Paediatric Focus

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The Broadest Coverage of any Pneumococcal Conjugate Vaccine

Prevenar 13® (13-valent pneumococcal conjugate vaccine, Pfizer Laboratories (Pty) Ltd) was developed as a successor to Prevenar® and includes the 13 most prevalent serotypes in young children worldwide. Prevenar 13® is based on the scientific foundation of Prevenar® and uses the same CRM197 carrier protein and conjugation technology that have been utilised in various paediatric vaccines.

Invasive pneumococcal disease remains a leading cause of morbidity and mortality in children below the age of 5 years and accounts for approximately 11% of all deaths in this age group throughout the world. Pneumococcal infections remain the leading cause of death from a vaccine-preventable illness in children younger than 5 years of age. Prevenar 13® contains the 7 serotypes already included in Prevenar®, plus 6 additional pneumococcal serotypes, 1, 3, 5, 6A, 7F, and 19A which will increase the percentage of vaccine-preventable cases of IPD to up to 90% or more in most regions of the world. The paediatric serotypes, 6A and 19A, now included in Prevenar 13®, are known to be major causes of serious pneumococcal disease in a number of countries, including South Africa and have a tendency to develop resistance to commonly used antibiotics.

Increased serotype coverage of Prevenar 13® is expected to have a substantial public health and economic impact by preventing substantially more pneumococcal disease and childhood mortality than currently licensed pneumococcal conjugate vaccines.

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Prevenar 13® Forum meeting

Oubaai 2011

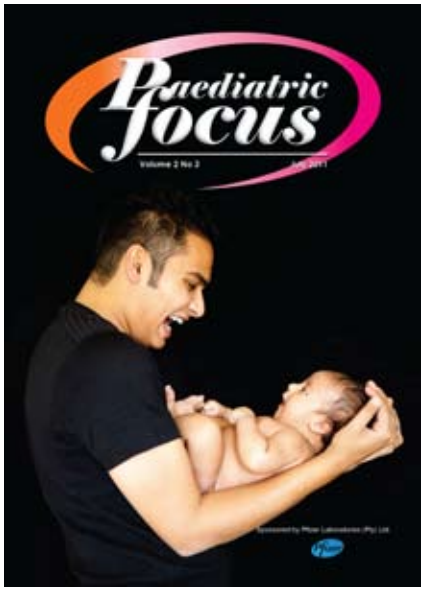
In June 2011 South African doctors heard that Prevenar 13 has been launched in this country. This is an important advance for the protection of children from Pneumococcal disease. The launch meeting had some of the world's premier Infectious Disease experts present who shared their wisdom. Ann von Gottberg revealed that already in South Africa Pneumococcal vaccines are having an impact, reducing invasive pneumococcal disease in children. Keith Klugman and Shabir Madhi were two of the pioneering workers who conducted the important trials on Pneumococcal vaccine in South Africa. They shared their insights into where gaps in Pneumococcal disease prevention still exist and what we may expect from Prevenar 13.

Hyatt Regency Oubaai in George

Ron Dagan from Israel presented some interesting theories about the pathogenesis of acute otitis media and especially more severe diseases. He suggested that Pneumococcal disease, apart from causing its own disease spectrum, also creates an environment for subsequent co-infection with Haemophilus influenzae. Non-typeable H' influenzae is an important pathogen that is probably responsible for more chronic otitis media.

We heard that vaccines are an important mechanism that protects communities from severe diseases such as those that cause significant morbidity and mortality. Once disease is left to happen we are at the mercy of antibiotics to help regain control of the patient's wellbeing and unfortunately "bugs" are becoming increasingly resistant to the antibiotics that we are left with. Vaccinations like Prevenar 13 offer an important hope for winning the battle on infectious diseases.

Robin J. Green



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Request for contributions

We welcome submissions of articles from paediatricians, GPs with a special interest in paediatrics and academics etc for publication in this newsletter. Please email articles to: Robin.Green@up.ac.za or lakeann@mweb.co.za

Editorial

Professor Robin Green (Editor)
Professor and Head Department of Paediatrics and Child Health,
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Ok so we have now got beyond the first year for this journal and the infant is now a toddler, growing up fast. You will have realsied by now that my current passion is the 'rational use of antibiotics' in medical practice and I believe that General Practitioners and Paediatricians have a vital advocacy role to play.

We, in the Department of Paediatrics at the University of Pretoria and Steve Biko Academic Hospital, have recently compiled Guidelines for the use of antibiotics in common paediatric conditions. By way of editorial then I would like to share the Respiratory Guidelines with you. Please feel free to use them or alternatively give me your feedback on modifying or changing. I would welcome your comments. My colleagues in the Department may give me permission to share those protocols for other conditions and I will then publish those in future editions of this journal.

So until the next edition, use antibiotics wisely.

Cheers
Robin J Green

Antibiotic Protocols for Paediatrics – Steve Biko Academic Hospital
Respiratory tract infections in children

Uncomplicated URTI
A child with a 'cold' should not receive an antibiotic
- Paracetamol (15 mg/kg/dose 4 hourly) for 24 hours if needed for fever
- Saline nose drops are appropriate

Acute otitis media
Antibiotic therapy
- Amoxicillin 30 mg/kg/dose 8 hourly po for 5 days
- No specimens should be sent for MC&S

Pharyngitis/Tonsillitis
Antibiotic therapy
- Pen VK 250 mg twice daily for 10 days (< 27 kg)
- 500 mg twice daily for 10 days (> 27 kg)
- (given 30 minutes before food)
- No specimens should be sent for MC&S

Pneumonia
Diagnosis
- Tachypnoea with fever
- Crackles on chest auscultation
- CXR - Consolidation with air-bronchograms

Antibiotic therapy
- Ampicillin 30 mg/kg/dose IVI 8 hourly for 5 days or,
- Ampicillin 30 mg/kg/dose 8 hourly + Amikacin 15 mg/kg/day for 5 days if HIV-exposed (or malnourished)
- Oral amoxycillin suitable for less severely ill children

Bronchiolitis
Diagnosis
- Tachypnoea with fever
- Wheezes on auscultation
- Hyperinflation on chest examination
- CXR – Hyperinflated

Antibiotic therapy

No antibiotic (unless < 2 months old)
- If less than 2 months old Ampicillin and Amikacin
- Oxygen only
- No bronchodilator nebulisation (unless hypoxic on oxygen and if positive bronchodilator response test)
- No oral steroids

Severe Pneumonia – PCP Syndrome
Diagnosis
- Infant 2-6 months old
- Severe hypoxia
- No adventitious sounds on chest auscultation
- LDH > 500 u/ml
- CXR – Interstitial changes

Antibiotic therapy
- Trimethoprim/Sulphamethoxazole 5mg/kg/dose 6 hourly preferrably IVI (of Trimethoprim) for 21 days
- Oral steroids 1mg/kg/day for 10 days – wean over 4 days
- Ganciclovir 5 mg/kg 12 hrly (if hyperinflation present) for 3 weeks

Pneumonia in PICU
- If hospital acquired or ventilator associated pneumonia or failed first line treatment Meropenem 40mg/kg/d 8hrly for 5 days
- Alternatives Ertapenem 20-40mg/kg 8 hourly (if no suspicion of Pseudomonas or Acinetobacter) for 5 days

Behaviour Disorders in Children -

What should our approach be?

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Pretoria

Behavioural difficulties in children especially disruptive behaviours (DB) involve a substantial amount of our time as Paediatricians, GP's and Mental Health Professionals. We formulate a treatment plan, often involving prescribing medication, once we have categorised symptoms into a diagnostic category (DSM and ICD classification systems).

We should not overlook important aspects that affect the course and the sustaining of these behaviours, when taking a history. DB lead to longstanding costs to society as well as high utilisation costs with regard to the mental health budget. A cohort of ADHD children followed for a 9 year period showed that direct medical costs were more than double for children with ADHD than for those without the diagnosis. Children with behavioural problems are mainly seen within education, social services and juvenile settings.[1]

DB (in early childhood) is common to all cultures. As children grow older they learn what constitutes acceptable social behaviour. Continued high levels of physical aggression is a **developmental deviance** often with a strong environmental and genetic contribution. Physical aggression is well researched and has serious consequences.

Aggression and aggressive behaviours

Parental recall, as to when physical aggression started, is often inaccurate. Chronic physical aggression (CPA), defined as a tendency to use physical aggression more frequently than the large majority of a birth cohort over many years, seldom starts after the early childhood period.[2] The severity of aggression increases with age and the intent to seriously hurt cannot be ignored. Until recently researchers avoided studying aggression in young children presuming that they cannot hurt or harm others, leaving us with a gap in our knowledge of aggression in early childhood.

Physical aggression that continues over time, is one externalising behaviour that is most consistently linked to later adolescent health risks such as substance abuse and risky sexual behaviour.[3]

Aggressive behaviours are seen in conditions such as ADHD, Post Traumatic Stress Disorder (PTSD) and Oppositional Defiant Disorder (ODD). This is considered an overtly disruptive entity occurring as early as pre-school, where being angry and resentful, arguing, loss of temper and refusal to comply with rules and regulations from adults, are symptoms.

Physical aggression that continues over time, is one externalising behaviour that is most consistently linked to later adolescent health risks such as substance abuse and risky sexual behaviour

Brain systems implicated in aggression include the dopaminengic system (functionally involved in emotional regulation, motor command, cognitive processing and neuro-endocrine control), the noradrenergic system (playing a critical role in human stress reactions) and the serotonin system (generally thought to be a state of hypofunction in aggressive individuals). High levels of homovanillic acid (HVA) have been found in adults with aggression in violent forensic samples and in youths with aggression and co-morbid ADHD.

The hypothalamic-pituitary-adrenal axis (HPA) and the hypothalamic-pituitary-gonadal (HPG) axis have been studied in aggressive youths with attempts to characterise the severity of aggression or type of aggression using cortisol level concentrations. McBurnett el al observed that low cortisol levels were associated with patterns of aggression and early onset in male children. Lopez-Duran el al, looking at cortisol activity in 73, 6-7 year old children, noted that those with patterns of reactive aggression had higher cortisol reactivity than the children with no aggression or pro-active aggression. High levels of dehydroepiandrosterone (DHEA) a precursor to testosterone and oestrogen, have been found in adolescents with conduct disorder as compared to a healthy group of adolescents.[4]

Genetic factors and parental contribution

In our parental interviews we need to ask questions about parents' own personal childhood histories, as a child's early environment, is in a sense, created by their parents' own developmental history impacting on brain development. A mother's early history appears to have the biggest impact on early gene expression. Her behaviour in adolescence, poor educational level, first pregnancy at a young age, depression, smoking, dysfunctional relations with the father and parenting, all constitute major environmental risk and may start to have an impact on the child's developing brain and eventual self-control problems during foetal life. Identifying post-partum depression is equally important. Boys are more vulnerable to high risk environments than girls.[2]

Environmental factors

Maternal depression including postpartum depression impacts negatively at every level of a child's life. The latter affects a mother's nurturing, proximity and responsiveness to her baby. Rumination and self absorption, features of depression, rob children of their mothers' attention leading to sad, irritable and withdrawn children. At a pre-school level this presents with difficulties regarding emotional expression, controlling aggressive impulses, sharing and co-operating with others. In fact all mechanisms from the prenatal period should be targeted, especially in females who have a history of social adjustment difficulties. One author described it as follows; "The epigenetic perspective suggests that successful prevention of DB may be easier to achieve by ameliorating the early environment rather than chasing bad genes."[2] Poverty is also another major risk for the development of DB placing huge stress on parenting skills and practices.

Our quest (from genetic studies) to link genes to behavioural problems, is promising. The 7-repeat allele of the Domain D4 receptor gene has shown to be associated with impulsivity and poor executive functioning.[2]

Parenting practices

Focusing on parenting style is important in our interviews as it has a predictive role in determining how children perform in the areas of social competence, their psychosocial development, academic performance and problem behaviours. Parenting practices influence brain development in brain structure and functioning. Early life experiences affect the grey and the white matter of the brain, and in particular, the corpus callosum's myelination process during a critical period of development. The sub-cortical structures develop early (amygdala and the hypocampus). The amygdala is already formed by the 5th week of gestation, myelinates by the age of 3 years and is connected to the orbito-frontal cortex, playing an important role in social and emotional behaviour.[5]

The hypocampus, important for spatial learning and memory, increases in the first years of life (MRI studies). Animals studies have shown that stress and glucocorticoids selected during stress can be neurotoxic to the hypocampus. Parenting can influence children's neuro-endocrine response to stress, in turn influencing hormonal responses that affect the brain. Brain development involves three neural processes. The first being **gene-driven** which is regarded as more or less insensitive to experience. This is followed by **experience-expectant** processes, which occur while the brain is primed to receive certain classes of information from the environment. This period of synapse overproduction is programmed to allow the emergence of basic skills used in interaction with the environment to guide the subsequent elimination of excess synapses. This is also known as the pruning phase.[5]

Experience-dependent synapse formation is the third important process unique to individual experience and is localised in areas in the brain involved in processing the information from the experienced event. Thus early stresses, whether they are emotional or physiological, may condition young neural networks to produce effects throughout brain development and can inhibit a child's flexibility to adapt to new challenges.[5]

Authoritarian and indulgent parenting (the former high on demands and low in responsiveness towards the child) needs to be discouraged as they do not encourage positive character building in children and can lead to aggression. Authoritative parenting encourages good character traits and parenting programmes to teach and encourage positive parenting styles and interaction are needed.[6]

An area often neglected in disruptive behaviours is that of 'attachment'. This summarises the quality of the relationship between a child and care-giver. Insecure attachments to their mothers can have a negative impact on their relationship with peers, depression and promoting development of aggression. Studies looking at high risk families have produced evidence that insecurity is related to psychosocial problems. 'Disorganised attachment' representing a response to frightened, threatening and dissociative parental behaviour, has been identified and often seen where a parent has a mental illness. A difficult temperament with a disorganised attachment appears to be a **dual risk** for behavioural problems. A study with 12 month old infants with difficult temperaments and disorganised attachments, showed them to be more aggressive at the age of 5 years than children with only one of these risks.[7]

Authoritative parenting encourages good character traits and parenting programmes to teach and encourage positive parenting styles and interaction are needed

Temperament is an intrinsic characteristic in children. Situations where parent-child mechanisms are established that are mutually responsive, promote a positive mood in children which increases their pro-social behaviour. The so-called difficult temperament is linked to externalising problems. These are children who adapt with difficulty and are intense. They often evoke difficult emotions from parents and it is important to ask parents about their perceptions of their child's temperament as part of the interview.[7]

Attachment theorists believe that continued activation of a positive attachment system will inhibit negative effects of the environment and promote cognitive development. A negative effect has been shown on cognitive scores, in the presence of negativity and conflict in mother-child relationships.[7]

Conclusion

By incorporating a broader approach to assessing behaviour and in particular DB in children, we will start making inroads into the prevention and reduction of risk in this population. This is a vast task best approached by a multi-disciplinary approach and not merely by a medical practitioner administering medication. However the role of medication may be helpful in certain settings while one 'contains' and gets the needed non-medical interventions in place.

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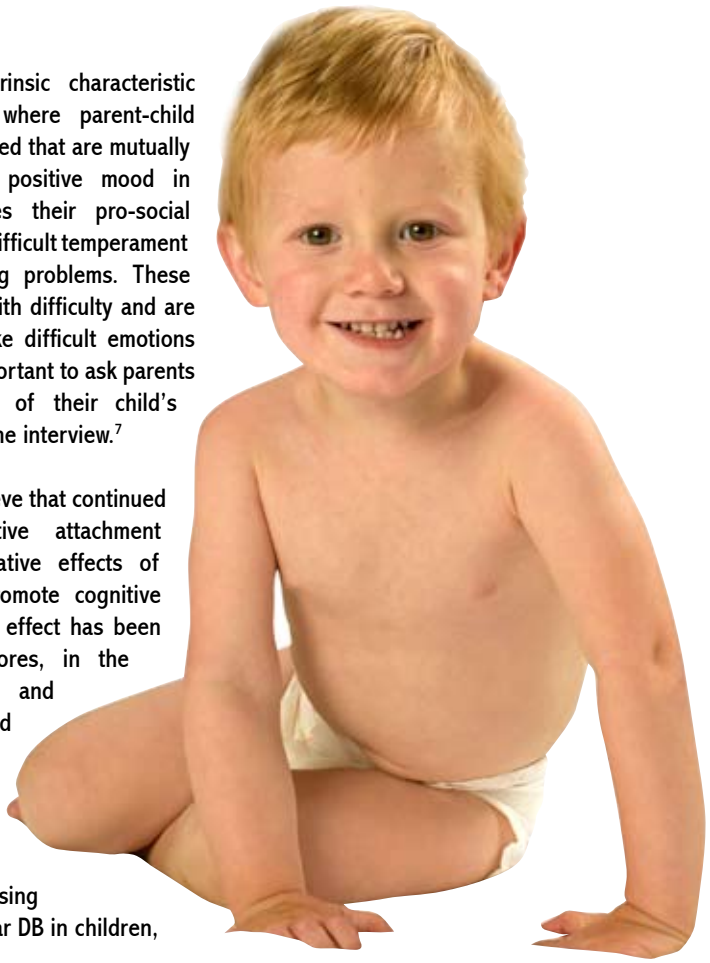

Preschool asthma: diagnosis, phenotype and pharmacotherapy

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It is both difficult and important to correctly diagnose and manage asthma in preschool children. Up to 50% of children will suffer from at least one episode of intrathoracic airway narrowing and present with wheeze before 3 years of age. There are numerous reasons for preschool children to wheeze. The agreement on the definitions of wheezing disorders in this age group is poor. Preschool wheeze poses frequent diagnostic and management challenges to practitioners.

Asthma is one of various causes for preschool wheeze. It typically begins in early life and remains the most common chronic childhood disease. Uncontrolled asthma can contribute significantly to morbidity. It can be well controlled if correctly diagnosed and managed. The challenge to practitioners is to be skilled at correctly "selecting" the asthmatic child from the population of preschool wheezy children, and to then offer effective management. This short review aims at highlighting concepts from recent consensus and guideline documents[1,2,3,4] on wheeze disorders and asthma in preschool children.

When is it asthma?

Asthma is an airway disease that results from abnormal host response to different stimuli. It is defined as a chronic inflammatory disorder, associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing. It is not possible to routinely document airway inflammation or airway hyperresponsiveness in clinical practice and these clinical symptoms are variable and can be very non-specific in this age group.[2] Practitioners should therefore embark on a process of "adding evidence" to "build" a diagnosis in order to come to a reasonable conclusion. The diagnosis must be based on a composite of criteria. Different features in the history, clinical examination and some special investigations can be helpful in adding evidence to a correct diagnosis of preschool asthma.

History-taking is the most valuable diagnostic instrument in the assessment of preschool wheeze.[3] Recurrent episodes of wheeze are the most common symptom associated with asthma in this age group. Wheeze is unfortunately one of a number of forms of noisy breathing in young children. It is often misunderstood by parents and by healthcare workers. Proper history-taking should confirm true wheeze as a presenting symptom. History-taking should also focus on the temporal pattern of recurrent wheeze. Recurrent episodes of wheeze that presents, or persists, after the age of 3 years will favour asthma as the more likely diagnosis. The onset of wheeze at a younger age, and especially in the infant, should warn against other possible reasons to wheeze. Asthma is more prevalent in children with a family history of atopy. The presence of atopy, or early allergic sensitisation, will increase the likelihood of asthma. History-taking should further aim at identifying possible asthma trigger factors. Viral airway infections trigger acute asthma exacerbations in asthmatic patients. They are also often the primary reason to wheeze and cough in younger children who do not suffer from asthma. It is therefore helpful to specifically determine if symptoms are also present in the absence of airway infections. Exercise-induced wheeze or cough, and wheeze or cough at night, in the absence of an airway infection, adds evidence to a likely asthma diagnosis. Wheeze that responds to bronchodilator therapy will further support possible airway hyperresponsiveness and an asthma diagnosis.

No special investigation can diagnose asthma with certainty in preschool children

The clinical examination often does not offer much help in diagnosing preschool asthma. It can however be of value when features of intrathoracic airway narrowing are present at the time of consultation, and especially if reversibility of these features can be demonstrated after bronchodilator therapy. The presence of signs of allergic disease, like allergic rhinitis and atopic eczema, also add support to an asthma diagnosis. The true value of proper clinical examination often lies in the exclusion of alternative causes that may present with a wheeze disorder in preschool children: A simple finding like failure to thrive may support an alternative diagnosis like tuberculosis or cystic fibrosis.

No special investigation can diagnose asthma with certainty in preschool children. Patients with suspected asthma, and especially when long-term asthma therapy is considered, should be evaluated for allergy. Allergic sensitisation at a young age increases the likelihood of the presence of asthma. Further special investigations remain a matter of clinical judgement and are aimed at excluding alternative reasons to preschool wheeze. Such special investigations are justified when symptoms are present from birth or infancy, are abnormally severe with slow or incomplete recovery, lead to repeated and prolonged hospital admission, continue in the absence of viral airway infections and in cases when parents are very anxious.[3]

A therapeutic trial of asthma medication may provide guidance to the presence of asthma.[2,3] The trial should include inhaled glucocorticosteroids (ICS) and as needed rapid acting $ß_2$-agonists (SABA) for 8-12 weeks. Marked clinical improvement during treatment, and deterioration when it is stopped, will add support to an asthma diagnosis.[2] The use of ICS should be terminated if a clear response to treatment is not demonstrated.

Wheeze and asthma phenotypes in preschool children

Several wheeze and asthma phenotypes have been recognised in preschool children. Initial reports were based on epidemiologic data and offered important insight, but limited value in the clinical management of individual patients. Definitions referring to aspects, like the temporal pattern and triggers of wheeze, may be of more value to the clinician and therefore remain a subject of active investigation. These phenotypes may offer guidance on the prognosis and on preferred treatment strategies in preschool wheeze and asthma.

A European Respiratory Society task force[3] suggested two important preschool wheeze phenotypes: The episodic (viral) wheeze phenotype appears to be the most common phenotype in preschool children and refers to patients who present with discreet episodes of wheeze, related to viral airway infections, and who are asymptomatic between these episodes. They tend to wheeze more frequently during the airway viral infection season and the frequency and severity of their symptoms decline over time. The second phenotype, multiple-trigger wheeze, refers to patients who wheeze to both viral and other

triggers such as allergen exposure, tobacco smoke, mist exposure, exercise, crying and laughter. These patients suffer from discreet exacerbations, but also suffer from symptoms between exacerbations.

The PRACTALL consensus report (4) resulted from an initiative by members of the American Academy of Allergy and the European Academy of Allergy, Asthma and Immunology. This report suggests different asthma phenotypes that form part of a broader asthma syndrome. The age of onset of symptoms, the relationship of symptoms to viral airway infections, the recognition of asthma triggers and atopy or the allergic status of the patient can be used to define the different phenotypes. Wheeze in young children (<2 years of age) mostly results from viral airway infections and persistent infantile wheeze warrants the careful exclusion of other causes of wheeze. The persistence of symptoms is the key defining factor in the 3-5 year age group. If symptoms disappear completely between episodes, and usually follow a viral airway infection the phenotype of virus-induced asthma is used. In an atopic or allergic child, with relevant association between allergen exposure and symptom occurrence, the phenotype of allergen-induced asthma is used. If no specific allergic trigger can be identified, the phenotype of non-allergic asthma can be considered. The exercise induced asthma phenotype can also be identified in this age group.

Pharmacotherapy in preschool wheeze and asthma.

Pharmacotherapy remains the cornerstone of treatment. The correct prescription of medication is important. The most effective delivery device to meet the patient's needs must also be selected. Inhalation via a metered dose inhaler (pMDI) and effective spacer device offers various advantages over nebulised treatment.[1,2] The initial dosing and combination of medication will depend on the severity of asthma at the time of diagnosis. Periodic re-assessment of the level of asthma control, with appropriate adjustment of treatment levels, must follow in accordance with guidelines.[1,2,3,4]

Inhaled SABA's are the most effective bronchodilators and the reliever drugs of choice in preschool asthma. Ipratropium bromide inhibits vagally mediated bronchoconstriction but is less potent and offers a slower onset of action than SABA. There is no evidence for the chronic use of ipratropium bromide in the management of asthma.

Daily controller medication should be prescribed to patients with persistent asthma symptoms. Inhaled glucocorticosteroids (ICS) remain the most effective controller medication. Leukotriene receptor antagonists (LTRA's) offer anti-inflammatory effects via different pathways than ICS.

Inhaled SABA's are the most effective bronchodilators and the reliever drugs of choice in preschool asthma

ICS maintenance treatment should be prescribed in persistent asthma (multiple-trigger wheeze and allergen-induced asthma phenotypes). The benefit appears to be smaller in preschool children than older children. Budesonide (BDP) equivalent doses of up to 400µg/d may be used and should not be increased to higher doses when the response is poor.[1,3] Lower doses should be used for controlled asthma. ICS is preferred for children >3 years of age and the benefit should be clearly confirmed before continued use in children <2 years of age. Add-on therapy with a LTRA is recommended for those asthmatic patients who are not controlled on 400µg/d BDP equivalents.[1,2,4] Some guidelines will also consider long-acting $ß_2$-agonists (LABA) as add-on therapy, but only in combination with ICS and only in children >4 years who are well monitored.[1,4]

Maintenance treatment with ICS (400µg/d BDP equivalent) does not reduce the number or severity of wheezing episodes in episodic (viral) wheeze. Routine ICS maintenance treatment is therefore controversial in this phenotype and it should not be used without demonstrated benefit.[1,3]

LTRA's may be used as alternative first line treatment for patients suffering from mild persistent asthma (multiple-trigger wheeze, allergen-induced asthma phenotypes) who would not use ICS. It is the recommended add-on medication for preschool asthmatic children who are not controlled on ICS alone and is currently the treatment of choice for children suffering from the episodic (virus) wheeze or virus-induced asthma phenotypes. The option of intermitted LTRA use (administered for 10-12 days from the onset of signs of a common cold) can be considered in this phenotype.[3,4]

Conclusion

New consensus reports and guideline documents offer positive attempts to address the problem of preschool wheeze and asthma. The need for scientific evidence and uniform definitions and diagnostic criteria is again highlighted. Attempts at defining wheeze and asthma phenotypes may benefit the understanding and management of preschool patients.

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Management of motor disability, with particular emphasis on Botulinum Toxin, in children with Cerebral Palsy

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Cerebral Palsy (CP) is the most prevalent cause of motor disorders in childhood.[1] The prevalence is 2-3/1000 live births. The prevalence increases to 100/1000 live births in extreme prematurity (28 weeks).[2]

Cerebral palsy is defined by Bax et al in 2005 as a group of disorders of the development of movement and posture causing activity limitation that are attributed to non-progressive disturbances that occurred in the developing foetal or infant brain. The motor disorders of cerebral palsy (CP) are often accompanied by disturbances of sensation, cognition, communication, perception and/or behaviour, and/or by a seizure disorder.[7,8]

Discussed in this article is the concept of both Spasticity and Dystonia, both of which are present in various degrees in most children with CP.

Spasticity can be strictly defined as an increase in muscle tone; specifically an increased resistance to muscle extension, which also means an increased tonic and phasic stretch reflex (Lance 1980).

Dystonia is a syndrome of persistent muscle contractions that leads to distorted and repetitive movements of abnormal position. It can be exacerbated by voluntary movement and can be interrupted by sensory "tricks".

Aetiology

The aetiology of CP is dependant on the time of the insult and the lesion pattern. During the first and second trimester, mal-developments are more prominent. In the early third trimester, periventricular leukomalacia and intraventricular haemorrhages are sited as prominent causes. During the late third trimester, lesions of the cortical and sub-cortical as well as deep grey matter lesions become important.The motor disorder in CP involves supra-spinal motor centers, cortico-spinal tracts, segmental spinal circuits and the musculo-skeletal system.

Classification

Phenomenology is important in the management of children with CP:

1. Type - Spastic, Dyskinetic (Dystonic or Choreoathetoid) or Ataxic .
2. Distribution i.e. unilateral, bilateral.
3. Severity – using GMFCS (Fig 1).[3] Reclassification of the child is essential at every visit, especially in the first 4 years.
4. Co-morbidity.

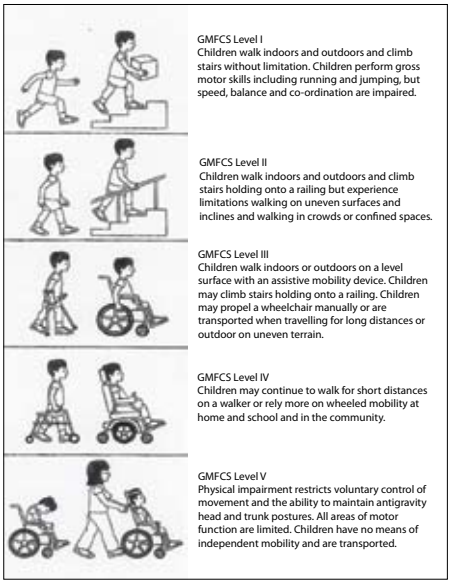

Fig 1.[3] GMFCS = Gross Motor Function Classification Scale

Management strategies in spasticity

The management of children with CP requires a multi-disciplinary team approach.

It is very important to set goals - this is not only for the medical personnel, but in particular for the child and their parents. Goals are generally to:

- maximise active function
- ease care
- prevent secondary problems e.g. subluxation, pain, contractures etc.

In addition to setting realistic attainable goals, one needs to take into account previous treatment modalities. Furthermore the child's functioning interests need to be strongly considered.

Other factors influencing the treatment plan include:

- the child's age
- presence of co-morbidities
- ability to do home based treatment
- follow-up
- financial issues.

The various treatments available in the management of CP are discussed briefly with emphasis on the use of Botulinum toxin (BT):

1. **Physical therapy** is first and foremost in the management plan. The importance of physio and regular stretching is essential in the ongoing management as well as supportive in the face of other treatment strategies e.g. Botox and surgery. But probably its most important role being preventative against contractures and subluxation.
2. **Orthotics** are used on various parts of the body. They have been found to reduce contractures and joint deformities as well as improve certain movements around joints. They have, however, not been found to increase stride length nor walking speed. Recently new orthotics, aimed at stimulating the sensory pathways are being used specifically for better truncal control.
3. **Oral medications** are easy to use but side-effect profile keeps them restricted to certain patients. Baclofen is the most frequently used medication. It has a spinal and supra-spinal point of action at the GABA-B receptor (agonist) and it inhibits spinal interneurons through post synaptic hyper polarisation. Treatment provides improvement in painful flexor and extensor spasms, but not in functional gain.
4. **Neuro-muscular blocks**
   There are 3 types that are used in the local therapy of spasticity:
   - local anaesthesia of short duration with completely reversible effect.
   - destructive measures (alcohol and phenol) with longer lasting effects, but severe side-effects.
   - Botulinum toxin (BT) with temporary, specific effects at the neuro-muscular end plate.

   The latter will be discussed in detail.
5. **Rhizotomy** - the severing of between 25-50% of the spinal afferent (posterior) rootlets, between L2 and S2, results in improved spasticity of the lower limbs. Its use is limited to certain types of CP.
6. **Intrathecal Baclofen (ITB)** is indicated in patients with severe spasticity - unresponsive to standard therapy. Effects of ITB on spasticity are distinctively higher than oral doses of Baclofen. Simultaneous treatment with BT is possible, often dosages can be reduced using this combination, and combining it with other oral myo-relaxants has not been proven worthwhile because of increased side-effects on central nerves.
7. **Surgery** at muscles, tendons, joints and bones is controversial particularly before the age of 6 years (except for hip surgery). It is said to have a high relapse rate. Only after the age of 8 years do

specific clinical pictures indicate surgical measures. The most common indications are equinus, adductor spasticity and internal rotation of hip and knee flexion. Combined treatment with BT, orthosis and physiotherapy demonstrates the best results.

Botulinum toxin

- Exotoxin produced by Clostridium difficile.
- 7 serotypes (A-G), all target the neuromuscular junction. Only five are active in humans (A,B,E,F,G), two (A and B) are commercially available.
- Denervation occurs because the vesicles cannot fuse with the synaptic membrane and thus acetylcholine cannot be released.
- This induces a localised weakness in hyperactive muscles, on which is based its therapeutic use.
- To date all published data on CP has been done with Botulinum toxin type A.

There are three preparations of BT serotype:

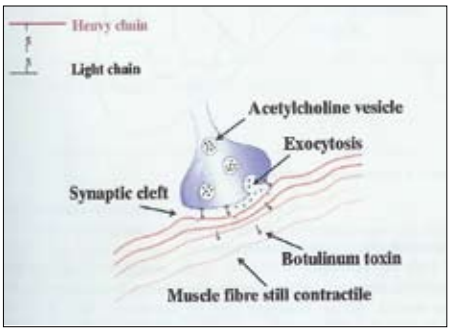

Fig 2. Denervation action of Botulinum Toxin[4]

A-Botox (Allergan), Dysport (Ispen Ltd) and Xeomin (Merz Pharma). All preparations are distinctive concerning their molecular structure and manufacturing process.
For children with CP this pharmaceutical difference has significant implications for clinical use. Individual dosages must be calculated independently for each BT preparation and fixed dose conversion factors are not applicable.

The use of BT in children with CP represents a major therapeutic intervention, but should not be considered as stand alone therapy.
With ongoing child motor development, spastic movement disorders develop into distinctive motor patterns that should be recognised and used to guide therapy.

Initially a focal approach was used, however in a multifocal condition such as CP, a number of muscle groups need to be targeted. This has led to the multi-muscle, multi-level approach, in which a number of over-active muscles are injected to achieve an improvement of limb posture and movement.

The aim of BT in CP would thus be the following:

- Attempt to reduce focal muscle spasticity.
- To reduce or eliminate an abnormal movement.
- Delay surgery when it is inevitable – the effect of the toxin is to maximise the length of the muscle fibres, which improves joint mobility and also plays an important role in limb growth and reduces leg length discrepancy.
- To obtain an analgesic effect.
- To help hygiene care.

Dosage

Dosage calculations for each preparation are based on:

1. Total units per treatment session.
2. Total units per kg body weight per session.
3. Units per muscle.
4. Units per injection site.
5. Units per body weight.

NB Units represents a different biologic potency for each BT preparation.

Additional dose modifiers

1. Severity of CP according to GMFCS.
2. Accompanying diagnosis e.g. dysphagia, aspiration and respiratory problems.
3. Predominant movement abnormality e.g. spasticity or dystonia.
4. Activity of muscle fibre.
5. Muscle size.
6. Dynamic versus fibrotic muscles.
7. Knowledge of motor-end plate.

In summary

- Type A – Botulinum Toxin – doses have slowly been increased over the past couple of years, mostly because multi-level injections are now being advocated. Anywhere between 6-30u/kg of Botox, and 1-20u/kg Dysport may be used depending on the number of muscles injected. A total maximum dosage of 400-600 Units of Botox and 500-1000 Units of Dysport is advocated.
- No overloading of a single muscle (no more than 100u/muscle or more than 0.5ml).
- No fixed ratio in children.
- Specific knowledge and use of preparations is essential.
- Number of injection sites varies according to the size of the muscle. It is thought that increasing the number of injection sites helps reach a maximum number of neuromuscular junctions. The distribution of neuromuscular junctions within a muscle is not clearly defined, but covers a wide area around the middle of the muscle.
- Use of ultra sound and EMG to improve accurate site injection e.g. Iliopsoas and parotid gland.
- Use of concomitant casting post BT.
- Interval between injections must be adapted according to the response in individual patients. However not less than 3 months for risk of resistance. Usually spacing of injections varies between 4-8 months.

Adverse effects

Three types of adverse effects can occur:

1. Focal - local weakening beyond therapeutic goal can occur when muscle size dosing guidelines and diluting guidelines are not respected or when inadequate localisation techniques are not applied.
2. Generalised weakness.
3. Procedural side-effects - haematoma is rare when one uses a small (27 or less gauge needle), infection - none reported in the literature, specific risks of morbidity and mortality related to sedation or anaesthetic need to be addressed in future evaluations, with specific reference to GMFCS.

Assessment and evaluation of treatment with BT

Purpose built classification tools and standardised clinical assessments enable people to speak the same language and to evaluate interventions using consistent and valid instruments. Some tests include the Ashworth scale, Tardieu scores, range of movement, gait analysis and others.

Non-responsiveness to BT can occur as a result of:

- insufficient injection.
- predominant muscle fibrosis.
- formation of antibodies. Despite higher dosages per session having recently been administered to children with CP, secondary non-responsiveness due to the presence of antibodies is no longer clinically relevant due to the use of reformulated BT.

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Reportback: 29th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID)

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THE HAGUE, NETHERLANDS: JUNE 7-11, 2011.

The 29th Annual Meeting of The European Society for Paediatric Infectious Diseases (ESPID) took place in the historical and beautiful city of The Hague. The Hague is well known as the International City of Justice and hosts the International Criminal court, the International Court of Justice and the United Nations Tribunal for Rwanda. It is the third largest city in the Netherlands, after Amsterdam and Rotterdam (population about 500,000). The admixture of historical and cosmopolitan, contemporary and globalised, was certainly well reflected in the spectrum of the conference, which was attended by more than 3000 delegates from more than 90 countries.

The highlights of this year's meeting were excellent discourses by 2 Nobel Laureates, and a soul searching and highly provocative address by Richard Horton, chief editor of The Lancet. Prof. Francoise Barre-Sinoussi of Paris (winner of the 2008 Nobel Prize for Medicine for her contribution to the discovery of the Human Immunodeficiency Virus) presented an update on current research in the 'Regulation of Retroviral Infections, Pathogenesis and Anti Viral Treatment of AIDS'. Despite significant advances, we are very far from a cure or an effective vaccine for this scourge. Prof. Ada E Yonath – a biochemist from the Weizman Institute of Science, Israel, presented an elegant summary of her lifelong work on the structure and function of ribosomes, with special reference to how antibiotics affect ribosomes. The three-dimensional pictures shown by her made it easy to understand drug-ribosome interactions, and the mechanism of emergence of drug resistance. This work presents further opportunities for the development of new drugs, or prevention of drug resistance. Ada Yonath was awarded the Nobel Prize for Medicine in 2009. Richard Horton of The Lancet presented data on the current state of child health globally. The picture painted was bleak– especially with regards to neonatal and childhood mortality. He challenged the European Paediatric Society and the wider Paediatric healthcare community to tackle this problem head on to help improve child health worldwide. In many countries, South Africa included, infant and neonatal mortality has increased over the past decade. Childhood mortality in the developing world remains abysmally high, mainly due to preventable and treatable diseases like malnutrition, HIV-AIDS, diarrhoea, malaria and respiratory infections. The resurgence of Tuberculosis and the increase in MDR and XDR TB worldwide was highlighted.

Many of papers and posters presented were clinically useful and selected highlights are presented below:

1. **Prof. Fred Zepp (Mainz, Germany)** presented data on the increasing incidence of Pertussis infections in older children and adults in Europe, despite widespread early childhood immunisation. Protective immunity is estimated to last 4-12 years after vaccination, and 4-20 years after infection. To overcome waning immunity, booster vaccinations have been proposed for adolescents (10-18yrs), and 10 yearly for adults. In South Africa, our own recent Measles epidemics have followed a similar course, with similar age groups being affected. Can the European Pertussis prevention strategy be applied to our own efforts to prevent Measles?
2. **Dr Nicole Ritz (Melbourne, Australia)** reported on a study comparing the immune response to BCG vaccine given at birth (n=54) vs. 2 months (n=44). Mycobacterial- specific immune response was measured using:
   i. intracellular cytokine assays and
   ii. concentrations of 12 cytokines in supernatants.
   Results showed comparable proportions of Th1 cytokine producing CD4 and CD8 T cells, and multifunctional CD4 T cells. Concentrations of all measured cytokines in supernatants were also comparable in both groups. The data therefore did not support delaying BCG vaccination in high prevalence TB countries. The South African connection to this study was Dr Willem Hanekom of the S A TB Vaccine Initiative from the University of Cape Town.
3. **Dr R Singleton (Anchorage, Alaska)** reported on the impact of the 13-valent Pneumococcal vaccine (PCV13) on Invasive Pneumococcal Disease (IPD) in native Alaskan children. Before the advent of PCV7, native Alaskan children from the Yukon Delta had IPD rates tenfold higher than non native Alaskan Children (547 vs. 56 per 100,000/year). After PCV 7 vaccine, IPD rates decreased to 148/100,000 in 2001-2004. The rate then increased to 433/100,000 in 2005-2008 mainly due to non-vaccine serotypes. In 2009, a clinical trial of PCV13 was undertaken. Post PCV13, IPD infection rate dropped to 139/100,000 in 2009-2010. Significantly, no IPD cases occurred within the under 5 year population after May 2010. Local data are required to assess the efficacy of PCV7 vs. PCV13 vs. PCV/HiB vaccines available in SA.

4. **At one of the "Meet the Professors"** sessions, K English (USA) and D Bogaert (The Netherlands) discussed Bacterial-Viral Co-Infections of the respiratory tract. They emphasised that much of what we know about the etiology of pneumonia in children is wrong. There is considerable overlap in the clinical and radiological features of pneumonia caused by viruses, pyogenic bacteria and "atypical" bacteria such as Mycoplasma.

   Recent studies using molecular diagnostic methods indicate that co-infection is very common in children with pneumonia. This may involve co-infection with more than one virus, a virus and bacterium, or even two bacteria. Bacterial pneumonia complicating influenza has increased severity, may respond poorly to antimicrobials and may cause fatal infection. In South Africa, Prof P M Jeena (University of Kwazulu Natal, and Prof Heather Zar (University of Cape Town) have in the past presented similar findings in some of their studies. These co-infections may be further exacerbated in HIV infected children.

5. **A notable poster was from M P Kronman et. al. (Philadelphia, USA).** They conducted a Paediatric Population based Cohort Study of Antibiotics exposure increasing the risk of developing Inflammatory Bowel Disease (IBD). In a cohort of 1,072,444 children, 766 developed IBD during the study period.

   The children were followed up for a period of two years following prescription of a new course of antibiotics shortly after a recent course. The median latency period between the first visit for IBD symptoms and the first IBD diagnosis was 3.6 months (inter-quartile range 0.4-17.3). The Hazard Ratio for the association between each course of antibiotics and developing IBD was 1.05 (95% confidence Interval, 1.03-1.07, $p<0.001$). Sensitivity analyses of other exposure measures (e.g., ever- vs. never- exposed to antibiotics) and different latency periods yielded similar results.

   They found that children have a 5% increased risk of developing IBD for every course of antibiotics received. Reductions in inappropriate courses of antibiotics may reduce the risk of developing IBD. Every healthcare professional should be highly circumspect when prescribing antibiotics.

The highlights of this year's meeting were excellent discourses by two Nobel Laureates and a soul searching and highly provocative address by Richard Horton, chief editor of The Lancet

6. **The impact of neonatal infection on 5-year neurodevelopmental outcomes of very pre-term Infants (EPIPAGE Study-France: Mitha, A., et. al.)** was also presented in Poster format. All live births between 22 and 32 weeks' gestation from 9 regions of France in 1997 were followed up and evaluated at 5 years of age. Neurodevelopmental outcomes (cerebral palsy and cognitive impairment) were studied according to early onset sepsis (EOS) and late onset sepsis (LOS).

   At 5 years of age the rate of cerebral palsy was 9% and cognitive impairment 12%. Compared with uninfected infants, cerebral palsy was significantly increased in the EOS alone group (OR=1.82) and was increased further when LOS was associated (OR=2.57). There was no association between neonatal infection and cognitive impairment. This is the first study to assess the respective impact of EOS and LOS on 5-year neurodevelopmental outcomes.

7. **Dr A J Cant (Newcastle upon Tyne, UK)** discussed the Recognition of Primary Immunodeficiencies (PID) in Children. Textbook PID descriptions are not helpful as recurrent infections are common in young children and most do not have PID. Pattern recognition is a key to diagnosis, whilst a positive family history is an important clue. Failure to thrive and need for intravenous antibiotics, is significantly associated with diagnosing PID. In general, 2 major invasive infections, or 1 major with frequent minor infections, or recurrent infections warrant further investigation.

8. **Dr Mike Levin (Imperial College, London)** presented findings of a multi-centre, multi-author study on the role of fluid resuscitation in the treatment of children with shock and life-threatening infections who live in resource limited settings. The study was conducted at hospitals in Uganda, Kenya and Tanzania. Children with severe febrile illness and impaired perfusion were given boluses of 20-40 ml of 5% albumin (AB), or 0.9% saline solution (SB), or no bolus (NB or control group) at admission (stratum A); children with severe hypotension were randomly assigned to one of the bolus groups (stratum B). All children received appropriate antimicrobials, IV fluids and supportive care according to guidelines. Children with malnutrition and gastroenteritis were excluded. End points were 48 hour mortality, pulmonary oedema, raised intracranial pressure, and mortality or neurological sequelae at 4 weeks. Malaria status and clinical severity were similar across groups. In stratum A, by 48 hours 10.6% of AB group, 10.5% of SB group and 7.3% of NB group patients were deceased. Relative risk of death with SB vs. NB was 1.44, AB vs. SB was 1.00 and bolus therapy vs. no bolus was 1.45. In stratum B, 69% of AB group and 56% of SB group had died. Bolus fluid resuscitation increased the absolute risk of death at 48 hours by 3.3%. The risk of death, neurologic sequelae, or both at 4 weeks increased by almost 4%. During the trial international standards of practice and management of illnesses was followed. These measures in themselves contributed to a better outcome than had been achieved by prior therapies. The findings of this study challenges the importance of bolus resuscitation as a life-saving intervention in limited resource settings. This study has since been published in the NEJM (364.26, June 30, 2011).

All in all, the 29th ESPID conference presented important updates and points for future improvements, and The Hague is certainly a city worth visiting.

It is estimated that up to 1 million children under the age of five die from pneumococcal disease - which includes pneumococcal meningitis, pneumonia, otitis media and bacteraemia – every year.[1]

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