.

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Review Article

THE ROLE OF BRONCHOSCOPY IN WHEEZING PRESCHOOL CHILDREN

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ABSTRACT

Lower airway tract illnesses with wheeze are common in the preschool child and occur in approximately one-third of all children. Most children with preschool wheeze do not need further investigation, but referral is needed in the following cases: if the child does not respond to treatment, if the diagnosis is in doubt, if there are other comorbid conditions present and if the wheezing is audible without a stethoscope. When the wheeze is harsh, low pitched and monophonic, large airway obstruction must be considered. The role of bronchoscopy in pre-school wheezing includes evaluating the airways for any structural and anatomical abnormalities. Thirty per cent of children investigated by airway survey will benefit from bronchoscopy. In 40–60% of children with recurrent or persistent wheeze an organism is isolated from the bronchoalveolar lavage specimen. The reported complication rate in these studies was very low.

A selective group of preschool wheezing children who are not responding to treatment have symptoms of large airway obstruction; symptoms suggestive of gastro-oesophageal reflux or unilateral chest signs may benefit from flexible bronchoscopy to diagnose the cause of their wheezing.

Keywords: bronchoscopy; preschool wheeze; large airway obstruction; bronchoalveolar lavage

INTRODUCTION

Lower airway tract illnesses with wheeze are common in the preschool child and occur in approximately one-third of all children. These children can be divided into two groups based on their symptoms and can follow the pattern of episodic viral or multiple trigger wheeze.[1] These phenotypes can change over time in an individual child.[2,3]

Bush et al divided childhood wheezing into four groups:

1. Normal child
2. Serious conditions which it is essential to diagnose or refer
3. Minor conditions that may exacerbate or mimic wheezing, for example gastro-oesophageal reflux (GER)
4. True wheezing syndromes, including episodic viral wheeze and multiple trigger wheeze.[4]

The history and physical examination are used to categorise children and to decide whether further investigations are necessary. Although preschool wheezing is common, there is a paucity of evidence to guide clinicians in selecting diagnostic tests.

Most children with preschool wheeze do not need further investigation, but referral is needed in the following cases:

- if the child does not respond to treatment;
- if the diagnosis is in doubt;
- if there are other comorbid conditions present, and
- if the wheezing is audible without a stethoscope.

Serious conditions must be considered when the following are present: symptoms from the first day of life; a child with wheezing who is not thriving; chronic wet cough; sudden onset of symptoms; continuous, unremitting symptoms; systemic illness; digital clubbing; severe chest deformity; stridor; fixed wheeze, or asymmetric signs on auscultation.

When the wheeze is harsh, low pitched and monophonic, large airway obstruction must be considered. This wheeze is prominent centrally and the lungs are generally not hyper-inflated as in small-airway obstruction. Subcostal retraction is also more common in small-airway obstruction. Table I shows the causes of large-airway pathology.

BRONCHOSCOPY

Killian introduced bronchoscopy into clinical practice in 1897.[5] Bronchoscopy is an important diagnostic tool in the management of respiratory tract diseases in children. In addition to allowing direct visualisation of the respiratory passages, it allows for endobronchial treatment of airway lesions and the collection of samples for histopathological, microbiological and cytological investigations.[6]

TABLE I: CAUSES OF LARGE-AIRWAY PATHOLOGY

Acquired causes:
- Pulmonary tuberculosis
- Mediastinal masses
- Foreign-body aspiration
- Post-intubation injuries
- Other causes:
  - tumours
  - Cryptococcus
- Intraluminal tumours
  - bronchial adenoma

Congenital causes:
- Bronchogenic cyst
- Duplication cyst
- Vascular malformations
- Tracheal stenosis
- Tracheobronchomalacia

Bronchoscopy is not only used in the removal of foreign bodies but helps with diagnosing congenital lung abnormalities and acquired lung pathology; it also plays a role in the investigation of children with recurrent and/or opportunistic respiratory infections.

Godfrey et al published a study on the utility of flexible bronchoscopy in children, examining 200 consecutive procedures.[9] In this study, the main indications were wheezing (26%), recurrent pneumonia (21%) and atelectasis (12.5%).[7] Similarly, in another study, 536 fibre-optic bronchoscopies were performed on children (<14 years), where the commonest indications were persistent atelectasis (31%), stridor (25%), tuberculosis (12%), suspected foreign-body inhalation (11%) and persistent wheezing (10%).[8]

In a multicentre European study, the primary diagnosis prior to bronchoscopy was recurrent or persistent pneumonia (17%), followed by wheezing unresponsive to treatment (15.5%), persistent atelectasis (14%) and stridor (13%).[9]

ROLE OF BRONCHOSCOPY IN PRESCHOOL WHEEZING

Routine investigations for children with wheezing who are not responding to treatment include a blood test such as IgE and RAST, IgG, IgM, IgA as well as IgG subclasses. A sweat test and genetic testing for cystic fibrosis could be considered. Gastro-oesophageal reflux needs to be excluded with the use of contrast studies and pH monitoring. Nasal ciliary brushings can be used to exclude primary ciliary dyskinesia (PCD).

A scan using high-resolution chest computed tomography (HRCT) is indicated if bronchiolitis obliterans or other structural abnormalities are considered.

The role of bronchoscopy in preschool wheezing includes evaluating the airways for any structural and anatomical abnormalities. This includes the upper and the lower airways. It is also important to always evaluate the upper airways with flexible nasoendoscopy and laryngoscopy and not just a flexible bronchoscopy through a laryngeal mask airway. Large airways can be either structurally or functionally abnormal or can present a combination of abnormalities. Tracheomalacia and bronchomalacia can be missed if the child is not breathing spontaneously. Vascular abnormalities are more commonly found than airway stenosis. These abnormalities can include double aortic arch, innominate artery compression, left pulmonary artery sling or left main bronchus (LMB) compression by a patent ductus arteriosus remnant.[10] The pattern of compression seen on bronchoscopy can be a guide to the type of vascular compression present.

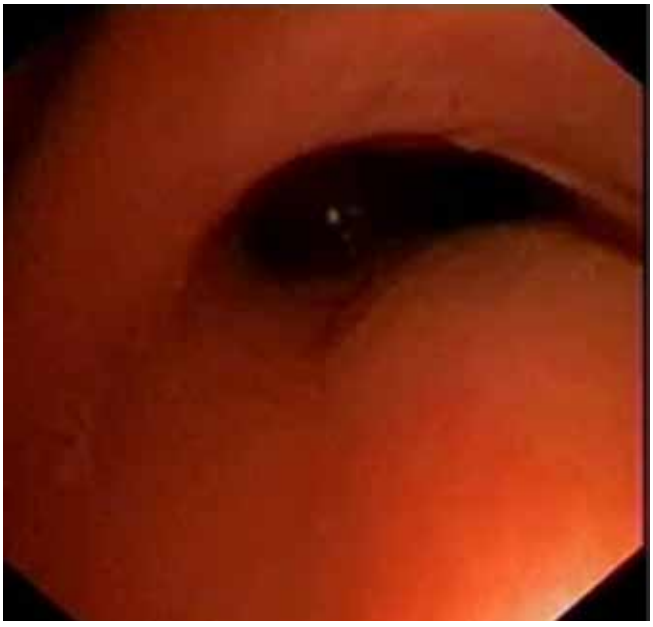

Figure 1: Bronchoscopy image of double aortic arch with anterior compression of the trachea from the right and posterior compression

The trachea will be compressed both anteriorly and posteriorly by a double aortic arch and only anteriorly in the case of the innominate artery (see Figure 1). A left pulmonary artery sling causes compression of the distal trachea and the carina. Airways can also be compressed by congenital and acquired cardiac conditions and it is mostly the LMB that is vulnerable.

The two important congenital causes of airway obstruction are bronchogenic cyst and airway narrowing due to compression or stenosis (see Figures 2 and 3). Both cause wheezing that is indistinguishable on clinical grounds but diagnostic at bronchoscopy. Bronchogenic cysts can occur at different anatomical locations, with those located in the subcarinal and paratracheal region more commonly causing airway compression. Tracheobronchial anomalies can present with stridor, wheeze, cough, recurrent pneumonia or recurrent and persistent atelectasis. Airway abnormalities can present in association with other conditions such as genetic syndromes, congenital heart defects and vascular abnormalities. Tracheal stenosis is a rare but life-threatening congenital malformation. Tracheomalacia is more common and may be associated with vascular rings or trachea-oesophageal fistula.[11]

Only a few articles have been published on the value of bronchoscopy in persistent wheezing in children. In one such

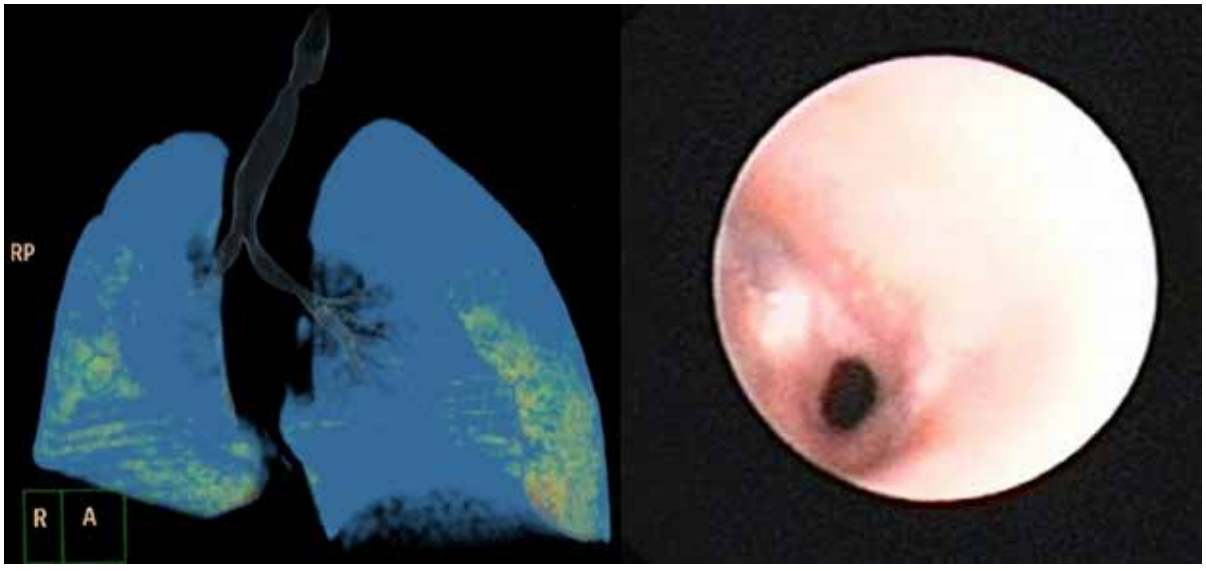

Figure 2a: Chest CT-scan reconstruction: narrow segment of trachea and hypoplastic right lung
Figure 2b: Bronchoscopy images demonstrating tracheal stenosis

study of 113 children (median age 14 months) with persistent wheezing, pathological findings were found in 48% of cases. This included tracheobronchomalacia (*n* = 38), foreign-body aspiration (*n* = 14) and vascular compression (*n* = 2).[12]

Gu et al reported on 156 children with refractory wheezing and found that 21.8% of them had airway malformations, which included tracheomalacia, airway stenosis and tracheal bronchus. The rate of malformations was higher in children less than 12 months of age (31%). A bronchoalveolar lavage (BAL) performed in these children showed that neutrophil-mediated airway inflammation was characteristic in those with refractory wheezing. From BAL specimens a virus was identified in 13.9% (*n* = 17) and bacterial organisms in 59.6% (*n* = 93). In the BAL, Mycoplasma pneumoniae were found in 51.6% (*n* = 63). Other bacteria isolated included Haemophilus influenza (*n* = 12) and Streptococcus pneumonia (*n* = 12).[13]

Boesch et al recently reported on children with persistent or recurrent wheezing. The potential anatomical cause for wheezing was identified in 45.7% of patients and inflammatory changes were identified in 49.5% of procedures. Tracheobronchomalacia was the most commonly identified anatomical lesion.[14]

Both Marguet et al and Le Bourgeois have previously reported high levels of neutrophils in the BAL of wheezing children. These may be related owing to the high level of interleukin 8 secretion in these patients.[15,16]

Saglani et al have reported on the use of investigation of young children with severe recurrent wheeze and if there is any clinical benefit in doing so: 37 out of 47 children had abnormal bronchoscopy findings. Their findings included structural abnormalities (*n* = 13), excessive mucus (*n* = 20) and macroscopic inflammation (*n* = 10). Bacteria were cultured from BAL specimens in 27% of cases. In addition, an endobronchial

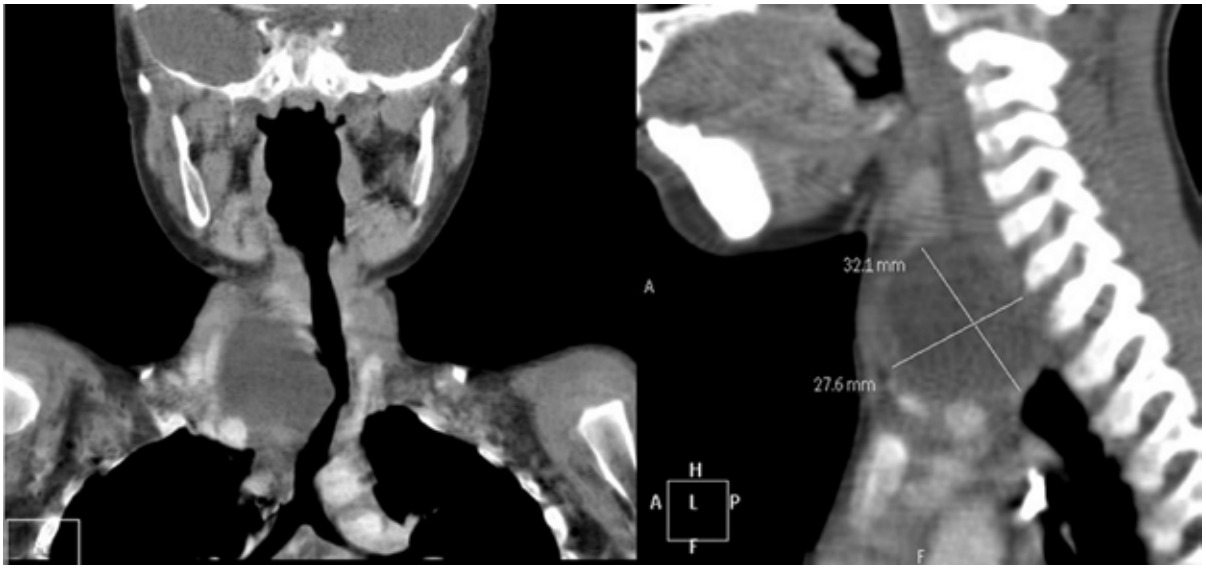

Figure 3: CT scan images of bronchogenic cyst in the neck causing tracheal compression

biopsy was done which showed that 44% had eosinophilic changes and 28% had a thickened reticular basement membrane.[17]

The American Thoracic Society (ATS) recently published their clinical practice guidelines on the diagnostic evaluation of infants with recurrent or persistent wheezing. They evaluated the following questions: Should infants with persistent wheezing despite treatment with bronchodilators, inhaled corticosteroids or systemic corticosteroids undergo airway survey via flexible bronchoscopy and should a BAL be done?[18] Regarding both of these questions, very low-quality evidence was found. In the case of bronchoscopy, case series only were identified. Collectively, 1 364 patients were identified and 452 (33%) were found to have anatomical abnormalities that led to wheezing. This included tracheomalacia, bronchomalacia, vascular rings and airway compression by a vascular structure. No serious complications of bronchoscopy were recorded, except for transient hypoxemia in 5–10% of cases.[18]

Most children with wheezing caused by tracheomalacia, bronchomalacia or tracheobronchomalacia are managed conservatively, especially if the symptoms are mild and the airway malacia is the only abnormality present. Most of these children improve with time. Only children with life-threatening symptoms, recurrent pneumonia or severe failure to thrive require an intervention that includes constant positive airway pressure or airway surgery. In most of these cases the surgery will be aortopexy, which relieves most wheezing resulting from tracheomalacia, but is less effective in cases with tracheobronchomalacia. About 80–100% of patients with vascular rings or vascular compression of the airways improve with surgery. Most wheezing caused by vascular rings and vascular airway compression in unlikely to self-resolve and needs surgical correction.[18]

In conclusion, approximately 30% of children being investigated by airway survey will benefit from bronchoscopy. This would be through surgery or indirectly by avoiding unnecessary tests and treatment. Also, very importantly, parents can be reassured about the lesion and the most likely outcome.

Data are available from 20 studies on performing a BAL in wheezing children. In 40–60% of children with recurrent or persistent wheeze an organism is isolated from the BAL specimen. The reported complication rate in these studies was very low. Furthermore, children with a positive BAL culture received a prolonged course of antibiotics, and in one study 48% of children receiving antibiotics the cough resolved compared to only 16% of those who did not received an antibiotic.[18] It is estimated that 20–30% of children with persistent wheezing who have a bronchoscopy and BAL performed were found to have a lower respiratory tract infection, which improved following a course of antibiotics.[18]

BRONCHOSCOPY IN WHEEZING PRESCHOOL CHILDREN IN DEVELOPING COUNTRIES

In countries with high incidence of TB and HIV, these must also be considered as causes of wheezing that is not responding to treatment. TB can present in young children with airway obstruction as a result of enlarged lymph nodes compressing the large airways. The bronchus intermedius, left main bronchus and trachea are the most common airways at risk of being externally compressed, or the airway can be narrowed by a combination of external compression and ulceration into the airways.[19] The role of bronchoscopy is twofold in these cases: it enables the airway to be accessed directly and diagnostic samples can be obtained for culture and/or GeneXpert.[20]

In HIV-infected children with airway obstruction, Cryptococcus lymph-node enlargement, viral papillomata, Kaposi's sarcoma and other opportunistic infections must be considered. Bronchoscopy may be diagnostic and diagnostic biopsies can be collected.

FOREIGN-BODY ASPIRATION (FBA)

The diagnosis of a foreign body in a paediatric airway may be difficult, because this phenomenon most commonly occurs in infants and toddlers who are unable to communicate the circumstances leading to the aspiration event. The signs and symptoms may be non-specific. Barrios et al have reported that among all the clinical symptoms, the history of a choking crisis has the highest diagnostic sensitivity and specificity (97% and 63% respectively).[21] Wheezing in the absence of known pulmonary disease should be considered indicative of FBA until proven otherwise, especially if the wheezing is unilateral.

GASTRO-OESOPHAGEAL REFLUX (GER) AND PRESCHOOL WHEEZING

Both bronchoscopy and BAL may be of value in evaluating the preschool child with wheezing and symptoms of GER. It is important to exclude upper airway pathology that can lead to aspiration. This includes vocal cord palsy and dysfunction, laryngomalacia and a laryngeal cleft. When a laryngeal cleft is suspected, both flexible and rigid bronchoscopy with palpation of the inter-arytenoid notch must be done as the diagnosis may be missed if only a flexible bronchoscopy is performed. Although rare, an H-type trachea-oesophageal fistula must also be excluded. Boesch et al identified a laryngeal cleft in 17% of cases with persistent or recurring wheezing.

GER may be associated with chronic or recurrent asthma-like symptoms secondary to bronchoconstriction reflexes and/or inhalation of gastric content. The lipid-laden macrophages index (LLMI proportion) of lipid-laden alveolar macrophages in a BAL sample has been used as an index to establish the degree of gastric aspiration. BAL cells are stained with oil-red and the amount of lipid per single macrophage is evaluated by a semi-quantitative method described by Colombo and Hallberg, giving a score of 0–4 to each cell, according to the amount of lipid in the cytoplasm. [22] The final index is determined by evaluating 100 cells.[22] The utility of the LLMI as a marker for GER in respiratory disease has been controversial, its use problematic for the following reasons:

- It is found in a variety of other pulmonary conditions.
- It is not the gold standard for recurrent aspiration.
- It does not differentiate whether aspiration is related to swallowing abnormalities or to GER.

In taking all the evidence into consideration, the LLMI is still used by clinicians as an adjunct investigation for children whose symptoms are suspicious for aspiration and therefore warrant bronchoscopy. Recently BAL pepsin was evaluated as a possible diagnostic test for GER.[23] It may be useful in cases where pH monitoring is inconclusive, but the symptoms are suggestive of GER.

USE OF ENDOBRONCHIAL BIOPSY IN PRESCHOOL CHILDREN WITH PERSISTENT WHEEZING

Markers of airway remodelling are epithelial injury, thickening of the reticular basement membrane, goblet cell and airway smooth muscle hypertrophy, hyperplasia and angiogenesis.[24,25] Some studies have suggested that remodelling occurs early during the course of asthma owing to long-standing airway inflammation. Most studies on wheezing show conflicting results, but reveal a poor relationship between inflammation and remodelling in young children.[26,27] Lezmi et al recently reported that in preschoolers with severe recurrent wheeze airway wall structure did not correlate with inflammatory cell counts and that atopy is associated with higher hypertrophy of the airway smooth muscle. Airway inflammation and remodelling may develop independently.[28] Currently, routine endobronchial biopsy has a limited role and remains a research tool.

CONCLUSION

A selective group of wheezing preschool children who are not responding to treatment and who have symptoms of large airway obstruction, symptoms suggestive of GER or unilateral chest signs may benefit from flexible bronchoscopy to diagnose the cause of their wheezing. Bronchoscopy in preschool children with persistent wheezing has a twofold role. It is important in helping to exclude anatomical abnormalities and may also help to identify pathogens, the type of inflammation present and whether aspiration is present. Overall, the risk of anaesthesia is justified in this population based on the high frequency of management changes that are exposed by the bronchoscopy findings. The changes in management range from medical management to surgical interventions, including the removal of foreign bodies. It is also important to be able to identify an alternative explanation for the wheezing that may result in the elimination of unnecessary medication. Future research is necessary that investigates the markers of more specific inflammation and environmental exposure.

DECLARATION OF CONFLICT OF INTEREST

The author declares not conflict of interest.

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Review Article

DIAGNOSIS AND MANAGEMENT OF PRESCHOOL ASTHMA

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ABSTRACT
Asthma is the most common chronic disease in childhood and remains under-diagnosed despite reports of increasing prevalence in most countries. Improperly treated asthmatics may suffer from avoidable complications including chronic daily symptoms, frequent emergency visits and unnecessary hospital admissions. Diagnosing asthma in affected preschool children is particularly important, as this age group is the most at risk for having severe symptoms and frequent asthma exacerbations. However, establishing a diagnosis of asthma in younger children can be challenging. This article summarises key elements of current recommendations on the diagnosis and management of preschool asthma. The goal is to increase awareness of typical signs and symptoms of preschool asthma and to provide healthcare providers with guideline-based recommendations for maintenance therapy.

INTRODUCTION

Asthma is a heterogeneous disease, usually characterised by episodic respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, as well as chronic airway inflammation and reversible airflow limitation on pulmonary function testing.[1] Asthma is the most common chronic disease of childhood. The asthma prevalence in Africa is approximately 10% of children of 6–7 years of age and is increasing over time.[2]

Most children with asthma present with their first symptoms in the preschool years.[3] This population is at greater risk, compared to other age groups, to experience emergency visits and hospital admissions for asthma.[4] The diagnosis of asthma can be challenging in preschoolers, who are unable to perform conventional lung-function testing by spirometry. Asthma in toddlers was previously classified according to wheezing phenotypes (ie episodic or multi-trigger wheeze and transient, persistent or late-onset wheeze); however, the clinical usefulness of this phenotyping has not yet been demonstrated and is therefore no longer commonly used.[1] Nonetheless, early diagnosis and proper treatment of childhood asthma is important and may, in addition to symptom control, allow for maximum lung growth and function in later life. This article presents the current approach to diagnosis and management of asthma and wheezing in preschool children as recommended by national and international guidelines.

DIAGNOSTIC APPROACH

Episodic airways obstruction and reversibility of airflow limitation are the cornerstones of an asthma diagnosis. Pulmonary function testing before and after inhaled bronchodilator medication is therefore commonly used to confirm suspected asthma in older children and adults. In the absence of objective measures of reversible airways obstruction a diagnosis of asthma can be challenging. Caregivers may report symptoms of airways obstruction in preschool children as cough, wheezing, shortness of breath or limitation with physical activity. All these symptoms may occur intermittently. Wheezing is the most specific sign of airflow obstruction, particularly when triggered by exercise, laughing, crying or environmental exposure outside of a respiratory tract infection. Cough is more indicative of asthma when happening at night or, similar to wheezing, when triggered by exercise, laughing or crying.[1] If related to a viral infection, an asthmatic child will often have a prolonged cough for more than ten days, have more than three episodes of prolonged cough per year and may continue to cough in between viral episodes. Symptoms of asthma are frequently overlooked by caregivers or healthcare providers and may only present as exercise-induced. A thorough medical history is therefore of great importance.

The family history plays a crucial role when suspecting asthma in a child. A family history of atopy is the most important risk factor for asthma in children, the strongest association is in the presence of maternal atopy.[4] Different international guidelines including the 2017 Global Initiative for Asthma (GINA) report

TABLE I: SIGNS AND SYMPTOMS OF PRESCHOOL ASTHMA (MODIFIED FROM BRITISH THORACIC SOCIETY, 2016)[4]

DESCRIPTION	PARAMETER	SENSITIVITY	SPECIFICITY	POSITIVE PREDICTIVE VALUE	NEGATIVE PREDICTIVE VALUE
Signs and symptoms	Cough	88%	7%	76%	15%
	Wheezing	54%	57%	80%	27%
	Shortness of breath	76%	52%	84%	40%
Combination of symptoms	Cough and wheezing	49%	59%	80%	51%
History of atopy	Personal history of rhinitis/eczema	47–62%	20–75%	72–86%	14–30%

have emphasised the importance of atopy among the diagnostic criteria for asthma in preschoolers,[1] whereas other guidelines put less emphasis on this.[3] While it is important to raise awareness to signs and symptoms of obstruction of the airways, wheeze, cough, shortness of breath and atopy have low predictive values for the diagnosis of asthma in preschool children, as illustrated in Table I. Therefore, a treatment trial can be helpful to confirm a diagnosis of asthma by documenting improvement or resolution of symptoms with asthma therapy. Current guidelines including the South African Childhood Asthma Working Group (SACAWG) 2017 update for the management of chronic asthma in children[5] recommend a three-month therapeutic trial with low-dose inhaled corticosteroid (see Table II). If feasible, it is recommended to arrange a follow-up as early as six weeks after starting the new therapy, in order to monitor inhalation technique and improve adherence. It may, however, take up to 3-4 months before the maximal therapeutic effect of inhaled corticosteroids can be seen.[1] Reversibility of airways obstruction is confirmed if there is improvement with the therapy and worsening of symptoms at its cessation.[1] Other guidelines also include a positive response to short-acting beta-agonist (SABA) as a sign of reversibility.[3] Validated tools to measure the severity of airways obstruction using clinical observations have been developed for paediatric patients. The Paediatric Respiratory Assessment Measure (PRAM) score[6] can also be used to measure treatment responses (see Table III). If the clinical history is atypical for asthma and/or there is no response to inhaled corticosteroids, alternative diagnosis needs to be considered (see Table IV).

TABLE II: PREFERRED LOW-DOSE ICS AS TOTAL DAILY DOSE (MCG) IN CHILDREN LESS THAN FIVE YEARS (SACAWG)[5] AND CHILDREN 6–11 YEARS (GINA 2018 UPDATE)[21]

INHALED CORTICOSTEROID	LESS THAN 5 YEARS	6–11 YEARS
Beclomethasone dipropionate (HFA)	50-100	50–100
Budesonide (pMDI and spacer)*** Budesonide nebulised***	100-200 250-500	100-200 250–500
Fluticasone propionate (HFA)	50-100	100–200
Ciclesonide #	N/A	80–160

***Most preparations are registered for twice daily use except Budesonide which can also be administered once per day.
Not registered in South Africa for use in children less than 12 years of age

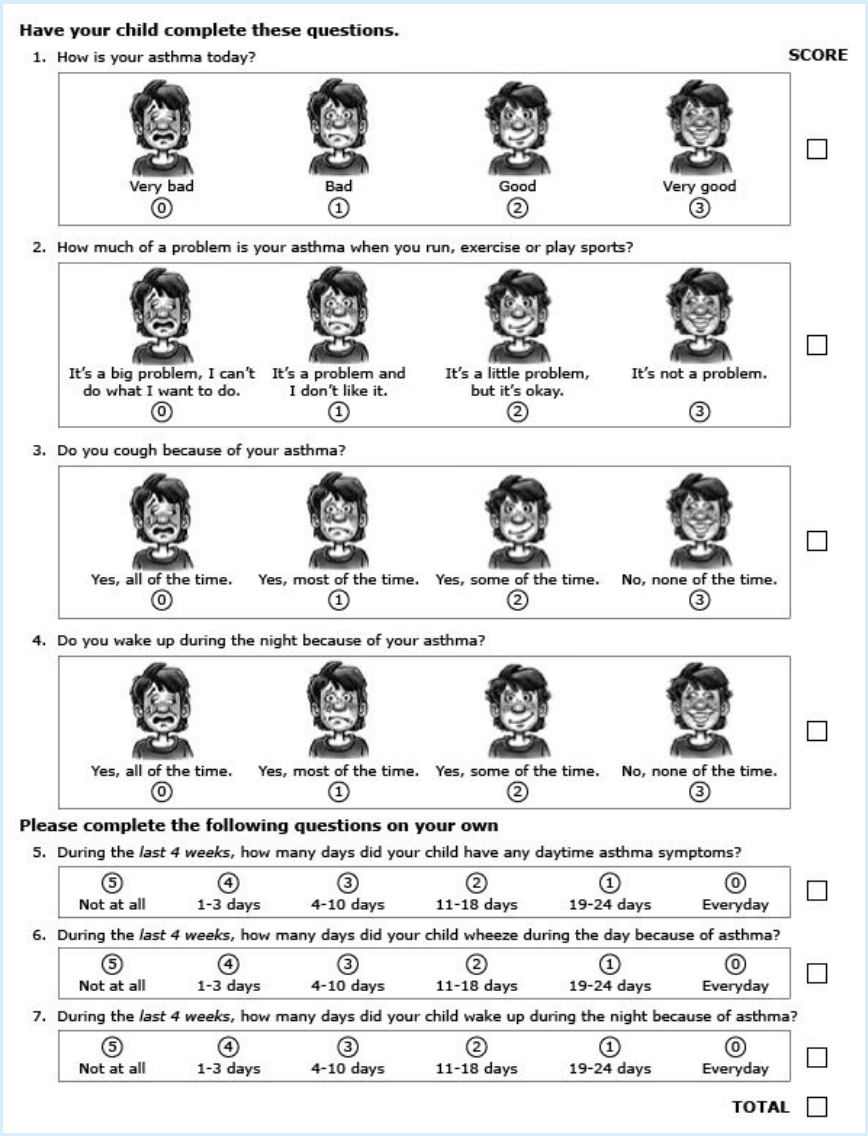
TABLE III: THE PRESCHOOL RESPIRATORY ASSESSMENT MEASURE (PRAM) SCORE[20]

CRITERIONS	DESCRIPTIONS		SCORE
O_2 SATURATION	≥95%		0
	92–4%		1
	<92%		2
SUPRASTERNAL RETRACTION	Absent		0
	Present		2
SCALENE MUSCLE CONTRACTION	Absent		0
	Present		2
AIR ENTRY	Normal		0
	Decreased at the base		1
	Decreased at the apex and the base		2
	Minimal or absent		3
WHEEZING	Absent		0
	Expiratory only		1
	Inspiratory (± expiratory)		2
	Audible without stethoscope or silent chest (minimal or no air entry)		3
PRAM SCORE (MAX 12):			
PRAM SCORE	0–3	4–7	8–12
SEVERITY	Mild	Moderate	Severe

TABLE IV: DIFFERENTIAL DIAGNOSIS OF WHEEZE IN CHILDREN UNDER FIVE YEARS OF AGE (SACAWG)[5]

CATEGORY	DISEASE ENTITY
Congenital upper airways	Laryngomalacia Complete cartilage rings Cysts, webs Tracheomalacia Vocal-cord paresis Subglottic stenosis
Congenital lower airways	Vascular rings/sling Bronchomalacia
Aspiration 'syndromes'	Gastroesophageal reflux disease (GERD) Swallowing incoordination Laryngeal cleft Tracheoesophageal fistula
Bronchiectasis	Cystic fibrosis Primary ciliary dyskinesia Persistent bacterial bronchitis Immunodeficiency (primary/secondary to HIV)
Bronchial obstruction	Lymph nodes enlarged by tuberculosis (TB), HIV or lymphoma
Endobronchial lesions	Foreign body Tumours TB granuloma
Cardiac	Enlarged cardiac chambers Pulmonary oedema Congenital heart disease (left to right shunts)
Miscellaneous	Bronchopulmonary dysplasia

TABLE V: CHILDHOOD ASTHMA CONTROL TEST OF CHILDREN 4-11 YEARS OLD (ALLERGY AND ASTHMA NETWORK)[16]



MANAGEMENT

The goals of asthma management are to:

- achieve good control of symptoms;
- maintain normal activity;
- minimise future risk of flare-ups (asthma attacks), and
- minimise medication side-effects.[1]

These goals are reached in partnership with the caregiver, the affected child and healthcare providers through monitoring the symptoms and providing education, skills training for effective use of inhaler, encouragement for good adherence and a written asthma action plan.

Inhaled corticosteroids (ICS) remain the treatment of choice for asthma management. The lowest ICS dose possible should be used to achieve symptom control. Medium-dose ICS, when taken properly, will decrease the number of exacerbations requiring treatment with oral steroids by 50%, shorten duration of exacerbations and cause less symptoms between episodes.[7] Preferably, inhaled medication should be given through a valved holding chamber or spacer. Chambers with face masks are used in younger children. Children that show a proper seal technique, sometimes as early as four years of age, should use a mouth piece for inhalation.[1] A pressurised metered dose inhaler (pMDI) with a valved holding chamber is the preferred method of drug delivery.[8] Use of a nebuliser is an alternative delivery method but should be reserved for children unable to adequately use a spacer device. Different from SABA, the effect of anti-inflammatories is not immediate. ICS start to have recognisable effects after 1–4 weeks and may not reach maximal efficacy before 3–6 months of use.[9]

A step-wise approach to achieve symptom control is generally recommended in asthma management:[1,3,5]

Step 1 – As-needed inhaled short-acting beta$_2$-agonist SABA) or low-dose ICS:
Preferred option: As needed short-acting beta$_2$-agonists (SABA) For mild and infrequent symptoms of wheezing, SABA monotherapy as needed is generally recommended as the preferred treatment.[1,3,5]
Other option: Low-dose ICS GINA guidelines now consider ICS as an alternative for treatment of children with intermittent viral-induced wheeze and no interval symptoms, in whom inhaled SABA is not sufficient.[1,10] Oral bronchodilator therapy is not recommended due to slower onset of action and higher rate of side-effects compared to SABA.
Step 2 – Initial controller treatment plus as-needed SABA
Preferred option: Daily low-dose ICS, plus as-needed SABA Persistent (ie more than eight days per month) or severe symptoms (requiring oral steroids or hospital admission) should be treated with daily low-dose ICS as preferred controller choice. This treatment should be given for at least three months to establish its effectiveness in managing asthma symptoms.[1,10]
Other option: Leukotriene receptor antagonist (LTRA) LTRA (Montelukast™) is an alternative treatment for step 2, although proven less effective in reducing symptoms than ICS.[5] It should be considered for children who are unable or refuse to receive ICS therapy, who have significant side-effects with ICS or those with allergic rhinitis (AR).[1]
Step 3 – Additional controller treatment, plus as needed SABA
Preferred option: Medium dose ICS (doubling low dose ICS) When symptoms remain uncontrolled with low-dose ICS, doubling the initial low daily dose ICS is the preferred option in the preschool population[1].
Other option: LTRA with low-dose ICS.
Step 4 - Continue controller treatment and refer for specialist assessment
Preferred option: Refer for expert advice and further investigation If a child fails to achieve and maintain good asthma control after three months on medium-dose ICS, with proper adherence, technique and in the absence of treatable comorbidities, international guidelines such as GINA recommend to refer to a specialist.[1]
Other options: High-dose ICS (perhaps combined with more frequent dosing) or low-dose OCS (for a few weeks only) or add LTRA or theophylline or add intermittent ICS to the regular daily ICS during exacerbations.

The best treatment of preschool asthma when step 3 is insufficient has not yet been established. Although not approved in this age group, inhaled ICS/LABA fixed combination therapy is now widely used as off-label medication in children five years of age and younger. In older patients, adding a LABA to a low-dose ICS provides additional control symptoms with a reduced risk of exacerbations.[1]

Similarly, other frequently prescribed ICS medications may also not be approved for the preschool age and therefore be used off-label. Beclomethasone diproprionate, a prodrug that is rapidly activated by hydrolysis to the active monoester 17-beclomethasone monopropionate, is an ultra-fine particle compound with better lung deposition compared to larger particle ICS.[11] However, whether this results in superior efficacy remains to be proven.[12] Ciclesonide is an inactive prodrug that is converted to its active metabolite desisobutyrylciclesonide in the airways, and due to low oral bioavailability, has potentially less systemic side-effects. It is used once daily which may result in improved adherence. Since ciclesonide is a relatively new medication, there are fewer studies on its long-term safety and efficacy.[13] Fluticasone proprionate is a large-particle steroid with the highest binding receptor affinity.[14] Therefore, it is considered the most efficient ICS. A comparison of fluticasone with budesonide and beclomethasone in adults and children in a recent Cochrane review, concluded that at comparable doses, fluticasone was slightly more effective than budesonide or beclomethasone but with concurrent higher risks of unwanted side-effects.[15] The availability and the relative costs of different treatment options need to be considered for controller choices in younger children.[10]

At every visit, the healthcare provider should attempt to quantify asthma control by asking about daytime symptoms, limitations of activity and night-time awakenings from cough, recent exacerbations (asthma attacks or flare ups) that may have caused an emergency visit, a hospital admission, prescription of oral steroid courses or repeated use of SABA. Reassurance of good adherence with the prescribed medication dose and adequate technique (watch patient using their inhaler and correct errors), as well as screening for potential side-effects of therapy, modifiable risks factor (eg environmental exposures) and comorbidities (eg AR) and alternative diagnoses should be assessed before considering to step up the treatment.[1] Routine follow-up is recommended every 3–4 months. Validated tools, for instance the Childhood Asthma Control Test (see Table V)[16] can be used to quantify symptoms and asthma control in preschool children. Other tools are also available such as the TRACK score, Primary Care Asthma Control Screen (PACS) and the 30-second asthma test.[1] The lowest possible dose of medications should be used to achieve asthma control with normal activity level and very few symptoms and exacerbations. Healthcare providers should consider stepping down on medication at every visit, if symptoms are well controlled for at least three months. ICS can be stopped from a low dose in the presence of minimal symptoms during the season when the child is usually the most symptomatic.[3]

When prescribing corticosteroids, caregivers need to be informed of the potential risks for unwanted effects and the expected benefits of the medication. Patients should be monitored for common side-effects including growth retardation and adrenal suppression routinely on follow-up, specifically when using higher ICS doses or systemic corticosteroids. The child's height should be measured at least yearly. Growth velocity can be affected by ICS in the first 1–2 years of treatment in the prepubertal children. Nonetheless, a meta-analysis study concluded that ICS users had only a slight reduction in their adult final height of about 1 cm or 0.7%.[17]

EVOLUTION OF PRESCHOOL ASTHMA

The earlier the onset of wheezing, the better the prognosis. In 60% of affected preschoolers, the asthma will have resolved by age six years.[18] Risk factors for persistence of asthma into later childhood include a family history of atopy with or without asthma. Female sex is a risk factor for the persistence of asthma into adulthood. The severity of asthma

during preschool years, according to the number of wheezing episodes and the trajectory of symptoms over time, are also associated with recurrent wheeze that can persist during adolescence.[18]

MANAGEMENT OF EXACERBATIONS

Poorly controlled asthma is a risk factor for future exacerbations. These are defined as an acute or sub-acute worsening of symptoms sufficient to cause distress or risk for health and necessitating an unscheduled visit to a healthcare provider or emergency room, requiring treatment with oral corticosteroids.[1] Strong predictors of an imminent exacerbation are increased daytime cough and wheeze as well as night-time use of beta-agonists.[19]

Cornerstones of the management of an exacerbation are frequent administration of SABA, systemic (oral or injected) corticosteroids and supplemental oxygen in patients with desaturations.[1] Healthcare providers and caregivers need to be familiar with recognising and treating asthma exacerbations.

CONCLUSION

Asthma in preschool children is important to recognise as the first symptoms of asthma usually present early in life. This population is more at risk of experiencing emergency visits and hospital admissions due to asthma, compared to older children and adults. Even without spirometry testing, healthcare providers should be able to suspect and establish a clinical diagnosis in preschoolers with a positive history of airway obstruction and reversibility. A personal or family history of atopy and symptoms of airflow obstruction that occur outside of a viral episode make a diagnosis of asthma more likely.

Alternative diagnoses should be considered in the presence of atypical symptoms or unresponsiveness to asthma therapy. The cornerstones in the management of asthma in preschoolers are family education and ICS with different add-on medications in case of poor symptom control. The healthcare providers should arrange regular follow-up visits ideally every 3–4 months to assess for symptoms, adherence with prescribed medication dose, inhalation technique and side-effects of the medication. In the future, more accessible objective measurements of the lung function in this age group might become widely available to ensure an easier diagnosis and monitoring.

DECLARATION OF CONFLICT OF INTEREST
The authors declare no conflict of interest.

This article has been peer reviewed.

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Ethics Article

DISCLOSING MEDICAL ERROR – CHANGING THE CULTURE OF MEDICINE

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ABSTRACT
Medical error is common; it constitutes the third leading cause of death in the United States. Doctors are often afraid to disclose errors, fearing resultant litigation. Respect for persons dictates that full disclosure be made to the patient and family, even if no harm results from the error. Support for the healthcare professional should be augmented by a reflective process that promotes learning and growth.

INTRODUCTION

> 'Virtually every practitioner knows the sickening realisation of making a bad mistake. You feel singled out and exposed – seized by the instinct to see if anyone has noticed. You agonise about what to do, whether to tell anyone, what to say. Later, the event replays itself over and over in your mind. You question your competence but fear being discovered. You know you should confess, but dread the prospect of potential punishment and of the patient's anger. You may become overly attentive to the patient and family, lamenting the failure to do so earlier and, if you haven't told them, wondering if they know.'[1]

A recent discussion among clinicians and others concerned how much information should be disclosed to the family of a patient who had suffered hypoxic neurological damage, possibly because of suboptimal care. Those clinicians present felt that full disclosure was warranted, but members of management were concerned about the possibility of litigation and thus cost to the state. How do we address this culture in medicine where we withhold information about medical error from patients and families, and attempt to cover up mistakes that may or may not have had a negative impact on patient care and outcome? How do we ensure that junior staff and students understand that telling the truth is one of the cornerstones of the doctor–patient relationship, even if that means admitting to an error?

MEDICAL ERROR

According to the Merriam-Webster online dictionary, an error is:

- 'an act or condition of ignorant or imprudent deviation from a code of behaviour';
- 'an act involving an unintentional deviation from truth or accuracy', or
- 'an act that through ignorance, deficiency, or accident departs from or fails to achieve what should be done'.[2]

Medical error is 'the failed processes of medical practice that leads to adverse outcomes'.[3] A 'near miss' is a medical error that is identified and stopped before it can cause harm to the patient.[4] Post and Blustein distinguish between 'adverse outcomes' and 'medical error'.[5] Adverse outcomes are

> 'undesired and unintended negative results of medical care that create actual or potential harm to the patient. These untoward occurrences may be the result of carelessness or ineptitude, or they may reflect foreseen but unavoidable risk even when standard of care was practiced.'

Medical errors are potentially avoidable, whereas the latter are considered unavoidable.[5]

In the United States medical error is the third leading cause of death, after heart disease and cancer. It is estimated that more than 250 000 people die annually in the United States because of medical error.[6] One of the problems in trying to evaluate the contribution of medical error to death statistics is that it may not be captured as a cause of death on a death certificate. I was unable to find comparative statistics for South Africa.

Medication-related errors include administering the incorrect medication or dose of the correct medication, incorrect route of administration, or administering the medication at the incorrect time or to the wrong patient. Errors in dosing are by far the most common medication-related error.[7] In a prospective study at a tertiary academic hospital in Gauteng, a total of 663 medication errors occurred in 227 patients over a period of 16 weeks in the neonatal intensive care unit (ICU) and paediatric wards. The majority were administration errors (51%) and prescribing errors (47%). In the majority of cases no harm resulted to the patients, but a degree of harm affected 33% of the children.[7]

Other types of medical error include operating on the wrong side of the body, other surgical errors, anaesthetic errors and

inadequate follow-up of special investigations. Patient harm from medical error may be a consequence of individual error or a system problem. Important risk factors causing medical error are poor training of clinicians and clinician fatigue.[3]

PERCEPTIONS REGARDING DISCLOSURE OF MEDICAL ERRORS

Despite institutional and individual attempts to prevent medical errors, they will almost certainly happen. The question then becomes whether and how to inform the patient that this has occurred. Some of the consequences to the health professional resulting from medical error could be public shaming and disgrace, a negative impact on reputation, loss of trust of patients and colleagues, loss of self-confidence, loss of employment, depression, sanction by the professional body, and civil suits and litigation. Consequences to the public health system could be costly legal action, which in turn affects the funds available to treat other patients.[3]

How often do doctors disclose medical errors? In a study of house officers published in 1991, 76% of them indicated that they had not disclosed serious errors to patients.[8] Gallagher et al investigated doctors' and patients' attitudes regarding disclosure of medical error through a series of focus group discussions.[9] The patients in the study indicated that they required full disclosure of all harmful errors, what and why they occurred, what would be done about them, and how to prevent future repetitions. The doctors felt that harmful medical errors should be disclosed, but were careful as to what they said and often did not indicate that the adverse event was due to an error. Patients had mixed responses when asked whether near miss errors should be disclosed; doctors felt that these should not be disclosed. The patients wanted an apology from the doctor, but the doctors were concerned that an apology constituted an admission of guilt and posed a risk of litigation. The doctors in this study also indicated that they did not know how to obtain emotional support if they were involved in a medical error situation.[9]

WHY SHOULD WE DISCLOSE MEDICAL ERRORS?

ETHICS

Disclosure of medical error accords with the ethical principles of respect for persons and truth telling. It promotes trust in the doctor and healthcare system and the doctor–patient relationship. Patients have a right to know when errors in their treatment occur, even if such error has not resulted in harm. Hébert et al describe the argument that disclosing medical error may cause the patient anxiety as an outdated form of 'therapeutic privilege', where the doctor believes the patient has to be protected from 'harmful' information.[10] Reporting of medical error is also important to prevent recurrences and improve the safety of patients.

Patients increasingly require honest information from the health professional, including when errors occur.[11]

Post and Blustein believe that the requirement for informed consent also implies that the doctor will take 'due care in treating the patient' and that if any adverse event should occur, that will be disclosed to the patient so that they may avoid further harm and pursue compensation for any harm that has already occurred.[5]

POLICY AND LAW

Both policy and the law dictate that the doctor has a fiduciary duty to the patient, and that this imposes a professional obligation to disclose medical error.[5] The fear of resultant medical malpractice lawsuits should not deter doctors from being honest with patients about medical error.[5,11] In fact, most litigation by patients and their families follows poor communication from the health professional about adverse events and poor outcomes. In 2010 in the United States, 34 states and the District of Columbia had passed legislation to prevent disclosure communications being used as evidence of liability in malpractice suits (the so-called 'apology law').[5]

In 2001 the Joint Commission on Accreditation of Healthcare Organizations (now called the Joint Commission) issued a national disclosure standard in the United States. This standard required that patients be informed about 'all outcomes of care, including "unanticipated outcomes"'.[12] It did not indicate exactly what needed to be disclosed nor that a medical error had occurred, but it was an important step forward as it was a requirement for hospital accreditation. Other countries also promoted disclosure: Australia had its 'Open Disclosure Standard' and the United Kingdom had the 'Being Open' initiative. Subsequently, the United States linked disclosure of unforeseen adverse outcomes with high-quality healthcare, aiming to improve patient safety. This also made provision for training of clinicians in how to disclose adverse events and medical error to patients.[12]

COMMUNICATING WITH PATIENTS ABOUT MEDICAL ERROR

Gallagher et al published a study in which they asked more than 2 500 medical and surgical specialists in the United States and Canada about disclosure of harmful medical error via a mailed questionnaire containing various scenarios and response options.[13] The responses varied considerably, with 56% of doctors mentioning that an adverse event had occurred, but not disclosing the error, whereas 42% of the respondents said they would indicate that an error had occurred. Sixty-one per cent of the doctors indicated that they would express regret about the error, but only 31% would actually apologise for it.[13] According to hospital risk managers, most disclosures are likely to include the following aspects:

- an explanation of what occurred (92%);
- the intention to investigate what happened (87%);
- an apology (68%), and
- an admission that harm had resulted (66%).

In only 33% of cases, would there be an acknowledgement of responsibility for the harm.[14]

TABLE I: KEY ELEMENTS OF THE SAFE PRACTICE FOR DISCLOSING UNANTICIPATED OUTCOMES TO PATIENTS*[12]

CONTENT TO BE DISCLOSED TO THE PATIENT
Supply facts about the event: • Error or system failure, if known. • Information about analysis of the event. Express regret for the unanticipated outcome Formal apology if the unanticipated outcome was caused by error or system failure
INSTITUTIONAL REQUIREMENTS
Integrate disclosure, patient safety, and risk-management activities Establish disclosure support system: • Education and coaching. • Emotional support for healthcare professionals, administrators, patients and families. Develop tools to track and improve disclosure

** Data from National Quality Forum in the United States (reproduced virtually unchanged from Gallagher, Studdert & Levinson[12])*

TABLE II: A STEP-BY-STEP GUIDE TO DISCLOSING AN ERROR (FROM GORDON,[4] AND HÉBERT, LEVIN & ROBERTSON[10])

1. Ensure the patient is stable.
2. Obtain all the facts available: What happened; why did it happen; how did it affect the patient; what was done to ameliorate the error; what is the patient's current condition?
3. Report the incident to your line manager/supervisor and obtain assistance in talking to the patient and family. Contact your medical malpractice insurance company and the hospital clinical advisor/ administrator if you are in private practice.
4. Disclose the error to the patient, family, or both: state the facts without attributing blame. Tell them what happened, accept responsibility for the outcome where appropriate, explain what the potential consequences of the error are, and what is being done to correct/treat the consequences of the error.
5. Apologise and express empathy.
6. Undertake to continue to provide the best care possible to the patient. Outline a plan of care to correct the error and prevent a repetition.
7. Offer to obtain a second opinion if appropriate.
8. Document the adverse event as well as the discussion with the patient and family in the medical notes.
9. Offer follow-up meetings if the patient and family desire them.

Table I lists the most important elements in disclosing adverse events to patients.[12] An important element of these guidelines is the recognition that adequate training of staff is essential, and that support has to be provided to the health professionals who have been involved in the disclosure process.

A step-by-step guide to disclosing an error is listed in Table II.[4,10]

CONCLUSION

One of the main reasons that doctors fail to disclose error is the 'belief in the widespread myth of infallibility and total control that define the perfect healer. This image, born in medical schools, nurtured throughout medical careers, and sold to the public, is shared by physicians and their patients, leading to unrealistic expectations, unreasonable disappointments, and unbridgeable gaps in communication.'[5]

As Plews-Ogan et al write, 'acknowledging "the imperfect doctor" has been a challenging cultural shift.'[15] They make the point that most of the support for doctors after medical error has been to help them cope or survive, rather than turning the experience into a positive learning opportunity. They suggest the medical error event may be a 'catalyst not just for learning but for major growth and perhaps even wisdom'. Their suggestions to help the doctor deal with the consequences of medical error and use the experience to grow, include peer support, sharing of error stories, promoting a 'learning institution', encouraging 'self-forgiveness' and nurturing reflective practice.[15] In this way doctors would learn from their mistakes and manage the consequences of medical error in a positive way. Ultimately, this would also be to the benefit of patients.

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OCCUPATIONAL ALLERGY AND ASTHMA IN TOBACCO FARMERS: A REVIEW OF LITERATURE

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ABSTRACT

For decades, multinational tobacco companies and their associated organisations have claimed that tobacco production brings prosperity to farmers and farming communities, particularly in lower-middle-income countries. This is contrary to emerging research that shows tobacco production not only increases the economic burden of workers but is also responsible for a number of health problems. This article reviews current knowledge on occupational allergy, asthma and related respiratory diseases among tobacco farmers from various literature sources published between 1960 and 2018. The review found that workers in the tobacco industry are exposed to a large spectrum of potentially hazardous chemical and biological agents leading to allergic and non-allergic respiratory disease. Further research needs to explore in greater detail – using more objective markers – the exposure to tobacco dust, nicotine and pesticides, and their interaction in causing respiratory disease in this group of workers.

INTRODUCTION

Tobacco (*Nicotiana tabacum*) is cultivated throughout temperate and tropical regions worldwide, including North and South America, Europe, Africa and Asia.[1] For decades, multinational tobacco companies and their associated organisations have claimed that tobacco production brings prosperity to farmers and farming communities, particularly in the lower-middle-income countries (LMICs).[2,3] This is contrary to emerging research that shows tobacco production not only increases the economic burden of workers but is also responsible for a number of health problems. Workers in the tobacco industry are exposed to a large spectrum of potentially hazardous agents. These have been associated with several recurrent acute and sub-acute symptoms and potentially unknown long-term and chronic effects, particularly on the respiratory and nervous systems.[2,4]

Recent decades have seen a steady shift of tobacco production from high-income countries (HICs) to LMICs.[5] The negative health impacts of this shift are accentuated in the LMICs due to the lack of occupational health regulation, poverty as well as poor access to healthcare.[1]

This article reviews current knowledge on occupational allergy and asthma among tobacco farmers. MEDLINE, Google Scholar and SCOPUS databases were searched to identify relevant articles from 1960 to 2018. The key words used included: asthma, allergy, sensitisation, respiratory, pulmonary, immunological, rhinitis, work related, occupational, tobacco, *Nicotiana tabacum*, dust, nicotine, pesticides, organophosphates, neonicotinoids, growth regulators, bacteria, fungi, endotoxin, (1–3) β-D glucan, allergens and mites. The review articles found in the process were also examined for additional and earlier citations.

THE TOBACCO WORKING PRACTICE AND HIGH-RISK OCCUPATIONAL EXPOSURE SETTINGS

The tobacco farming process varies depending on the specific type of tobacco plant grown. Among the several varieties of tobacco, the most common are Virginia, Burley and Oriental.[6] Whereas the methods of cultivating, harvesting and curing these plants differ, specific health risks to tobacco farmers are common to all tobacco cultivation processes.[1] Figure 1 depicts the typical tobacco-working process.

In summary, the tobacco plant begins its life cycle as a seed sown and carefully tended in specially constructed seedbeds in nurseries for two months in order to produce seedlings. The seedlings are then transplanted into the fields. Here they are tended carefully for two to three months prior to being harvested. Between transplantation and harvesting, farmers monitor growth, carry out pest and disease control and remove flowers (topping the plants) to ensure heavier and higher quality leaves.[7] Tobacco may be harvested either leaf by leaf

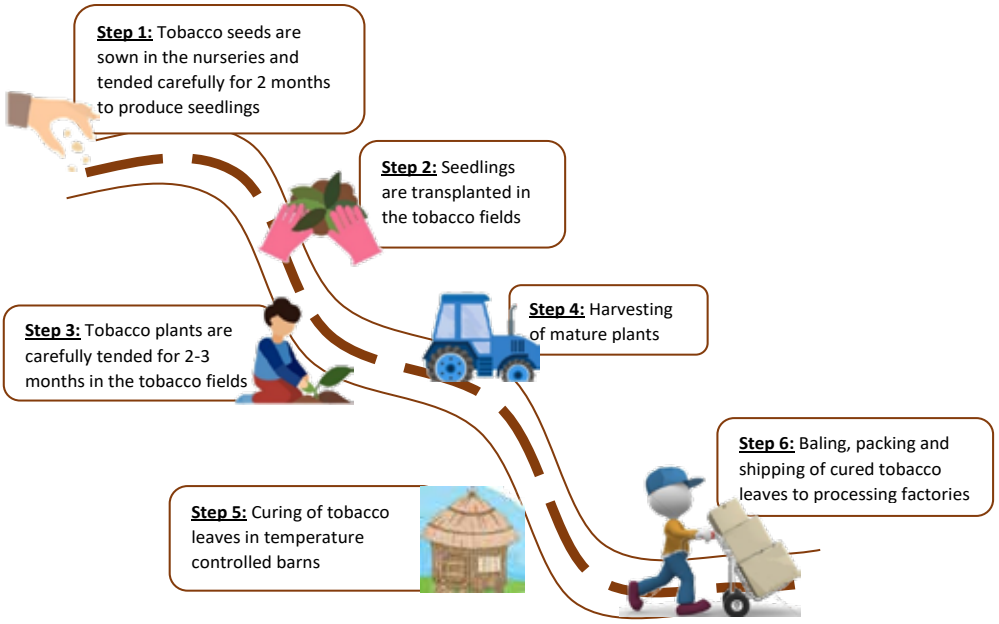

Figure 1: Typical tobacco farming work process

(Virginia and Oriental) or as the whole plant (Burley)(see Figure 2a). Leaf-by-leaf harvesting presents a higher risk of exposure to occupational agents present in tobacco plant compared to whole-stalk harvesting.[4] Post-harvest activities include curing (drying of tobacco leaves, often with wood smoke) (see Figure 2b), baling (compacting leaves into bales), sheeting (tying tobacco into burlap sheets), packing and shipping to processing factories.[2]

The abovementioned farming activities are associated with exposure to different occupational hazards that may cause respiratory disease among tobacco farmers. Table I summarises these activities and their associated potential respiratory hazards.

On the one hand, tobacco cultivation and harvesting exposes farmers to pesticides, fertilisers, growth regulators and nicotine (see Figure 2a).[8] On the other hand, tobacco curing carries high risk of exposure to tobacco dust, ammonium, nicotine, carbon monoxide, carbon dioxide, furanic aldehyde, moulds and fungi (see Figure 2b). The curing process which usually occurs in airtight barns at a constant temperature level (for 72–96 hours), may take up to eight weeks. This requires farmers to constantly enter curing barns to add leaves and branches to an open fire. During this period, farmers inhale large quantities of smoke, which increases their risk of acquiring respiratory disease.

After curing, the tobacco leaves are stored in closed spaces, usually inside farmers' homes due to lack of designated storage spaces. This practice further increases the risk of inhalation of hazardous tobacco dust, fungi and mould.[2]

The lack of adequate control measures including personal protective equipment (PPE) such as respirators, gloves and boots, due to the high cost of this equipment or to the fact that they are not adapted to a tropical climate, makes agricultural workers vulnerable to acute and chronic poisoning caused by pesticides applied during different stages of the tobacco production process.[7]

Figure 2a: Tobacco-leaf harvesting (source: https://www.herald.co.zw/changing-fortunes-of-former-farm-workers-in-zimbabwe/)

Figure 2b: A tobacco-curing barn (personal archives)

TABLE I: TASKS ASSOCIATED WITH POTENTIAL EXPOSURE TO OCCUPATIONAL AGENTS THAT MAY CAUSE RESPIRATORY DISEASE IN TOBACCO FARMERS

TASKS	DESCRIPTION OF DUTIES	SOURCES OF HAZARDOUS EXPOSURE
Cultivation	Seedling preparation, transplantation in fields and tending the tobacco plants.	Nicotine from fresh tobacco leaves, fertilisers, insecticides, herbicides, ripening agents and growth regulators.[8]
Harvesting	Selecting mature green tobacco leaves, cutting leaves at ground level, loading leaves onto wagons, and transferring leaves to curing barns.	Nicotine from fresh tobacco leaves and pesticides.[8]
Curing	Drying green tobacco leaves in curing barns, often using wood smoke. The leaves are fermented by moistening and leaving them in rooms for several months. Dried leaves are then bundled, pressed, and shipped to the processing factories.	Nicotine from fresh tobacco leaves, tobacco dust, volatile substances (nicotine, ammonium, carbon monoxide and carbon dioxide, furanic aldehyde), mould, fungi, endotoxins, mites.[8]

CHEMICAL AND BIOLOGICAL HAZARDS PRESENT IN TOBACCO WORK

Tobacco farmers are exposed to a complex mixture of chemical and biological agents. These are described in detail below.

CHEMICAL HAZARDS

Tobacco farming is a highly chemically intensive process. As a monocrop, tobacco plants are highly susceptible to pests and diseases and as a result, successful crop requires multiple application of large quantities of agrichemicals.[2,9] These include pesticides (fumigants, insecticides, herbicides and fungicides) and growth regulators (ripening agents and growth inhibitors) that are applied to the tobacco plant during different stages of growth.[9] In addition, tobacco farming requires intensive use of chemical fertilisers. This is due to the tobacco plant depleting soil fertility more rapidly than other crops because it absorbs more nitrogen, phosphorus and potassium from the soil.[2] Furthermore, tobacco farmers are exposed to nicotine through skin absorption when handling green tobacco leaves during the tobacco harvest. As a result these farmers have been shown to have elevated levels of cotinine in urine, blood and saliva.[10–12]

A Pakistani study reported a high concentration of neonicotinoid, carbamate, pyrethroid and organochlorine pesticide residues above the acceptable daily intake (ADI) for humans in the blood of tobacco farmers.[13] These included methomyl (63%), thiodicarb (56%), cypermethrin (62%), imidacloprid (49%), methamidophos (32%) and endosulfan (27%). In this study butyrylcholinesterase (BChE) activity was found to be significantly decreased in the pesticide exposed farmers compared to controls (p = <0.001). Another study conducted in the same population reported mild (33%) to moderate (11%) pesticide poisoning signified by depression of plasma cholinesterase (PChE) levels. The majority of farmers in this group reported not using any PPE and lacked formal training in safe pesticide handling.[14] Studies quantifying nicotine exposure have reported urinary nicotine in the range of 120–160 ng/mL [reference: 0–2 ng/mL] and cotinine 88–1 808 ng/mL [reference: 0–5 ng/mL].[11,12,15]

BIOLOGICAL HAZARDS

Tobacco farmers are also exposed to tobacco dust, which contains various immunologically active as well as toxic substances.[16] These include bacteria, endotoxins, mould, fungal spores, pollen, mites and insects.[17,18] Inhalation can occur when handling dry tobacco leaves during curing, baling, packing and loading for transportation.[7] Furthermore, the practice of storing tobacco leaves in closed spaces inside farmers' homes due to the lack of designated storage spaces further increases the risk of tobacco-dust inhalation.[2] A Zimbabwean study reported levels of respirable tobacco dust among tobacco farm workers of 19.13 ± 10.82 mg/m^3,[19] which is much higher than the occupational exposure limit for inhalable dust (10 mg/m^3).

RESPIRATORY HEALTH EFFECTS ASSOCIATED WITH TOBACCO WORK

The respiratory system is the most common site of injury when exposed to chemical and biological airborne pollutants.[20] In tobacco farming, chronic exposure to occupational agents has been shown to be associated with rhinitis, asthma and asthma-like symptoms, allergic alveolitis, chronic obstructive pulmonary disease (COPD) and other non-specific pulmonary symptoms (see Table II).

RHINITIS

Studies have reported the prevalence of rhinitis-like symptoms (nasal congestion, runny nose and itchiness around eyes and nose) among tobacco farmers to be between 8% and 34%.[20,21] These symptoms have been attributed to occupational and non-occupational exposures. Kearney et al reported a high prevalence of runny stuffy nose (34%), nasal allergies (17%) and sinusitis/sinus problems (12%) among migrant tobacco farmers related to poor indoor housing conditions.[20] On the other hand, occupational factors such as harvesting or topping tobacco plants were also associated with runny, stuffy nose in the same study.

ASTHMA

Although the prevalence of doctor diagnosed asthma among tobacco farmers has been reported to be 3%,[20] a higher prevalence of asthma-like symptoms such wheezing (3–24%), chest tightness (17%), coughing (7–18%) and dyspnoea (6–28%) have been reported. These were, however, less than the prevalence of upper-airway symptoms. A case report of a patient with features suggestive of occupational asthma due to dried tobacco leaves exposure has also been reported.[22] In this case, sensitisation to tobacco leaf was confirmed by a positive skin-prick test (SPT) using an extract of dried Paraguay Bell leaf. A specific bronchial-challenge test using the same tobacco, not contaminated by mould, was associated with a 23% fall in FEV_1. This suggested an IgE-dependent sensitisation to tobacco leaf as one of the mechanisms for occupational asthma in tobacco farm workers.

TABLE II: EPIDEMIOLOGICAL STUDIES OF WORK-RELATED ASTHMA AND OTHER RESPIRATORY SYMPTOMS IN TOBACCO FARMERS

STUDY – AUTHOR, YEAR	COUNTRY	STUDY DESIGN	SUBJECTS N (M:F)	RESPIRATORY SYMPTOM/ DISEASE PREVALENCE (%)	LUNG-FUNCTION TESTS (MEAN/ ABNORMALITY PREVALENCE)	RISK FACTORS – HOST AND ENVIRONMENTAL	TOOLS USED
Cargin et al, 2016[28]	Brazil	Cross-sectional	100 (100:0)	• throat irritation: 3% • cough: 1%	ND	Environmental Increased employment duration	• questionnaire
Fiori NS, 2015[30]	Brazil	Cross-sectional	2469 (59:41)	• wheezing in the past 12 months: 11%	ND	**Men:** Host • smoking: RR = 1.53 (95% CI 1.10–2.13) • age >55 years: RR = 1.71 (p-trend = 0.022) Environmental • exposure to dry tobacco dust: RR = 1.59 (p-trend 0.039) • strenuous work: RR = 1.72 (95% CI 1.14–2.61) • pesticide use >10 days per month: RR = 2.71 (95% CI 1.56–4.71) • ≥6GTS episodes: RR = 3.12 (p-trend <=0.001) • lifting sticks with tobacco leaves to the curing barns: RR = 1.48 (p-trend = 0.024) • harvesting lower tobacco leaves (protective): RR = 0.35 (p-trend <0.001) **Women:** Host • family history of asthma: RR = 2.02 (95% CI: 1.3–3.15) Environmental • tying hands of tobacco: RR = 3.89 (95% CI 1.17–12.94) • strenuous work: RR = 1.76 (95% CI 1.22–2.54) • ≥30 years of exposure to pesticides: RR = 2.32 (p-trend = 0.002) • exposure to chemical disinfectants: RR = 1.54 (95% CI 1.00–2.35) • ≥6GTS episodes in previous year: RR = 2.29 (p-trend = 0.005) • harvesting lower tobacco leaves (protective): RR = 0.46 (p-trend = 0.018)	• questionnaire
Kearney et al, 2014[20]	United States	Cross-sectional	352 (100:0)	• runny or stuffy nose: 34% • sinusitis/sinus problem: 12% • nasal allergies: 17% • wheeze: 11% • coughing up phlegm: 17% • chest tightness: 17% • woken up with tight chest: 17% • woken up with dyspnoea: 14% • doctor diagnosed asthma: 3%	FEV_1: 3.91 ± 0.69 L FEV_1 <predicted: 5% FEV_1/FVC%: 82.90 ± 2.22	Environmental • mould in the sleeping room and coughing up phlegm (p = 0.026) • presence of cockroach infestation in the sleeping room and chest tightness (p = 0.055) • presence of mould and asthma (p = 0.008) • pesticides in the home and tightness of chest (p < 0.001) • use of tobacco and coughing up phlegm (p = 0.013)	• questionnaire • spirometry
Mirabelli et al, 2011[21]	United States	Cross-sectional	122 (100:0)	• ever wheezing: 24% • wheezing in the last 12 months: 16% • wheezing in the last month: 8% • wheezing in the past three days: 3% • woken by coughing: 7% • woken up with dyspnoea: 6% • itchy eyes: 11% • runny or stuffy nose: 8% • nasal allergies, including hay fever: 19%	ND	Environmental *Higher odds of wheezing:* • topping tobacco: OR = 2.4 (95% CI: 0.9– 6.3) • barning or baling tobacco: OR = 1.7 (95% CI: 0.6–5.4) *Lower odds of wheezing:* • harvesting activities: OR = 0.3 (95% CI: 0.1–1.0)	• questionnaire

TABLE II: EPIDEMIOLOGICAL STUDIES OF WORK-RELATED ASTHMA AND OTHER RESPIRATORY SYMPTOMS IN TOBACCO FARMERS

STUDY – AUTHOR, YEAR	COUNTRY	STUDY DESIGN	SUBJECTS N (M:F)	RESPIRATORY SYMPTOM/ DISEASE PREVALENCE (%)	LUNG-FUNCTION TESTS (MEAN/ ABNORMALITY PREVALENCE)	RISK FACTORS – HOST AND ENVIRONMENTAL	TOOLS USED
Van Minh et al, 2009[31]	Vietnam	Cross-sectional	2120 1065 tobacco farming (50:50) 1055 controls (48:52)	• dyspnoea: 24%	ND	NR	• questionnaire
Osim et al, 1998[19]	Zimbabwe	Cross-sectional	50 (100:0) 20 tobacco farming, 30 controls	NR	**Workers:** FVC: 3.28 ± 0.51 L FEV_1: 2.68 ± 0.74 L PEFR: 6.41 ± 2.08 L/min **Controls:** FVC: 3.97 ± 0.83 L FEV_1: 3.09 ± 0.71 L PEFR: 8.62 ± 2.74 L/min	Environmental • tobacco flue curing activities • stacking tobacco leaves in bales • increased employment duration and reduced FVC: (r = −0.74; p = <0.01)	• questionnaire • spirometry
Ghosh et al, 1980[27]	India	Cross-sectional	440 290 tobacco farming (70:30) 150 controls (74:26)	**Workers:** • cough: 19% • cyspnoea: 29% • Emphysema: 12% **Controls:** • cough: NR • dyspnoea: NR • Emphysema: 8%	**Workers:** VC: 2.66 ± 0.06 L FEV_1%: 64.10 ± 1.17L **Controls:** VC: 2.92 ± 0.007L FEV_1%: 72.00 ± 1.104L	Host • smoking and reduced VC (p = <0.01)	• questionnaire • spirometry

ND=Not Done, NR= Not reported, FEV_1= Forced Expiratory Volume in one second, FVC=Forced Vital Capacity, VC=Vital Capacity, PEFR= Peak Expiratory Flow Rate, GTS=Green Tobacco Sickness

ALLERGIC ALVEOLITIS (TOBACCO WORKERS' LUNG)

Tobacco farmers are known to be at risk of developing allergic alveolitis due to organic tobacco dust exposure. A Russian study of 510 allergic alveolitis patients reported tobacco farm workers to have a more severe disease compared to wood and cotton workers, with fungal infection exerting a substantial effect on the clinical course of the disease.[23] An analysis of chest radiographic changes of 143 tobacco farmers with allergic alveolitis revealed three clinical variants of the disease, namely, obstructive bronchitis, bronchial asthma and recurring pneumonia, with all workers demonstrating sensitisation to tobacco antigen.[24,25] Among these three clinical variants, the obstructive pattern associated with pulmonary hyperinflation was the predominant abnormality in the lung-function parameters.[26]

SPIROMETRIC ABNORMALITIES

An Indian study reported a higher prevalence of emphysema (12%) among tobacco growers when compared to unexposed controls (8%).[27] Growers compared to controls, were also found to have significantly lower mean vital capacity (VC) (2.66 ± 0.06 vs 2.92 ± 0.01 L) and FEV_1/FVC% values (64.10 ± 1.17 vs 72.00 ± 1.10 L). In another study of US tobacco farmers, spirometric findings suggestive of an obstructive picture (FEV_1 outside the normal range of predicted values) were reported in 5% of workers.[20] However, all workers in this study had an FEV_1/FVC ratio above 70% (82.90 ± 2.22), a finding that was attributed to a possible healthy worker effect. Similarly, Zimbabwean tobacco growers exposed to flue curing and stacking tobacco leaves were shown to have a significantly lower mean FEV_1 (2.68 ± 0.74 L) and FVC (3.28 ± 0.51 L) values compared to controls (3.09 ± 0.71 L and 3.97 ± 0.83 L) respectively.[19] These findings suggest that both obstructive and restrictive lung-function abnormalities are present in tobacco farmers.

OTHER RESPIRATORY SYMPTOMS AND DISEASES

Several non-specific respiratory symptoms have been reported among tobacco farmers. These include cough, eye irritation, phlegm, throat irritation and sinusitis/sinus problems.[20,21,28] In addition, a case of eosinophilic pneumonia in a Japanese tobacco harvester has also been documented.[29] The patient demonstrated eosinophilia on full blood count (FBC) and bronchoalveolar lavage (BAL) fluid with a negative serology for parasitic infection. She had a positive skin scratch test using tobacco leaf and leaf extract, and a biopsy of the dermis on the patch tested area revealed an eosinophilic infiltration. Her chest computed tomography (CT) showed patchy consolidation. The investigators attributed the patient's condition to tobacco leaf exposure via inhalation while she was harvesting and sorting tobacco leaves.

This wide range of symptoms emphasises the complexity of pathophysiological mechanisms through which occupational

TABLE III: CASE REPORTS OF WORK-RELATED RESPIRATORY DISEASE IN TOBACCO FARMERS

STUDY	COUNTRY	OCCUPATION	RESPIRATORY HEALTH EFFECTS	DURATION OF EXPOSURE PRIOR TO SYMPTOMS	CONFIRMATION DIAGNOSIS OF ALLERGY OR ASTHMA
Yoshioka et al, 2011[29]	Japan	Tobacco harvester	Eosinophillic pneumonia	Two months	• eosinophilia on FBC with negative serology for parasitic infection • patchy consolidation on chest CT • marked eosinophilia on BAL fluid • positive skin-scratch test using tobacco leaf and leaf extract • eosinophilic infiltration of the dermis on biopsy of the patch-tested area
Wendling et al, 1994[22]	France	Tobacco farmer	Occupational asthma	NR	• SIC with 23% drop in FEV_1 after 20 minutes of sorting dry tobacco leaves

BAL= Broncho-alveolar Lavage, CT= Computed Tomography, FBC=Full Blood Count, FEV_1= Forced Expiratory Volume in one second, NR= Not reported, SPT= Skin Prick Test

exposures present in tobacco work may cause respiratory disease.

PATHOPHYSIOLOGICAL MECHANISMS

RHINITIS

Tobacco dust exposure is responsible for rhinitis symptoms among tobacco workers. A study done among workers chronically exposed to tobacco dust revealed loss of cilia and squamous epithelial metaplasia in the nasal mucosa of tobacco workers when compared to unexposed controls. However, these workers failed to demonstrate hyper-eosinophilia in nasal swabs and their tobacco specific IgE and total IgE levels did not differ from controls. This suggested that rhinitis associated with tobacco-dust exposure may be mediated largely through irritant rather than allergic mechanisms.[32]

ASTHMA

Both allergic and non-allergic mechanisms have been implicated in asthma causation among workers exposed to tobacco dust. Work related asthmatic symptoms were reported in a female tobacco worker.[33] In this worker, occupational asthma was confirmed by positive SPT and specific inhalation challenge tests using tobacco dust, suggesting an allergic mechanism as the cause for the asthma.

In vitro studies have shown tobacco dust to cause concentration-dependent contractions of guinea pig trachea.[34,35] Using tobacco-dust extracts containing significant quantities of bacterial components (e.g. endotoxin), Schachter et al demonstrated that the constrictor activity of the tobacco-dust extract is mainly in its non-lipid, low molecular weight fraction (<10 kDa).[34] The study suggested that tobacco dust causes airway smooth muscle constriction mainly through non-immunologic mechanisms involving a variety of airway mediators and possibly cholinergic receptors. In a follow-up study, Schachter et al demonstrated greater contractile response to tobacco-dust extract in guinea pig tracheas pre-sensitised with ovalbumin than tracheas that were not pre-sensitised.[35] This finding suggested that pre-sensitisation with an unrelated antigen may enhance the response to an occupational agent.

ALLERGIC ALVEOLITIS

Immune mediation may be one of the pathophysiological mechanisms in the development of tobacco worker's lung. A Finnish study conducted among workers exposed to tobacco dust demonstrated serum antibodies against *M faeni*, *T vulgaris*, *A fumigatus* and *A umbrosus*.[36] In this study, the prevalence of antibodies was significantly higher among workers with respiratory symptoms and fibrotic radiographic signs than among other workers. *Aspergillus* species from tobacco mould appeared to be the main antigen causing tobacco worker's lung. It is also postulated that exposure to tobacco dust and its constituents may have direct toxic effects on pulmonary macrophages leading to the release of lysosomal enzymes and other immune mediators that cause pulmonary inflammation with subsequent chronic allergic alveolitis.[18] These findings indicate that raw tobacco dust and its constituents may either cause allergic or toxic reactions or both, leading to the development of allergic alveolitis.

HOST-ASSOCIATED RISK FACTORS FOR RESPIRATORY DISEASE

There are few host-associated factors associated with respiratory disease among tobacco farmers.

GENETICS

The role of genetics in the development of asthma and other work-related respiratory illnesses among tobacco farmers has not been well documented. A positive history of asthma in one or both parents was associated with an increased risk of wheezing among female tobacco farmers in a Brazilian study (RR = 2.02).[30] This is similar to the findings for adult onset asthma, for which parental asthma has been shown to be a risk factor.[37]

AGE

Increasing age has been shown to increase the risk of wheezing among Brazilian tobacco farmers.[30] In this group of workers, males aged 55 or above were shown to have the greatest risk of reporting wheeze in the past year (RR = 1.71). The direct association between age and wheezing in male tobacco growers may be attributed to cumulative exposure to cigarette smoke.[38] No association was found between increasing age and wheezing among females, possibly due to the lower prevalence of smoking.[30]

SMOKING

Current smoking among males was associated with wheezing in Brazilian tobacco farmers (RR = 1.53).[30] Both animal and human studies have demonstrated cigarette smoke inhalation to induce acute bronchoconstriction.[39–42] Furthermore, it has been suggested that simultaneous and persistent exposure to smoking and airborne allergens may have an additive or synergistic effect on the occurrence of adult-onset asthma.[43]

OCCUPATIONAL RISK FACTORS FOR RESPIRATORY DISEASE

MODE OF EXPOSURE

Both inhalational and dermal routes appear to be important. In a study of Brazilian tobacco farmers, inhalation of dry tobacco dust was associated with an increased risk of wheezing (RR = 1.59).[30] This study also found that individuals with multiple green tobacco sickness (GTS) episodes in the past year were at a higher risk of developing wheeze (men: RR = 3.12, women RR = 2.29). GTS results from acute nicotine poisoning caused by dermal absorption of nicotine from mature tobacco plants with subsequent neurotoxic symptoms including headaches, dizziness, nausea and vomiting. With GTS being caused by dermal absorption of nicotine, this finding suggests a possible role of dermal exposure for occupational asthma in tobacco workers, as has been recently reported in some occupational settings.[44]

EXPOSURE TO CHEMICAL AGENTS RELATED TO TOBACCO WORK

Chronic pesticide exposure in tobacco farming has been shown to increase the risk of wheezing among tobacco farmers. In a Brazilian study, the occurrence of wheezing was associated with pesticide use for more than ten days a month in men (RR = 2.71) and in females with long duration (>30 years) of use (RR = 2.32)[30]. The same study also found exposure to chemical disinfectants to increase the risk of wheeze (RR = 1.54).

While occupational exposures play an important role in the development of respiratory symptoms, the effect of domestic exposure particularly in tobacco farmers living on farms is also important.[2,20] In a US study of Latino migrant farm workers involved in tobacco farming, mould exposures in the home was associated with phlegm production and asthma ($p < 0.05$).[20] The study also identified other domestic risk factors for respiratory diseases including cockroach infestation and pesticide exposure in the home ($p < 0.05$). These findings highlight the need to address domestic exposures when designing interventions for reducing occupational exposures.

HIGH-RISK JOBS/TASKS

Various high-risk jobs and tasks have been implicated in the development of respiratory disease among tobacco farmers. Fiori et al reported an increased risk of wheezing among female farmers involved in lifting sticks with tobacco leaves in the curing barns (RR = 1.48), and male farmers involved in tying hands of tobacco (RR = 3.89).[30] Harvesting the lower tobacco leaves appeared to be associated with a lower risk (females RR = 0.35 vs males RR = 0.46), which has also been reported among migrant Latino tobacco farm workers (RR = 0.3).[21] Being a cross-sectional study, these findings suggest a possible healthy worker effect since tobacco harvesting carries a higher risk of exposure to nicotine and pesticides, as it requires substantial physical effort, takes place in a hot and humid environments and requires significant leaf handling.[30] Other high-risk tasks reported include topping, barning, flue curing and stacking of tobacco leaves into bales.[19,21] Furthermore, strenuous work has also been shown to increase the risk of wheeze in male (RR = 1.72) and female (RR = 1.76) tobacco-farm workers.[30]

LEVEL OF EXPOSURE

In-vitro studies have demonstrated a dose-response relationship between exposure to tobacco-dust extract and development of possible bronchoconstriction in guinea pigs.[34,35] On the other hand, increased employment duration has been associated with a decrease in FVC ($r = -0.74$; $p < 0.01$) among Zimbabwean tobacco farmers.[19] Similarly, Cargnin et al reported increased employment duration to be associated with respiratory symptoms including throat irritation and cough among tobacco farmers.[28]

CONCLUSION

This review confirms that tobacco farmers are at increased risk of allergic and non-allergic respiratory disease as a result of exposure to different chemical and biological hazards related to tobacco farming. Future studies are needed to address the following issues in greater depth:

- Quantification of exposure to tobacco dust, nicotine and pesticides particularly in tobacco farmers from LMICs.
- Improved identification of asthma phenotypes using objective measures.
- Investigation of the interaction between pesticides, nicotine and tobacco dust in causing respiratory disease.
- Investigating the long-term health effects of mixed exposures in tobacco work.
- Identification of the effects of newer pesticide groups such as neonicotinoids, in causing respiratory disease in tobacco farmers.
- Investigating exposure–response relationships in epidemiological studies of tobacco workers.

DECLARATION OF CONFLICT OF INTERESTS

The authors declare no conflict of interest

ACKNOWLEDGEMENT

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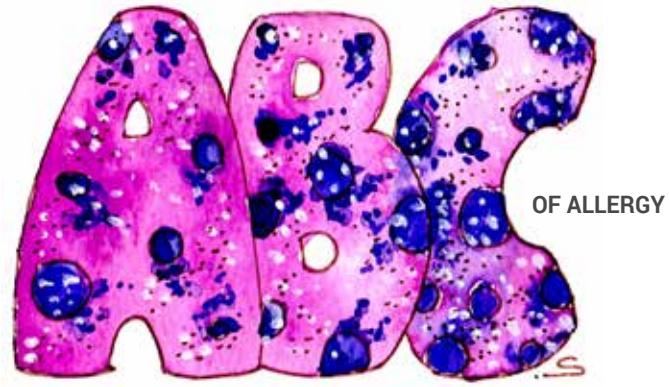


TH1 VERSUS TH2 IMMUNE RESPONSE

Shaunagh Emanuel and Di Hawarden

One of Dr Do-a-Lot's students returns from an allergy congress where he heard a speaker mention the 'Th1 versus the Th2 immune response' and asks her what this means. Dr Do-a-Lot elaborates, using some military-inspired poetic licence to illustrate her discussion.

The helper T-cells (Th cells) are the communicators of the immune system. They achieve this by producing cytokines in order to make themselves understood by other cells.

Cytokines

Cytokines are hormonal messengers that instruct cells to behave in specific ways, which result in biological effects. A great variety of cytokines signal between immune cells resulting in myriad immune responses. From a functional point of view, they can be divided broadly into those cytokines that are responsible for pro-inflammatory responses (inflammation produced in response to an immune challenge) and those that are anti-inflammatory. Ironically, it is the 'anti-inflammatory' group of cytokines that promotes allergy.

T- and B-cells

T- and B-lymphocytes are white blood cells that develop from stem cells in the bone marrow and differentiate along the lymphoid cell line. They are the central players in the sophisticated *adaptive* or *acquired* immune response found only in vertebrates.

Pamela the plasma cell producing antibodies

T-lymphocytes are responsible for mounting the highly specific *cell-mediated* part of the acquired immune response to an invader. B-lymphocytes are ultimately responsible for the *humoral* immune response through the production of antibodies.

Helper T-cell

Helper T-cells are T-lymphocytes that express CD4 cell surface molecules. They are part of the 'intelligence branch' of the immune system, having been extensively trained in communication skills in the thymus. They do not actively engage with an immune threat, but rather give cytokine-mediated orders to other cells to do so.

Cytotoxic T-cell

Cytotoxic T-lymphocytes (Tc) express CD8 surface molecules. On receiving orders they specifically target and attack infected cells, thereby vanquishing intracellular microbes.

Th1 and Th2

Two important sub-types of helper T-cells are Th1 and Th2 cells.

Th1 cells produce Th1-type cytokines including interferon gamma, interleukin 2 and tumour necrosis factor-beta that result in *pro-inflammatory* responses that are dominated by immune activity mediated against intracellular microbes. They are also responsible for certain autoimmune responses.

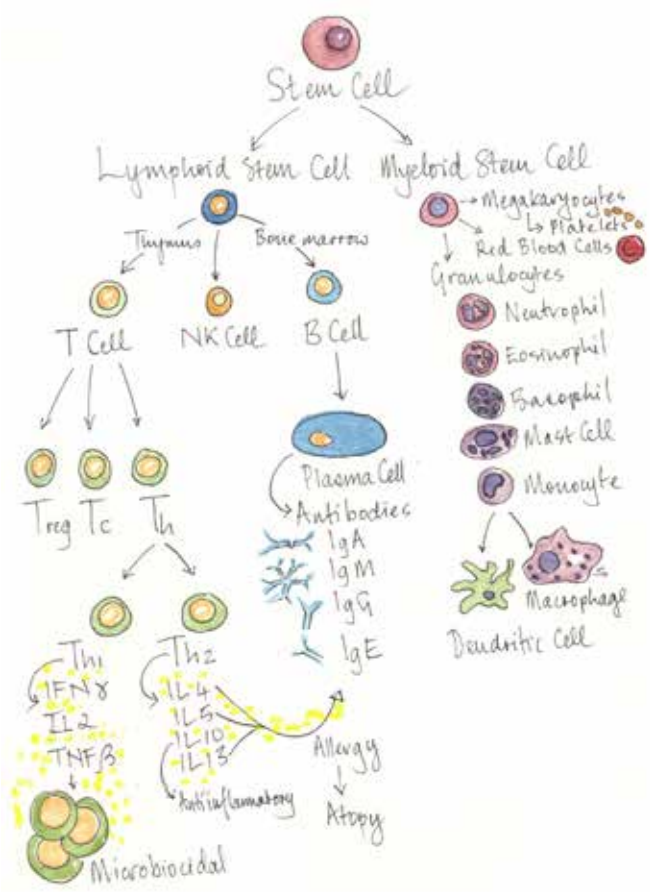
Th2 cells produce Th2-type *anti-inflammatory* cytokines including interleukins 4, 5, 10 and 13. Through the activity of their cytokines the Th2 cells play a role in containing the inflammatory effects of the Th1 cells, mediate eosinophilic responses against helminths and facilitate antibody responses against extracellular invaders, however they are also involved in the development of atopy and allergy.

Helper T-cells

Ideally, a balance should exist between Th1 and Th2 processes that keeps immune responses in check, thereby preventing excessive tissue damage caused by the inflammation that occurs as a result of an immune challenge.

Th1/Th2 cell and atopy

It appears that Th1 versus Th2 polarisation is influenced by both environmental and genetic factors, and that the development of



Dr Do-a-lot draws a simple cartoon illustrating the development of the cells of the immune system including the helper T-cells with cytokines

atopic allergy may, at least in part, be attributed to an immune system that leans towards a Th2 type of response. Speculation exists regarding the factors that might influence a shift in this atopy-inducing direction. Research is ongoing, and more insight is needed in this immunologically, epidemiologically and clinically important field before firm conclusions can be drawn and effective management strategies developed.

Which response is Th1 again?

Dr Do-a-Lot says that sometimes she finds it hard to remember which type of immune response is typically due to Th1 and which is due to Th2. As a way to remind herself she thinks of the number '1' as a spear which she associates with fighting microbes which is typical of a Th1 response. The number '2' she associates with being duplicitous; playing the role of attenuating an immune attack but at the same time promoting allergy.

Dr Do-a-lot draws a cartoon to illustrate the Th1 vs Th2 immune response

Dr Do-a-Lot directs her students to refer to The ABC of Allergy in the *Current Allergy and Clinical Immunology Journal* of the Allergy Society of South Africa (Volume 30, September 2017) for a reminder about where 'Harold the helper T-cell' fits in to the immune scheme of things in the article 'Introduction to Immunity'.

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Case Report

MASTOCYTOMA MISCHIEF: ACTIVATION OF A SOLITARY MASTOCYTOMA AS A SOLE MANIFESTATION OF PEANUT ALLERGY IN A CHILD

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INTRODUCTION AND CLASSIFICATION OF CUTANEOUS MASTOCYTOSIS

Mastocytosis is a heterogeneous group of disorders characterised by an increase in mast cells in the skin and extracutaneous organs.[1,2] Cutaneous mastocytosis (CM) accounts for 90% of cases of mastocytosis, and represents an increase in mast cells confined to the skin.[3] CM may manifest as maculopapular cutaneous mastocytosis (MPCM), diffuse CM or solitary mastocytoma of the skin.

Maculopapular CM may manifest as *urticaria pigmentosa* (UP) or *telangiectasia macularis eruptiva perstans* (TMEP). UP refers to the clinical presentation of diffuse brown or red-brown to tan non-scaly macules and papules, disseminated on the trunk and extremities. This is the most common form of CM in children (accounting for up to 85% of cases). TMEP is a rare form of CM presenting mainly in adults as an erythematous patch that may be in a cape-like distribution on the upper back, or as erythematous-tan macules with telangiectases.

In diffuse mastocytosis patients present with brownish indurated erythroderma. In infants with diffuse mastocytosis, bullae formation is common, and this presentation may be referred to as 'bullous mastocytosis'.

Solitary mastocytoma of the skin makes up approximately 10% of CM and comprises a dense aggregate of mast cells in the dermis of the skin to form a solitary lesion, usually >3 cm in diameter.[4,5]

Clinical symptoms of mastocytosis are due to the release of mast-cell mediators such as histamine, tryptase, leukotrienes, platelet-activating factor and other chemokines.[1,2,5] This case describes a child of 10 years of age with a previously undiagnosed solitary cutaneous mastocytoma which caused some unexpected mischief upon peanut ingestion.

CASE PRESENTATION

BH, a ten-year-old boy presented with the following issues:

- wide local reaction in response to bee stings;
- recurrent large hive on the chest after peanut consumption; tree nuts all tolerated;
- symptoms of allergic rhinitis (AR).

Further history revealed that he seemed to tolerate small amounts of peanut butter as a very young child, but that from the age of six he developed an itchy patch on his chest in response to peanut consumption. He had therefore largely avoided peanut since, but admitted to the occasional bite of a peanut-butter sandwich at school which caused a mild itch in the chest region. Interestingly, the chest also seemed to become itchy after a hot bath and when swimming in cold water, which sometimes also caused a 'welt' on the chest. He had never had any breathing difficulties in response to peanut, and tolerated legumes, tree nuts, sesame, dairy, egg, wheat, fish and soya without any issues. He was otherwise fit and well, well grown for his age, with no signs of asthma and no systemic concerns. He had a congested nose with rhinorrhoea especially in the mornings. He had been stung by a bee on at least three occasions and had a progressively worsening wide local reaction to the bee sting but no systemic complications.

EXAMINATION

Examination showed a fit and well boy, with moderate swelling of the nasal inferior turbinate bones. His chest was clear. On examination of the skin there was a 3 × 3 cm flat light-brown area of discolouration of the skin on the anterior chest. This had never been noticed before by the mother or child (see Figure 1). Rubbing of this patch led to more pronounced reddish-brown discolouration of the patch and erythema in the surrounding skin (see Figure 2). There were no further lesions on the rest of the skin.

INVESTIGATION

Investigations were performed as follows:

TABLE I: SKIN-PRICK TESTS (SPT) (>3 MM USUALLY CLASSIFIED AS POSITIVE)

SPT	RESULT (MM)
House-dust mite (HDM) Der P	5 mm
HDM Der F	4 mm
Timothy grass	5 mm
Bermuda grass	4.5 mm
Dog	0.0 mm
Alternaria mould	0.0 mm
Cladosporium mould	0.0 mm
Plane tree	1.0 mm
Pine tree	1.0 mm
Peanut	2.5 mm

TABLE II: BLOOD TESTS	
TEST	RESULT
Tryptase level (baseline)	4.50 ng/mL (normal <11.5 ng/mL)
Specific IgE Bee venom	2.30 kU/L (normal <0.35 kU/L)
Specific IgE Peanut	3.91 kU/L (normal <0.35 kU/L)
Specific IgE Ara h 2	0.03 kU/L (normal <0.35 kU/L)

The following diagnoses were made:

1. Solitary mastocytoma.
2. AR with HDM and grass sensitisation.
3. Wide local reaction to bee sting (moderate reaction).
4. Possible peanut allergy.

FURTHER TESTING

In view of the low-grade sensitisation to peanut, and the history of a mild and seemingly not consistent reaction to peanut, a decision was made to perform an incremental controlled oral food challenge to peanut butter. Initial low doses were tolerated, but upon reaching 5 g peanut butter (approximately 1.25 g peanut protein) he started to complain of an itchy chest within five minutes. Inspection of the area of the solitary mastocytoma showed a distinct welt in that area (see Figure 3), with no other rashes and no systemic features. The challenge was stopped and he responded well to a dose of 10 mg cetirizine.

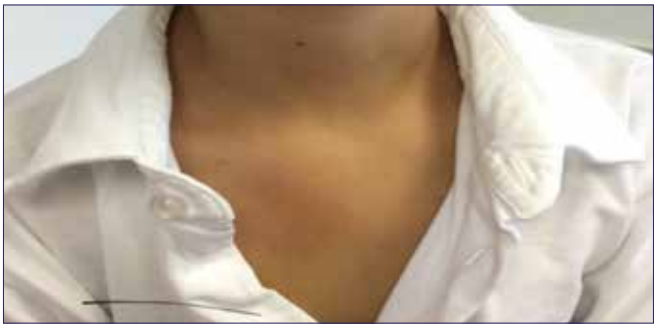

Figure 1: Subtle brown discoloration on anterior chest at rest – never noticed before

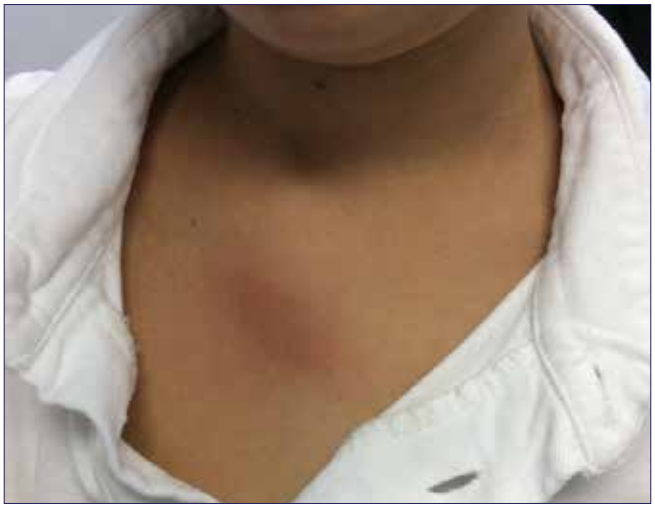

Figure 2: More pronounced discoloration and erythema after rubbing the lesion (Darier's sign positive)

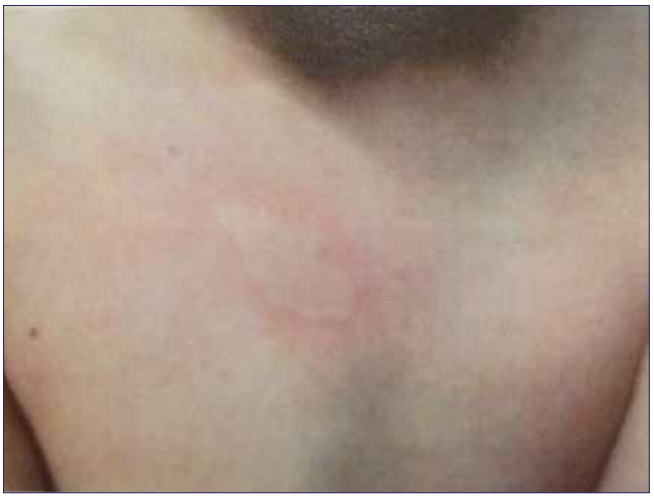

Figure 3: Welt at site of mastocytoma after peanut ingestion

FURTHER MANAGEMENT

- The patient was advised to avoid all sources of peanut and to return for a food-allergy review every 12–18 months.
- He was given HDM reduction advice, and started on a daily intranasal corticosteroid and saline spray.
- He was given an action plan for both peanut and bee allergy.
- An Epipen 0.3 mg was prescribed in view of the increased risk of a more severe reaction to subsequent bee stings.
- He was advised to start on a daily antihistamine (10 mg cetirizine) to try and reduce the reactivity of the mastocytoma.

DISCUSSION

Solitary mastocytomas of the skin represent relatively rare dermal tumours of mast-cell origin.[5,6] Mast cells originate from the pleuripotential progenitor cells in the bone marrow that express CD34, CD17 (kit) and CD13.[7] Most patients present as sporadic cases, but rare families with multiple affected individuals have been reported. C-kit autoactivating mutations that allow for persistent mast-cell development are thought to play a role in adult mastocytosis and some cases of childhood disease.[7]

The *solitary mastocytoma* most often presents as a solitary red–brown macule or patch of >3 cm. On occasion, a cluster of smaller lesions can occur termed 'mast-cell nevi'. It is the second most common manifestation of CM, accounting for 10–15% of cases. Onset is usually within the first two years of life, though the lesions may appear later in childhood and even in adulthood. It has a predilection for the trunk, but other reported sites have included the wrist, eyelids, palm, orbital area and vulva.[8]

Stroking of the skin lesions produces erythema, swelling or blistering after a few minutes, known as 'Darier's sign', which is pathognomonic of CM. On occasion, activation may be associated with extra-lesional symptoms including pruritus, flushing and headaches.

The solitary mastocytoma may be inactive and asymptomatic for long periods of time. Potential trigger factors in CM are shown in Table III.

TABLE III: POTENTIAL TRIGGER FACTORS IN CM

1.	Physical stimuli (eg heat, cold, pressure, sunlight, rubbing, exercise)
2.	Emotional factors (eg stress, anxiety)
3.	Dental procedures and surgery
4.	Insect bites and snake venoms
5.	Infections and vaccinations
6.	Medications known to cause mast-cell activation: NSAIDS, morphine, codeine, dextromethorphan, alcohol, procaine, atropine, thiamine, quinine, reserpine, amphotericin B, radiographic contrast media.*

** General anaesthetic complications have been described in children with UP. Solitary cutaneous mastocytomas carry a much lesser chance of anaesthetic complications, though care should still be taken to minimise the use of histamine-releasing drugs such as codeine.[9]*

Excessive consumption of histamine-rich foods have been cited as another potential trigger in the CM disorders.[3] Although IgE-mediated food allergies may occur simultaneously in children with cutaneous mast-cell conditions, the author could find no other case reports of an activated mastocytoma as the sole manifestation of an IgE-mediated food allergy such as described in this case report.

Management of a solitary cutaneous mastocytoma in children usually involves watching and waiting as there is a very good prognosis for spontaneous involution of the mastocytoma in adolescence.[4] This is in contrast to adult-onset CM disorders which are more likely to be persistent and associated with systemic features.

Antihistamines may be taken when the mastocytoma is activated, or on a preventative basis if the patient is experiencing frequent cutaneous symptoms in response to everyday triggers such as bathing. Topical potent corticosteroids and topical tacrolimus inhibitors have been successful in the treatment of some patients.[4] Some adults have also responded well to surgical excision of a solitary mastocytoma.

CONCLUSION

This unique case demonstrates focal mast-cell activation after peanut consumption in a previously undiagnosed solitary cutaneous mastocytoma. We shall follow this patient up with interest to see whether spontaneous regression of the mastocytoma over time may also result in tolerance to peanut, especially in view of the low-level sensitisation to peanut, negative Ara h 2 and clinically mild allergic reaction.

DECLARATION OF CONFLICT OF INTEREST
The author declares no conflicts of interest

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PID123

Primary Immunodeficiency

MENDELIAN SUSCEPTIBILITY TO MYCOBACTERIAL DISEASE (MSMD)

Zinhle in a wheelchair

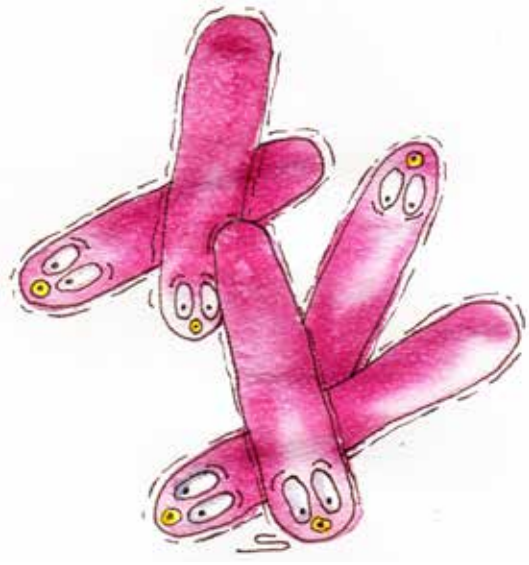
Dr Goodheart is called to see a little girl called, Zinhle, who, despite tuberculosis (TB) treatment, is failing to gain weight, has chronic anaemia, septic arthritis and a persistently raised CRP/ESR (a non-specific measure of inflammation). She is referred from a chronic-care facility where she was sent for rehabilitation of chronic septic arthritis of her ankle which was not responding adequately to treatment. She is wheelchair-bound and unable to walk. She has already received standard TB treatment for clinical suspicion of pulmonary infection, without initial sputum or culture confirmation. Because of failure of response to standard anti-tuberculous treatment she has just been started on treatment for suspected drug-resistant TB. An earlier Ziehl-Neelsen (ZN) stain was positive for acid-fast bacilli (AFB) in the sputum but no growth was obtained on culture. Three months later the stain is now negative, but has come back culture-positive for AFBs and also non-tuberculous mycobacteria. The presence of mycobacteria was confirmed by Polymerase Chain Reaction (PCR) from sputum and lymph-node samples, but not further speciated; *Mycobacterium avium intracellulare* is suspected (this belongs to the group of MOTTs – mycobacteria other than TB).

The doctor starts her evaluation with a thorough review of the history: Zinhle lives with her family in a nearby township. Both parents are employed. She has two half-siblings from another father. Nobody in the family has been ill with infections (specifically TB) and there is no known TB contact. At six months of age Zinhle had also been treated for suspected TB, while still living in the Eastern Cape. She has received full vaccinations including BCG at birth without any complications being recorded at the time.

On examination Dr Goodheart observes that Zinhle looks chronically ill and wasted. An extensive BCG scar is noted as well as active arthritis of the left ankle. The girl's lungs are clear but Dr Goodheart finds abnormally enlarged lymph nodes in the neck.

With this persistent history of TB, she initiates further investigations of sputum and the chronically swollen left ankle. A methicillin-sensitive *Staphylococcus aureus* (MSSA) is initially cultured from the ankle biopsy and aspiration. Dr Goodheart thinks this is an unusual course and in conjunction with an unusual TB organism this alerts her to a possible PID. She therefore consults the immunology specialist, Dr Bala, for review of the biopsy sample and for further advice. The samples sent to Dr Bala's reference laboratory show granulomatous inflammation, even after many months of treatment. A bone scan ordered subsequently at Dr Bala's hospital shows multiple 'hot spots' in Zinhle's vertebrae, pelvis, tibia and orbit.

Dr Bala also requests baseline immunological investigations, including lymphocyte subsets and immunoglobulin levels which both turn out to be normal. Lymphocyte stimulation tests show



MOTTs – mycobacteria other than TB

abnormally low proliferation to protein A and candida stimulation (implying reduced lymphocyte function), but are normal for other T-cell stimulants. The neutrophil burst test is also normal, excluding Chronic Granulomatous Disease (CGD). The IFN-γ release response to TB-specific antigen is impaired but not completely absent. Both doctors agree that an immunodeficiency disorder has to be considered in the presence of atypical bacteria, persistence of TB on treatment and abnormal lymphocyte function.

Zinhle is admitted then to a neighbouring Tuberculosis Children's Hospital where she continues extended MOTT treatment for another six months.

She improves slowly and visits Dr Goodheart regularly at her clinic. Meanwhile, Dr Bala has been talking to her colleagues at the molecular laboratory and they agree to investigate Zinhle for genetic susceptibility to TB. Although several PIDs can cause susceptibility to TB non-specifically, Dr Bala suspects a TB-specific genetic defect in Zinhle (see Box).

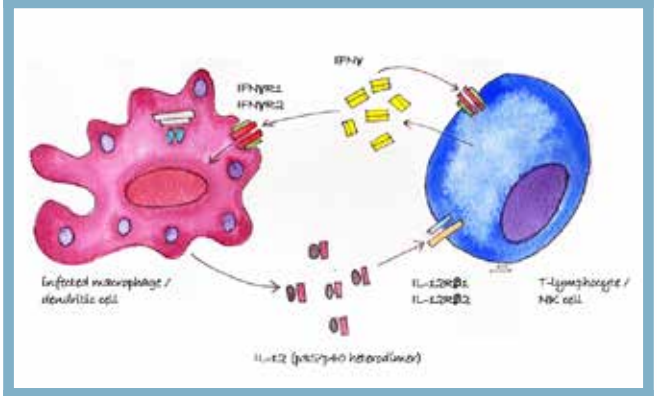
When the report from the molecular laboratory arrives, exome sequencing indeed shows a mutation, specifically a heterozygous partial deletion of 4 nucleotides in exon 6 of IFNR1, which has already been identified in other patients with MSMD and which is responsible for an impaired response to interferon gamma. This confirms Dr Bala's diagnosis of MSMD. Zinhle recovers gradually but Dr Goodheart knows that her patient will be at risk for recurrent TB and MOTT infections and she will have to be followed-up closely. The doctor also refers the family for genetic testing to find out whether other family members are affected. Dr Bala points out to her colleague that special treatment with Interferon gamma might be an option but this is very expensive and has many side-effects. It will have to be considered for Zinhle if she does not recover from her unusual TB infection.

Zinhle is happy to be back at school and out of the hospital. She does not understand why the doctors are so concerned about her.

Box: PIDs resulting in increased risk of mycobacterial infection

Severe PIDs such as Severe Combined Immunodeficiency (SCID), Hyper-IgM (HIGM) syndrome, CGD and Hyper IgE Syndrome (HIES) are susceptible to a broad range of diverse infections, which can include mycobacterial infections.

In contrast, patients with an isolated inborn error of the IL-12/23-IFN-γ pathway are almost exclusively prone to infections with mycobacteria other than TB and non-typhoid salmonella infections, which are non-virulent in healthy individuals. This is known as 'Mendelian susceptibility to mycobacterial disease (MSMD)'.



The figure shows the **crosstalk between infected macrophages and T-lymphocytes/NK cells in mycobacterial immunity:** Infected macrophages (or dendritic cells) release IL-12, which binds to the IL-12 receptor (IL-12R) on natural killer (NK) cells or T-cells. Binding of IL-12 induces intracellular that result in the activation of genes. The secretion of IFN-γ by NK and T-cells by binding to the IFN-γ receptor (IFNR) on macrophages, elicits a cell-mediated immune response to intracellular pathogens within the infected macrophage. IFNR activation induces a wide range of IFN-γ-responsive genes. Several proteins in this signalling loop can be mutated and are associated with MSMD: IFN-γR1, IFN-γR2, TYK2, IL-12p40, IL-12R-β1, STAT-1, NEMO, IKBA, CYBB and IRF8, among others.

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THE IMMUNOLOGY OF MIND CONTROL – EXPLORING THE RELATIONSHIP BETWEEN THE MICROBIOME AND THE BRAIN - PART 1

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ABSTRACT

In this series of articles, the relationship between the human species and the human gut microbiome will be evaluated to determine if it is symbiotic, parasitic or somewhere in between. The possibilities, based on animal studies, are explored and compared to studies in human beings. In particular, close attention is paid to the relationship between the gut microbiome and the central nervous system, especially its effect on human behaviour. This relationship is termed the 'microbiome–gut–brain axis'. The gut microbiome has an influence on stress (both acute and chronic), anxiety, loneliness and depression, through a number of pathways. It has also been associated with the development of neurodegenerative diseases, such as Alzheimer's and Parkinson's, with associated cognitive decline. The concept of 'mind control' of human beings by organisms in the microbiome is relatively new, but has been demonstrated with multiple examples in the animal kingdom. Therefore, it is not surprising that certain components of the microbiome have also been associated with the development of schizophrenia. Since the common treatments used for these conditions are not equally effective in all patients, it is vital for clinicians to explore other avenues to be used as therapeutic targets. Recent research has also evaluated the impact of vitamin D and olfaction on the brain, and its possible use as adjunctive therapy. The gut microbiome, in particular, requires further research to aid in the development of future therapies for certain conditions. Animal studies in this regard have shown promising results, but human studies are infrequent, often with disappointing results. Randomised control trials in human beings are required to prove or disprove the effects of the gut microbiome on complex psychiatric diseases.

Key words: immunology; mind control; microbiome; brain; relationship

INTRODUCTION

Both a species, and individuals of that species, are greatly affected by social behaviour. Social behaviour is regulated by complex neurological and biochemical processes as well as by underlying brain structures.[1] Similarly, normal social behaviour may be disrupted by neurological disorders such as depression, stress, social anxiety disorders, autism and schizophrenia, among many others.[1]

The human body contains a sizeable and diverse community of microbial cells, with their genetic material, collectively known as the 'microbiome'.[2] A new concept in modern science links gut microbiota to the potential to modulate the brain and behaviour.[1] This concept has been termed the 'microbiota–gut–brain axis'.[1] The gastrointestinal tract is the point of communication between the gut microbiota, the immense network of millions of neurons in the body and the body's largest concentration of immune cells.[3]

Literature suggests the microorganisms in the gut microbiome outnumber human host cells in the body by 100:1, whereas microbial genes of the gut microbiome outnumber human host genes by approximately 150:1.[4,5] 'We are thought to be more microbiome than human',[6] however, this does not automatically suggest a correlation between microbiome number and influence on human behaviour.[6]

It may not be surprising however that the gut microbiota can impact various areas of the host's physiology.[3] In addition, not only human physiology but human behaviour may very well be influenced by parasites and bacteria in our gut microbiome, where perturbations may result in individuals behaving in an odd and unpredictable manner.[6] The fact that bacteria effectively engage in mind control should not come as a surprise. If the weight of the microbiome organ is the same as that of our brains, then it is plausible that over millions of years microbiota have learned to know us so well that they may be able to affect

every part of our dispensations, driving us, for example, to go out and find them food or help them reproduce.[7]

Mind control is a real and prevalent threat to human beings. It is already used by many organisms on their hosts in the animal kingdom. For example, the *Cordyceps* fungus infects ants, causing them to travel to treetop canopies where they die. The fungus then reproduces and its offspring float down to the forest floor to infect more ants.[6] *Dicrocoelium dentriticum* causes ants to climb to the tops of grass blades, in order to enhance their chances of being eaten.[8] Nematomorph worms cause their cricket hosts to kill themselves by jumping into water and drowning so that the worms can return to their natural habitat; *Paragordius tricuspidatus* has a similar effect on grasshoppers.[6,8] Parasitic trematodes infect snails and make their eyeballs bulge and change colour – to blue, yellow and red – so that birds may better see them and then peck off their eyestalks, allowing the trematodes to complete their lifecycles in the bird's guts. These horrors are not restricted to invertebrates alone.[6] The intestine is densely populated with commensal bacteria that interact directly with protozoan parasites, and are able to influence their behaviour. Protozoa living in human blood or tissue may be affected by the interplay between the gut microbiome and the host's immune system and metabolism.[9] The mind-altering influence of the microbiome is a result of a long history of co-evolution, rather than malicious manipulation of the host's behaviour. However, it has been suggested that the gut microbiome is the puppeteer Gepetto, while the brain is Pinocchio, its puppet.[8]

It is important to note that these data are largely based on animal studies (insects and small animals) or correlative analysis in patient populations. Additional research, in the form of randomised control trials is required in order to make conclusions regarding this hypothesis in human beings.[7]

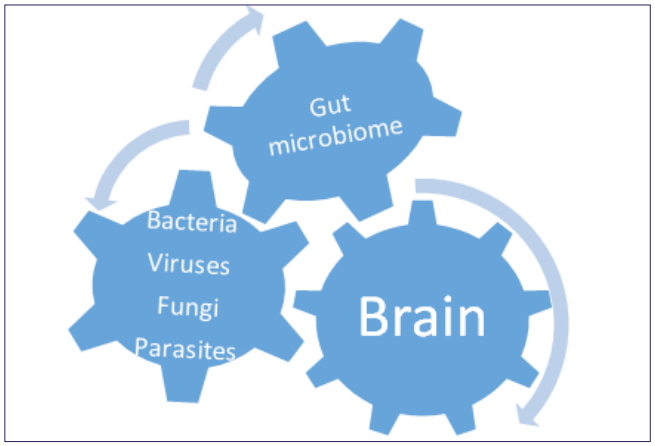

Figure 1: The symbiotic spectrum poses the question whether the relationship between the gut microbiome and the brain is mutualistic, commensalistic or parasitic in nature, or possibly a combination of all three.[8]

Only two bacterial divisions are prominent in the gut microbiome: the anaerobic gram-negative Bacteriodetes and gram-positive Firmicutes.[4,5,7] Interestingly, only 20–30% of microbes in the human colon can be cultured.[10] In order to test specific hypotheses, the medical community realised other techniques were required to fully assess the microbial function and diversity, as well as its potential effects.[11] Therefore multiple advances in analytic techniques (such as 16S rRNA sequencing, single-cell genome sequencing, metagenomic sequencing, cultivation, metabolomics, among others) have been employed in order to better characterise the diversity of the gut microbiome. This is because different bacterial species, including fungi, protozoa and viruses, vary in number and diversity throughout development as well as among different human populations.[2,4,10,11] These new techniques will aid in our understanding of the sites, pathways and molecular mechanisms within the gut–brain axis as well as establish new roles for the microbiome in health and disease; a still controversial issue in literature.[11,12]

The gut microbiome is often referred to as the 'forgotten organ'.[13] Our initial understanding of the gut microbiome and its effects relied upon the germ theory of disease postulated by Louis Pasteur, focusing on microbes as agents of disease. However, new ways of thinking and discussing concepts of microbiology have emerged looking at the commensalistic and/or symbiotic relationship of the gut microbiome rather than simply its parasitic realtionship.[11]

The gut microbiota's signature may be seen in several aspects of behaviour and in several neurological and metabolic disorders. These disorders affect social behaviour both directly and indirectly in various ways: via neural (vagus and the enteric nervous system), immune (cytokines), metabolic (short-chain fatty acids) and endocrine (cortisol) pathways.[1]

Microbiota produce neuroactive molecules which may affect the gut epithelial barrier and eventually the brain. The gut microbiota strongly influence the autonomic nervous system, via the enteric neurons and vagus nerve, to relay messages to the brain. They can alter the function of the hypothalamic-pituitary-adrenal (HPA) axis resulting in the release of cortisol, which alters gut permeability and barrier function and, ultimately, change the composition of the gut microbiome. They also play a role in the development of the immune system, and may control cytokine release through lymphocyte activation. This may have paracrine or endocrine actions.[1]

Certain gut bacteria synthesise neurotransmitters, as well as approximately 20 neuropeptides produced in enteroendocrine cells. These neuropeptides serve as secondary brain messengers, regulating cognition and mood. They include calcitonin, corticotropin-releasing factor, substance P, pancreatic polypeptide, vasoactive intestinal polypeptide (VIP), glucagon-like-peptide-1 (GLP-1) and somatostatin, neuropeptide Y and peptide YY. The latter two play a vital role in energy homeostasis.[14] Neuroactive bacterial metabolites of dietary fibres, namely, short-chain fatty acids such as propionate and butyrate (among others), may also modulate behaviour and

TABLE I: POTENTIALLY HARMFUL AND BENEFICIAL BACTERIA OCCURRING IN THE GUT (ADAPTED FROM GHAISAS, MAHER & KANTHASAMY[19])

POTENTIALLY HARMFUL BACTERIA		POTENTIALLY HARMFUL OR BENEFICIAL BACTERIA	POTENTIALLY BENEFICIAL BACTERIA	
Production of enterotoxins	*Clostridia*	*Firmicutes*	*Bifidobacterium*	Aid in Digestion
	Staphylococcus	*Bacteroides*	*Lactobaccilus*	Antitumor Activity
Pathogen-producing toxins	*Proteus*	*Escherichia coli*	*Eubacterium*	Production of short-chain fatty acids
	Pseudomonas aeruginosa	*Enterobacteriaceae*	*Fusobacterium*	
		Veillonella	*Campylobacter jejuni*	Potential tumour marker

the brain by increasing peptide YY secretion. This reduces gut motility, resulting in enhanced absorption of nutrients and harvesting of energy. It is further linked to the development of diabetes and obesity, both diseases with social implications.[1]

The gut also communicates with the brain via hormone signalling pathways which activate the release from enteroendocrine cells of gut peptides (namely, ghrelin, galanin, orexin, leptin and gastrin) that may act directly on the area postrema of the brain. The response to these gut peptides has been linked to changes in anxiety, the sleep–wake cycle and sexual behaviour. Galanin plays a role in HPA-axis modulation in response to stress and has been shown to have deleterious effects on cognition, thereby acting as a link between stress, anxiety and memory. It has therefore been suggested that galinergic drugs should be considered as a therapeutic option for certain psychopathologies. Ghrelin similarly acts in the brain to mediate anxiogenesis and increases memory retention. The pancreatic polypeptide-fold family (pancreatic polypeptide, peptide YY and neuropeptide Y) have actions on a number of organs. Peptide YY and neuropeptide Y have been shown to have anxiolytic effects in rats, whereas the latter has also been implicated in obesity and feeding, memory retention, anxiety, depression and neuronal excitability. Lu et al, demonstrated the effect of low leptin plasma levels in rats exposed to chronic stress. Treatment of these rats with leptin reversed the behavioural changes, with associated neuronal activation in the limbic structures, particularly the hippocampus. Studies on diabetic mice have shown similar antidepressant effects of leptin.[3] Few randomised control trials have assessed the role of the gut microbiome in disease, therefore conclusions in this regard are difficult.[11]

Interestingly, mitochondria are thought to originate from bacteria via early formation of endosymbiotic relationships in the evolutionary history of eukaryotes. Cross-reactivity of mitochondria and immunological responses to the gut-microbiome constituents may have harmful effects on mitochondrial function through a process of molecular mimicry. This process plays a role in the inflammatory basal ganglia disorder, Sydenham's chorea and in rheumatic fever.[15]

Diet also plays a role in the gut-microbiome composition. In adults consuming Western diets, high in protein, sugar and fat, *Firmicutes* are the dominant phylum; whereas *Bacteroides* are more common in those individuals consuming fibre-based, agrarian diets.[10,14] Western diets contribute to gut-microbiome dysbiosis as well as reduced short-chain fatty acid production from fibre fermentation, contributing to a reduced anti-inflammatory role.[14] However, one mouse study revealed a 'protective effect' of a high-fat diet (reducing depressive and anxiety behaviours in chronic stress). This demonstrates the complex interactions and casual relationships between stress, diet and the microbiome–gut–brain axis.[7]

The gut microbiome is a dynamic entity that evolves continuously throughout the host's lifespan and reaches some stability only after the first three years of life.[2] The gastrointestinal tract is sterile in utero but is rapidly colonised at birth, primarily from maternal contact.[16] The composition of the early-infant microbiota is highly dynamic and unstable, but of low diversity.[17] The diversity and number of bacteria increase throughout early childhood, and are sensitive to a wide variety of factors such as infection, diet, stress and pharmacological interventions (such as antibiotic use), which result in both short-term and long-term sequelae to the host.[2,16,18] The resultant dysbiosis may impact both general and mental health negatively.[18] Of note, is the fact that it is becoming increasingly apparent that bacteria are required for normal brain development as well as brain function in adulthood.[7]

STRESS

Stress is defined as an acute threat to an organism's homeostasis. An adverse event or stressor, whether physical or psychological, will result in a cascade of physiological, emotional and behavioural reactions to allow the organism to cope with the situation. Chronic, severe, uncontrollable stressors, however, may trigger maladaptive changes in brain structure and function, with potential long-term effects on physical and mental well-being.[2]

The HPA axis is significantly involved in both mental and physical well-being of individuals. Positive and negative social

interactions have a marked impact on both the activity and the reactivity of the stress circuits. Gut microbiota have an impact on the HPA axis and vice versa, and this ultimately impacts social behaviour.[1] Research from both animal and human studies has shown that emotional stressors can negatively impact gut microbiota.[7,20]

As mentioned, gut microbiota can both directly and indirectly influence the stress circuits. Direct influence on the central nervous system (CNS) functioning occurs through neuronal activation of the stress circuits. The first point of contact for these microbiota is the gut lumen and the neurons of the enteric nervous system. These sensory neurons are less excitable in germ-free mice than their specific pathogen-free counterparts, whereas colonic neuron excitability may be enhanced by the probiotic bacterium *Lactobacillus reuteri*. Messages from the gut are then relayed to the brain via the vagus nerve. Direct central circuitry activation in the paraventricular nucleus of the hypothalamus has been observed in germ-free mice following oral administration of a non-infectious strain of *E coli* and *Bifidobacterium infantis*, demonstrating that pathogenic or commensal bacteria can alter the electrophysiological properties of enteric neurons and provide messages to the brain to which it, accordingly, reacts.[1] Sudo et al, demonstrated that germ-free animals had exaggerated HPA axis activation in response to stress, and that this hyper-response was reversed by reconstitution of animal faeces with a single bacterial strain, namely, *Bifidobacterium infantis*, but was further aggravated by enteropathogenic *E coli*.[3]

It is important to note that the germ-free model has several limitations. Researchers should therefore be cautious to extrapolate findings from these studies in germ-free mice to human beings.[12] Germ-free mice are delivered surgically and are transferred directly and raised in sterile isolators with no microbial exposure.[7,12] This gives rise to a wide range of differences in gut and brain biochemistry, HPA-axis response, metabolic function and social behaviour between germ-free and control animals (the latter of which have normal or pathogen-free flora and are reared by normally colonised mothers).[12]

Both acute and chronic stress activate the stress circuits indirectly and lead to modulation of the HPA axis.[1]

ACUTE STRESS

With regard to acute stress, a recent study revealed that the absence of gut microbiota in stress-sensitive rats aggravated the HPA and behavioural responses to acute stress. Germ-free rats had 2.8-fold higher serum corticosterone concentrations than their specific pathogen-free counterparts. The germ-free rats also had decreased glucocorticoid receptor mRNA expression in the hippocampus and increased corticotrophin-releasing hormone mRNA expression in the hypothalamus, indicating the exacerbation of neuroendocrine and behavioural responses to acute stress in the absence of gut microbiota. Germ-free mice exposed to restraint stress also demonstrated a significantly high corticosterone and adrenocorticotrophic hormone response, which was reversed after they received a probiotic bacterium, *Bifidobacterium infantis*.[1] This gives weight to the finding that a decrease in *Bifidobacterium* and *Lactobacilli* was observed under conditions of nervous-emotional and restraint stress.[1]

In studies observing the effects of maternal separation stress, neonatal stress in rats was shown to lead to an altered gut–brain axis as well as to alterations in the gut–microbiome composition. These effects were reversed by probiotics. Decreased numbers of *Lactobacilli, Campylobacter spp*. and *Shigella spp.* have been seen in conditions of maternal separation stress. It is important to note that the stress response circuitry at birth is functionally immature and develops alongside bacterial colonisation throughout the postnatal period, therefore being vulnerable to changes in the gut microbiome.[1]

Other studies have revealed similar results, with an 18–26% increase in *Bacteriodes* and a 10-fold decrease in *Lactobacilli* and *Bifidobacterium* in stressed conditions; one study demonstrates a decrease in *Lactobacilli* with an increase in aerobic bacteria under conditions of emotional stress, food deprivation, acoustic stress and restraint conditions.[1] These studies identify the direct involvement of gut microbiota in stress, and clarify the microbiota's role in HPA-axis programming early in life as well as in reactivity to stress over an individual's lifespan.[1]

CHRONIC STRESS

Chronic stress and depression are rampant in modern life. Both may cause measurable brain shrinkage. More than 140 proteins in the brain are affected negatively by electromagnetic frequency exposures emitted by cellphones and other electronic devices. Technology has forced most individuals to be multitaskers. The brain, however, cannot concentrate on two things at once but rather toggles quickly back and forth between tasks, with resultant decreased attention span, ability to learn, short-term memory and overall mental performance.[20]

As if this were not enough, chronic stress is also associated with dysregulation of the HPA axis. Prolonged stress results in disruption of the integrity of the intestinal barrier, resulting in increased translocation of gut microbes and direct access to both neuronal and immune cells of the enteric nervous system. Exposure to specific chronic psychosocial stress in mice leads to an increase in *Clostridium spp* and a reduction in *Bacteroides spp*. Pre-treating rats with a probiotic, namely, *Lactobacillus farciminis,* has been found to attenuate the HPA-axis stress response by preventing impairment of the intestinal barrier.[1]

Up to 60% of gastrointestinal diseases are linked to stress. Due to globalisation, individuals with gastrointestinal conditions have high stress rates and suffer further from anxiety, stress and pain due to marked lifestyle changes that impact on their quality of life.[14] These individuals also have alterations to their gut microbiomes.[14] In patients with irritable bowel syndrome (IBS), studies have reported decreased proportions of *Bifidobactrium* and *Lactobacillus* species and increased levels of *Firmicutes* such as *Bacteriodetes*.[10]

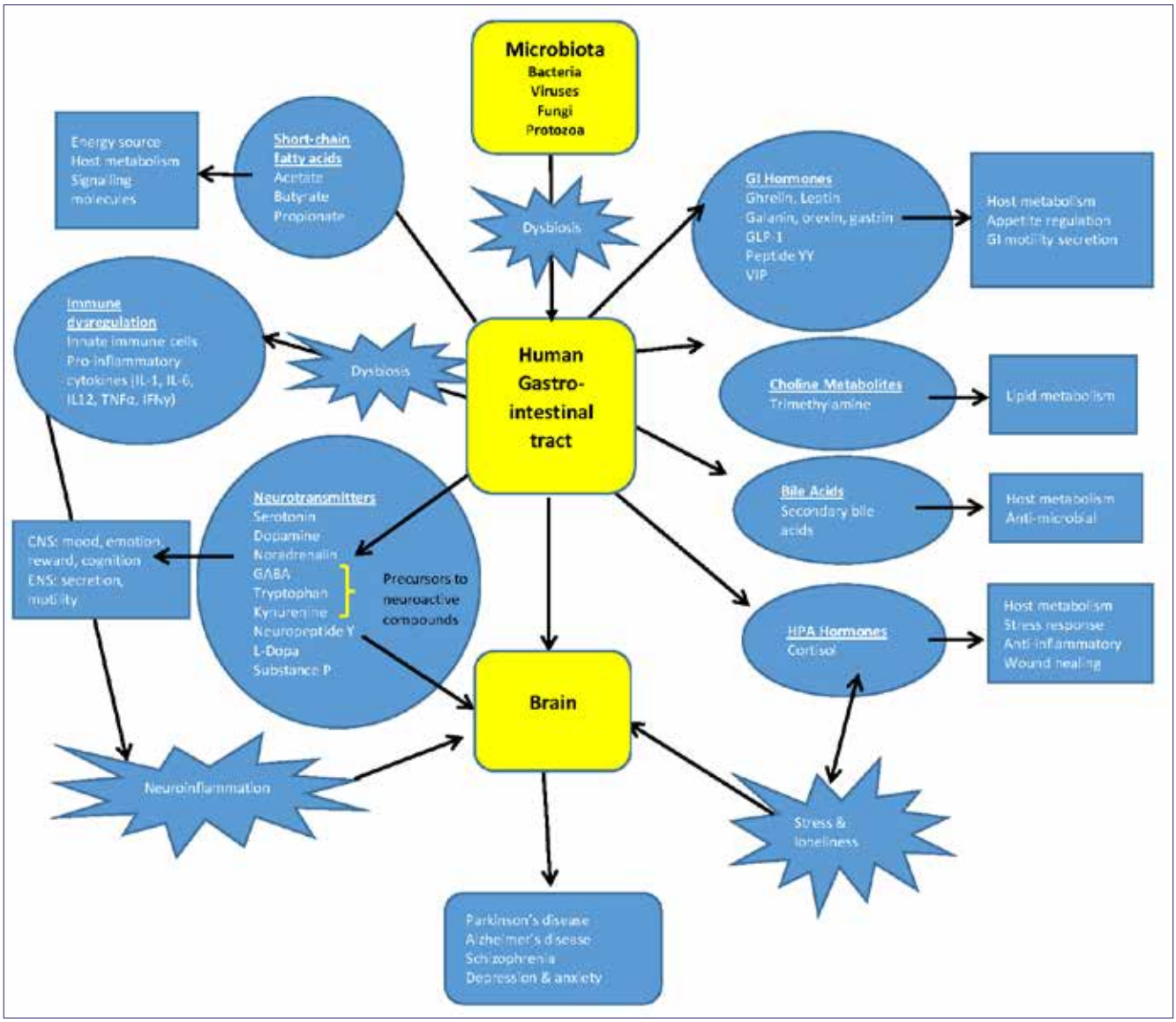

Figure 2: The microbiome gut–brain axis and its effects (adapted from Forsythe & Kunze,[3] Pandura et al,[14] O'Callaghan et al,[23] SJ functional medicine[24] and Ramezani & Raj[25])

ANXIETY

Anxiety and social behaviour are often inseparable. Social anxiety disorder (or social phobia) is an overwhelming and persistent fear of social situations that significantly impacts social behaviour. Gut microbiota seem to play a deceitful role regarding anxiety, with contradictory reports. Some studies have shown that germ-free mice have reduced anxiety-like behaviour, despite an elevated basal corticosterone level compared to their specific pathogen-free counterparts. However, other studies dispute these findings, revealing increased anxiety-like behaviours with associated increased corticosterone levels.[1]

Reconstituting the guts of germ-free mice with healthy microbiota in early life results in normalisation of elevated plus maze behaviour and some aspects of light/dark behaviour; however, reconstitution of the gut microbiome in adulthood fails to alter the anxiety-like phenotypic behaviour.[1] This suggests that gut microbiota contribute to developmental programming, and have an action during a developmental 'window of vulnerability' which subsequently may impact long-term physiological function.[3]

Antimicrobials also have an effect on the gut microbiome and anxiety-like behaviour. Oral administration of neomycin, bacitracin and antifungal pimaricin for seven days increases exploratory behaviour and decreases anxiety-like behaviour, a behavioural pattern similar to that seen in germ-free mice, however, this behavioural pattern returns to normal after a two-week rest period. This finding is further supported by a study documenting that germ-free mice treated with antibiotics demonstrated no behavioural changes.[1]

Prenatal and early postnatal life represents a critical period for the developmental trajectory of the brain, characterised by

rapid changes in neuronal and microbial organisation, and may be influenced by the gut–brain communication.[18,21] Problems relating to such communication during this critical period may result in an increased risk of mental illness and behavioural problems later in life.[18] This period is also, fascinatingly, a critical period for metabolic development.[21] Recent studies have shown that low-dose antibiotic exposure from birth to weaning age in mice led to an altered metabolic phenotype that persevered to adulthood. Interestingly, post-weaning antibiotic exposure had less of an effect on the adult phenotype.[21] This shows an increased vulnerability to gut dysbiosis in the early postnatal window, which may have long-lasting effects on mental health in adulthood.[18,21]

Probiotics are live microorganisms that assist in the maintenance of a natural balance of gut microbiota and, when administered in adequate amounts, confer a health benefit on the host.[1,10] They have been widely used in the treatment of IBS.[10] *Lactobacillus rhamnosus* ingestion affects the brain at both a molecular and a behavioural level, and has been reported to have anxiolytic properties leading to decreased despair-like behaviour. At a molecular level, *L rhamnosus* alters the mRNA expression of both $GABA_A$ and $GABA_B$ receptors in several brain regions. These receptors are associated with depression and anxiety. Ingestion of *Bifidobacterium breve* in mice increases fatty-acid concentrations (namely, arachadonic and docosahexaenoic acid) in the brain. These fatty acids are known to have an effect on depression, anxiety and memory. The combination of *B longum* and *L helveticus* used in a clinical trial of healthy subjects revealed a reduced serum cortisol level and improved psychological effects, with a reduction in depression and anxiety. Other studies have shown similar results.[1]

The evidence from human studies regarding the manipulation of the gut microbiome with prebiotics and antibiotics is inconclusive. A small meta-analysis in patients with inflammatory bowel disease (IBD) treated with probiotics suggested a small therapeutic effect; however, it is unclear as to whether gut-microbiome alterations arise from primary alterations at the gut-microbial interface or as a subsequence of changes in the brain-to-gut signalling.[12]

TABLE II: GUT BACTERIA PRODUCE ACTIVE METABOLITES FOR THE HUMAN ORGAN SYSTEM[22]

BACTERIUM IN GUT MICROBIOME	ACTIVE METABOLITE PRODUCED
Lactobacillus and *Bifidobacterium*	Gamma-aminobutyric acid (GABA)
Escherichia coli, Bacillus and *Saccharomyces*	Norepinephrine
Bacillus and *Serratia*	Dopamine
Candida, Streptococcus, Escherichia and *Enterococcus*	Serotonin

Enteric infections with pathogenic bacteria also affect the microbiota–brain–gut axis. Mice infected with *Trichuris muris* demonstrate increased anxiety-like behaviour with associated decreased hippocampal levels of brain-derived neurotrophic factor (BDNF) mRNA, increased levels of pro-inflammatory cytokines and an increased plasma kynurenine : tryptophan ratio. Both tryptophan and BDNF have established roles in anxiety and in other neurological processes. Ingestion of *Bifidobacterium longum* assisted in normalisation of behaviour and BDNF mRNA in these mice, but had no effect on kynurenine or cytokine levels. Lyte et al, and Gareau et al, were able to document similar results with *Citrobacter rodentium. C rodentium* infection resulted in anxiety-like behaviour seven to eight hours post-infection.[1]

A possible avenue of exploration regarding adjunctive treatment for anxiety is reconstitution of the gut microbiome from healthy individuals via faecal transplantation. The behaviour of germ-free mice after faecal transplantation has shown that these mice acquired a behavioural profile similar to that of the donor. This provides evidence that microbiota strongly drive individual behaviour, and may be considered therapeutic targets for stress and anxiety.[1]

CONCLUSION

Gut microbiota play a crucial role in the bidirectional interaction between the CNS and the intestines.[10] The long history of co-evolution between humans and the microorganisms in our gut microbiome may result in a mind-altering influence on the host's behaviour, and may impact various areas of cognition. The effects of imbalances in gut microbiota composition at different stages of life, and their subsequent short- and long-term impact on behaviour and brain modulation, need considerable consideration.[1] Germ-free mice have been shown to have disruptions in the development of brain mechanisms in relation to the HPA axis, hyperalgesia, behaviour and associated brain biochemistry. Premature conclusions regarding the extrapolation of these findings to human beings should be avoided.[10]

More studies (including carefully designed translational and clinical studies) need to be conducted to investigate the aftermath of these imbalances, as well as possible avenues of prevention and treatment in the clinical sector in order to avoid long-term or permanent effects.[1] Infant studies are of particular importance to ascertain the effects of alterations in the gut microbiome early in life on brain development, as well as gut–brain interactions and assess whether interventions aimed at reducing gut dysbiosis can alter these effects.[12]

The hygiene or microbiota hypothesis for allergic disease, and the possible association between gut microbiota and psychiatric conditions, as well as obesity, also need consideration, as do the relevance of probiotic or commensal strain exposure to certain inflammatory conditions, such as rheumatoid arthritis, asthma, IBD and chronic obstructive pulmonary disease (COPD), all of which have strong associations with mood disorders and depression.[3] Further studies in human beings are essential prior to any conclusive remarks regarding the effect of the gut microbiome on complex psychiatric disorders can be made.[7]

DECLARATION OF CONFLICT OF INTEREST
The authors declare no conflict of interest.

This article has been peer reviewed.

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ENVIRONMENTAL EXPOSURES: IMPACT ON PRESCHOOL WHEEZING

1. *True or false:* Environmental factors are the only risk factor associated with preschool wheezing.
2. *True or false:* Exposure to house-dust mite (HDM) may have both 'good' or 'bad' effects as a risk factor for preschool wheezing.
3. *True or false:* Only antenatal environmental exposures are important determinants of childhood wheezing.
4. *Choose the correct answer:* with regard to gene–environment interactions and wheezing, the following statement is correct:
   a. Epigenetic phenomena are heritable changes in gene expression.
   b. Children whose grandmother's smoked are not at a higher risk of developing asthma.
   c. Environmental exposures in childhood have no effect on the development of adult chronic respiratory conditions.
   d. Outdoor air pollution is most associated with epigenetic changes.

THE WHEEZING CHILD: CHILDREN'S INSTITIAL LUNG DISEASE: A RARE BUT IMPORTANT DIFFERENTIAL DIAGNOSIS IN CHILDREN WITH SEVERE WHEEZE

5. *Choose the **INCORRECT** statement:*
   a. Children's interstitial lung disease (chILD) is an umbrella term for more than 200 different rare lung diseases.

b. chILD is rare with an estimated incidence 0.1–16 per 100 000.

c. chILD often involves other compartments such as conducting airways, alveolar spaces, pulmonary vessels, lymphatic vessels and pleural spaces.

d. Wheeze is one leading symptom of chILD.

6. *Choose the **INCORRECT** statement:*

a. Currently the same classification scheme is used for children and adults.

b. Some chILD forms are specific to infants.

c. Some entities can be confirmed by genetic tests.

d. Lung biopsy is recommended when genetic tests are inconclusive.

7. *Choose the **INCORRECT** statement:*

a. In all wheezing children with suspected diffuse lung disease, more common causes than chILD should be considered first.

b. Primary ciliary dyskinesia is rarer than chILD.

c. Growth anomalies reflecting deficient alveolarisation is a distinct subgroup of chILD.

d. Neuroendocrine cell hyperplasia can has a typical radiological pattern.

8. *Choose the **INCORRECT** statement:*

a. Glucocorticosteroids are often used in children with chILD.

b. Azithromycin is helpful in some cases.

c. Hydroxychloroquin is ineffective in chILD and potentially harmful in all chILD subtypes.

d. Oxygen should be given in case of hypoxemia.

e. MRI is currently not a useful tool in the diagnostic workup of chILD.

ARE INFANT WHEEZING AND CHILDHOOD ASTHMA RISK FACTORS FOR THE DEVELOPMENT OF COPD?

9. *True or false:* There are many factors that can affect in utero lung development which can lead to decreased lung function in early life and wheezing in childhood.

10. *True or false:* The history of childhood asthma may increase the risk of COPD by 10–30 fold.

11. *True or false:* Maternal tobacco smoking increases in utero lung growth.

12. *Choose the correct answer:* regarding COPD:

a. COPD carries a high morbidity and mortality and was the tenth leading cause of death in 2016;

b. COPD is solely attributable to cigarette smoking;

c. in the GOLD guidelines COPD is defined as reversible airway obstruction and an FEV1/FVC ratio of <0.7;

d. COPD normally becomes clinically evident in the sixth to seventh decades irrespective of early-life events effecting lung development;

e. it is becoming evident from the literature that COPD may have different phenotypes.

FOOD ALLERGY AND PRESCHOOL ASTHMA

13. *True or false:* Loss-of-function mutations in the filaggrin gene contribute to increased risk for asthma.

14. *True or false:* Sensitisation to food allergen alone is sufficient to increase the risk of asthma.

15. *True or false:* Asthma and food allergy incidence continues to increase.

16. Being a heterogeneous syndrome, asthma is best sub-classified by:

a. Phenotype

b. Genotype

c. Exposome

d. Endotype.

THE ROLE OF BRONCHOSCOPY IN PRESCHOOL WHEEZING CHILDREN

17. *True or false:* Lipid-laden macrophages is diagnostic of gastro-oesopheal reflux.

18. *True or false:* The most common anatomical finding on bronchoscopy in children with preschool wheezing is tracheomalacia.

19. *True or false:* TB should be considered in preschool – wheezing with unilateral wheezing.

20. *Choose the correct answer:* The following are indications for bronchoscopy in children with preschool wheezing:

a. failure to thrive;

b. unilateral signs;

c. no response to treatment;

d. symptoms since birth;

e. all of the above.

ETHICS: DISCLOSING MEDICAL ERROR – CHANGING THE CULTURE OF MEDICINE

1. *True or false:* A ‘near-miss’ medical error is one that is identified and stopped before harm can be done to the patient.

2. *True or false:* The fear of litigation is the reason advanced for doctors being reluctant to apologise to patients after a medical error.

3. *True or false:* Doctors should not disclose medical errors to patients if they have not resulted in any harm to them.

4. *True or false:* Most medical malpractice lawsuits result from poor communication between the doctor and the patient/family.

5. *True or false:* Institutional requirements for disclosure of medical error include considerations of patient safety, risk-management activities and the establishment of support structures for healthcare professionals, patients and families.

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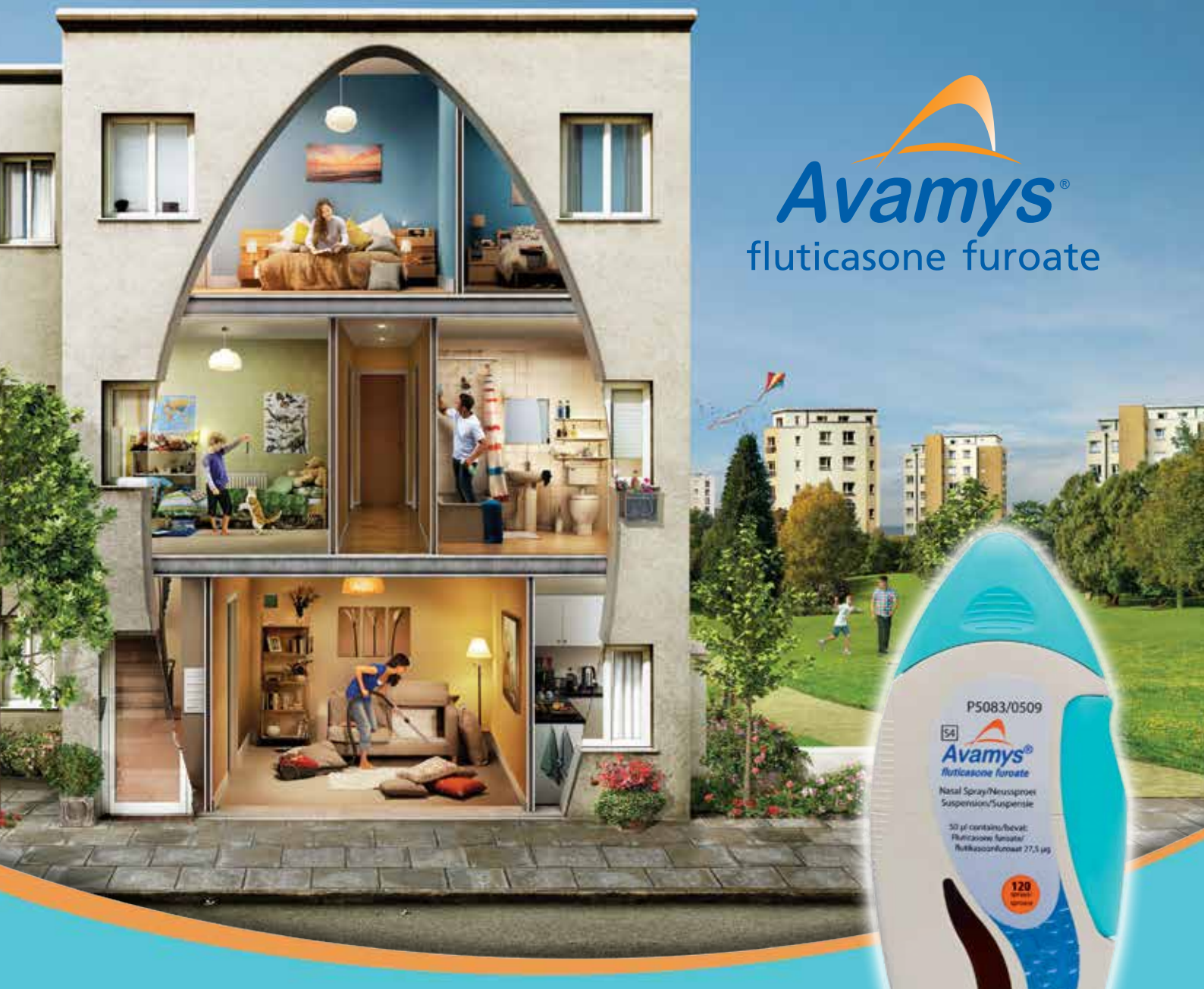

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