Emerging issues in Paediatric Respiratory Medicine

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My career path

University of Newcastle upon Tyne
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(3 years)
Outline of the talk

- Overprescribing of antibiotics/Antibiotic resistance
  - Challenges for the respiratory paediatrician

- Associations between asthma and other atopic diseases

- An overview of the physiology of sleep and sleep disorders
Antibiotic resistance rise continues

By James Gallagher
Health editor, BBC News website

10 October 2014 | Health

Antibiotics are losing effectiveness in every country, says WHO

World Health Organisation warns of ‘devastating’ consequences and says once-beaten diseases could re-emerge

Doctors told to stop prescribing antibiotics for coughs and colds to ensure infections don’t become resistant to them
Why do respiratory paediatricians use antibiotics?

- Therapeutic use
  - To treat acute and chronic respiratory infections

- Prophylactic use
  - To decrease the risk of respiratory infections

- Dealing with a vulnerable group of children
  - Increased susceptibility to infection
  - Structural lung abnormalities
  - Immunodeficiencies
  - Neurodisabilities
Overprescribing

- Use of higher doses of antibiotics than needed
- Longer duration of antibiotic courses
- Prescribing broad versus narrow spectrum antibiotics

Why?

- Diagnostic uncertainty- viral versus bacterial infections
- Socio-cultural factors/parental expectations
- Lack of robust evidence from the literature
Consequences of overprescribing

- Emergence of multidrug resistance
- Patient mortality
- Length of hospital stays
- Healthcare costs
- Impact on gut flora
Diagnostic challenge

Viruses in 20–45% of all lower respiratory infections

- respiratory syncytial virus, rhinovirus, influenza, metapneumovirus

Bacteria observed in up to 60% of patients whose symptoms last for 10 days or more

- Bacterial super-infections commonly occur after a viral infection
- Synergistic effect between influenza viruses and *S. pneumoniae*
Bacterial respiratory pathogens

Most prevalent

- Streptococcus pneumoniae
- Mycoplasma pneumoniae

Less prevalent

- Staphyloccocus aureus
- Moraxella catarrhalis
- Group A streptococci
- Streptococcus milleri
- Haemophilus influenzae
Antibiotic resistance

Fundamental mechanisms

1. Enzymatic degradation of antibacterial drugs
2. Alteration of bacterial proteins that are antimicrobial targets
3. Changes in membrane permeability to antibiotics
Streptococcus pneumoniae

- Increase in multidrug-resistant S. pneumoniae strains demonstrating resistance to three or more drug classes
  - 10-40% of cases

- Formation of S. pneumoniae biofilm during colonisation provides a barrier to effective antibiotic activity
  - thus limiting complete bacterial clearance
  - promoting the development of resistance

- Even with successful bacterial clearance with antibiotic treatment
  - risk for recolonization by potentially more dangerous serotypes or alternative pathogens (e.g. Staphylococcus aureus)
Mycoplasma pneumoniae

- Lacks cell wall
  - hence resistant to beta-lactams and to all antimicrobials targeting the cell wall
  - treated with macrolides
- Macrolide resistance up to 15% in Europe and the USA
  - approximately 30% in Israel and up to 90–100% in Asia
- Resistance associated with point mutations in the peptidyl-transferase loop of the 23S rRNA
- Alternative treatment- fluoroquinolones or tetracyclines
  - Side-effect profile
Neurodisability

- The most common and severe infections in children with severe neurological impairment are respiratory viruses
  - vulnerable group/unable to exclude a bacterial cause

- Recurrent aspiration
  - Poor cough and airway clearance

- Anaerobic acute lower respiratory infections
  - chronic lower airway inflammation and damage

- May cause both bronchiectasis and lung parenchymal damage
  - impairs clearance of airway secretions and predisposes to lower airway infection

- Repeated treatment for infection and contact with other children who have received repeated antibiotic courses
  - may lead to the colonisation with resistant organisms
Prophylactic antibiotics in cystic fibrosis

- Low-dose azithromycin has beneficial effects on severity of the lung disease for a period of 6 to 12 months after initiation of treatment

  - No clinical benefits of low-doses azithromycin after one year of treatment in CF (Samson, 2016)
    - Selection for macrolide-resistant strains of bacteria occurred

- Anti-staphylococcal prophylaxis
  - Cochrane review- No impact on lung function & hospitalisation
Vaccination/ antibiotic prescribing

- Yearly influenza vaccine for the high risk group

- Haemophilus *influenzae* vaccine

- Pneumococcal conjugate vaccine (PCV)
  - Effective against 7, 10 or **13** of the 97 serotypes described so far

- PCV13 vaccination- associated with a decline in antibiotic resistance in pulmonary infections
  - But this favours the spread of several resistant non-vaccine serotypes
Pneumococcal cases after PCV13 vaccine

Janoir et al 2016
Macrolide and wheezing

- Young children with recurrent wheeze
  - macrolides may be helpful in this challenging population

- Mechanisms:
  - antimicrobial effects
    - atypical bacteria
  - anti-inflammatory effects
    - attenuated pro-inflammatory cytokine expression
    - reduced neutrophil accumulation in the airway

- Risk of increased prevalence of macrolide resistance if the use of macrolides becomes widespread
Asthma and Atopy
What is atopy?

- Greek word = “strange or out of place”

- Refers to a personal or familial tendency to produce IgE antibodies in response to ordinary exposures
Wheezing in children

- Infantile wheeze
  - Prematurity, post-bronchiolitis, smoke exposure, “happy wheezer”

- Childhood wheeze
  - Atopic/asthmatic- multi-trigger wheeze
  - Episodic viral wheeze

- Adolescence
  - Atopic/asthmatic
Bronchial reactivity

- Physiological property of healthy airways
  - to develop a moderate airway obstruction in response to various non specific stimuli

- Airway smooth muscle
  - active effector of airway reactivity
  - present from trachea to terminal bronchioles

- Contraction
  - reduction in airway lumen
  - increased resistance to air flow
Airway smooth muscle (ASM) in asthma

- Increase in the amount of muscle
  - hypertrophy (an increase in individual muscle cell size)
  - hyperplasia (an increase in cell number)

- Alteration in its pharmacological reactivity
  - increase in contraction or a decrease in relaxation
  - inflammatory mediators and cytokines
ASM Secretory functions

- Inflammatory products induce the genes for
  - cytokines
  - chemokines
  - adhesion molecules
  - cyclooxygenase-2 (COX-2)
  - inducible nitric oxide synthase (iNOS)
Pathophysiology of asthma exacerbations

- Exposure to a trigger
- Eosinophil and mast cell degranulation and epithelial damage
- Release of histamine, prostaglandin and leukotriene
- Continuing T cell and B cell differentiation and proliferation, promoted by cytokine release
- Subsequent inflammation, bronchoconstriction and mucus production
  - cause airway obstruction and impairment of gas exchange
Airway Smooth Muscle and Asthma

ASM Function
- Enhanced Contraction
- Impaired Relaxation
- Length Adaptation

ASM Structure
- Increased ASM Mass
- Airway Wall Thickening

Airway Inflammation
- Cytokines/chemokines
- Cell Adhesion
- Cellular Infiltrate
- Edema
- Increased Mucus
- Increased IgE
Allergic March

- Natural history of atopic disorders
- Development of atopic dermatitis and sensitization to food allergens in early childhood
- Progressing to asthma and allergic rhinitis in later childhood or adult life
The allergic march - prevalence

(Goksör et al. 2015)
Prevalence of allergic diseases

- 26% in infancy
- 15% in preschoolers
- 16% in school age

- 2 or more allergic manifestations in infancy
  - 44% were symptom-free at school age

- Only one early manifestation
  - 71% symptom free at school age

- Symptom free in infancy
  - 89% remained symptom free at school age
Rise in disease prevalence

- In Australia, the prevalence of:
  - asthma in schoolchildren increased from 12 to 38% between 1982 and 1997
  - allergic rhinitis increased from 22 to 44%

- In Denmark, the prevalence of:
  - eczema increased from 17 to 27% among children aged 7–17 years between 1986 and 2001
Allergy epidemic

- Asthma affecting up to 20% of school-aged children
- Allergic conditions (eczema, food allergy, asthma, allergic rhinitis) affect 52% of UK children
- Commonest long-term childhood condition in the UK
  - 12.5 million GP visits per year
Eczema and asthma

- Tucson Children’s Respiratory Study
  - Longitudinal investigation of 1,246 children enrolled at birth
- 18% of children with persistent wheezing at the age of 6 years had eczema before 2 years of age
  - Compared with only 7% of children who never wheezed
Food allergy and Asthma

- 4 – 8 % of asthmatic patients have food allergy
- About 50% of food allergic patients have asthma
- Multiple food allergies is associated with an increased risk of asthma
  - Especially for egg and tree nut allergy
- Severe asthmatics have 3.3 times increased risk of anaphylaxis vs. non asthmatics
Allergic rhinitis and asthma

- The prevalence of asthma in patients with rhinitis varies from 10% to 40%
- In asthmatic patients, the co-occurrence of rhinitis is high as 80%
- Allergic rhinitis increases
  - Frequency of wheezing episodes- 10-fold
  - Risk of severe asthma exacerbations- 3-fold
Gender

- Males-
  - an earlier age of presentation with asthma
  - higher prevalence of asthma in pre- and peri-pubertal males than females

- Due to a smaller peripheral airway calibre before puberty and an increased prevalence of atopy

- Later in childhood and towards puberty
  - gradual shift to an increased prevalence and severity of asthma in young females
Genetic factors

- Maternal asthma is strongly associated with wheeze in infancy and early childhood

- A history of asthma in both parents nearly doubles the risk for asthma and rhinitis
German Multicentre Allergy Study (Gough et al. 2015)
Can asthma be prevented?

Prenatal
- Avoidance of passive and active smoking
- Possible modification of maternal microbiome (e.g. probiotics)

Perinatal
- Vaginal delivery versus C-section
- Microbial gut colonization
Can asthma be prevented?

(2)

Postnatal

- increasing favorable environment
  - mimicking farm residence, breastfeeding
  - Omega 3 supplementation/antioxidants
- decreasing hostile environments
  - smoking and air pollution
  - reduction of house dust mite exposure
- early life viral infections
  - may predispose certain infants (and not others) to asthma-exact immune pathway unknown
Sleep
What is sleep?

- State of natural unconsciousness from which a person can be aroused
- Active process
- 2-process model of sleep and wakefulness
  - circadian (process C)
  - homeostatic process (process S)
Why sleep?

- The Restorative Theory
  - time of growth and repair

- The Preservation Theory
  - evolutionary process

- The Memory Encoding
  - learning is enhanced when the body is well rested
Process C

- Driven by an endogenous circadian pacemaker
  - located in the suprachiasmatic nucleus (SCN) of the hypothalamus

- Begins when light strikes special cells within the retina of the eye
  - Secretion of melatonin increases
  - Cause the suprachiasmatic nucleus (SCN) to signal the pineal body to stop secreting the hormone melatonin
Melatonin production

- As the day progresses
  - melatonin falls
  - adenosine accumulates within the brain

- As night falls, the inhibitory effects of the retinal secretions on the pineal body are suppressed
  - Secretion of melatonin restarts
  - Higher melatonin levels within certain areas of the brain (e.g. the thalamus and hypothalamus) control the urge to sleep

- Melatonin reaches its highest levels during sleep
Process S

- Depends on prior sleep and wakefulness
  - reflects the need for sleep

- Sleep pressure rises during waking, declines during sleep and increases with sleep deprivation

- Slow-wave activity serves as a marker for sleep homeostasis

- Slow-wave activity shows a decline in the course of sleep
Sleep architecture

- Begins in non-rapid eye movement (NREM) sleep
  - stages 1–3
  - 75–80% of the total time spent asleep
- Rapid eye movement (REM) sleep- 20–25%
- NREM sleep occurs four or five times during a normal 8h sleep period
  - The first REM period of the night may be 10 min in duration
  - The last may exceed 60 min
- The NREM–REM cycles vary in length from 70–100 min initially to 90–120 min later in the night
NREM sleep

- Stage 1
  - only 1–7 min at the onset of sleep

- Stage 2
  - approximately 10–25 min

- Stage 3
  - Slow-wave sleep (SWS), often referred to as deep sleep

- The three stages of NREM sleep
  - each associated with distinct brain activity and physiology
  - As one progresses through stages 1–3, sleep gets deeper and waves become more synchronised
REM sleep

- Defined by the presence of desynchronised (low-voltage, mixed-frequency) brain wave activity

- REM sleep consists of tonic and phasic characteristics
  - Tonic characteristics persistent throughout REM
  - Phasic characteristics intermittent during REM
  - Tonic characteristics include a desynchronised EEG, muscle atonia and a lack of thermoregulation
  - Phasic characteristics include REMs, clitoral and penile tumescence, and dreams

- During the initial cycle, the REM period may last only 1–5 min
  - Lengthens
Proportion of REM sleep

- Newborn to 3 months 50%
- After 3 months, NREM sleep begins to dominate
- 3–5 months 40%
- By the end of the first year, REM- 30% of total sleep time
- The percentage of REM sleep is reduced to adult levels by 10 years of age
Sleep disorders

- Defined as any condition or process that alters the sleep–wake cycle

- Divided into two general classes
  - Parasomnias
  - Dyssomnias
Parasomnias

- Sleep terror (sudden awakening and unreasonable fear)
- Bedwetting
- Somnambulism (sleep walking)
- Somniloquy (talking in one’s sleep)
Dyssomnias

- Intrinsic (arising within the body)
  - primary insomnia, central sleep apnoeas, obstructive sleep apnoea, restless leg disorder

- Extrinsic (arising outside the body)
  - environmental conditions not conducive to uninterrupted sleep, such as noise or ambient temperature

- Alteration or interference with the circadian rhythm
  - jet lag or shift work
Apnoea

- Greek word meaning “without wind”
- Defined as a cessation or decrease in airflow by 90% for 2 breaths or more (compared to baseline flow observed before the event)
- “Hypopnoea”
  - Partial airway obstruction characterised by shallower or slower breathing
  - defined as a 30% reduction in airflow
    - duration of two or more breaths in association with either 3% oxygen desaturation or an arousal
- The apnoea–hypopnoea index (AHI)
  - number of apnoeas and hypopneas per hour of sleep
- Apnoeas and hypopnoeas can be further classified as being central, obstructive or mixed
Obstructive versus Central apnoeas

- **Obstructive apnoea** is a cessation of airflow at both the nose and mouth associated with out-of-phase movements of the rib cage and abdomen.

- In **central apnoea**, the respiratory pause is not associated with a physical attempt to breathe:
  - Polysomonoigraphy (PSG) shows no breathing movements from the thoracic cage or abdomen.

- A **mixed apnoea** has no inspiratory effort in the initial portion of the event:
  - followed by resumption of inspiratory effort before the end of the event.

- **Periodic breathing** is defined as 3 or more episodes of central apnoea lasting 3 s separated by ≤20 s of normal breathing.
Obstructive sleep apnoea syndrome (OSAS)

- Disorder of breathing during sleep characterised by
  - prolonged partial upper airway obstruction
  - and/or intermittent complete obstruction
  - which disrupt normal ventilation during sleep

- Prevalence ranges from 1.2% to 5.7%
Aetiology of OSAS

• Most frequent cause is adenotonsillar hypertrophy

• Other associated conditions
  • allergic rhinitis
  • nasoseptal obstruction
  • cleft palate repair
  • Down syndrome
  • craniofacial syndromes (Treacher–Collins, midfacial hypoplasia, Crouzon syndrome, Apert syndrome, Pierre Robin sequence)
  • Achondroplasia
  • Mucopolysaccharidoses
  • Neuromuscular disorders
Symptoms of OSAS

- Habitual snoring (3 nights/week)
- Laboured breathing during sleep
- Gasps/observed episodes of apnoea
- Sleep enuresis
- Sleeping in a seated position or with the neck hyperextended
- Cyanosis
- Headaches on awakening
- Daytime sleepiness
- Attention deficit/hyperactivity disorder
- Learning problems
Signs of OSAS

- Tonsillar hypertrophy
- Adenoidal facies
- Micrognathia
- Retrognathia
- High-arched palate
- Underweight or overweight
- Failure to thrive
- Hypertension
OSAS- polysomnography

- American Academy of Sleep Medicine
- 90% drop in the signal amplitude of airflow
  - compared with the pre-event baseline amplitude
- Continued chest wall and abdominal movement
- For a duration of at least two breaths
Central apnoeas

- Absence of inspiratory effort throughout the event and at least one of the following conditions is met:
  - the event is 20 s in duration
  - the event is associated with an arousal
  - 3% oxygen desaturation
  - Bradycardia in infants <1 year of age
Central apnoeas

- Associated with impaired cardiorespiratory control
  - brainstem stroke or compression
  - syringobulbia
  - Chiari malformation
  - high cervical spinal cord injuries
  - encephalitis
  - autonomic disorders such as Rett syndrome and familial dysautonomia

- Apnoea of prematurity
Apnoea of prematurity

- Physiological immaturity of respiratory control
- Incidence inversely correlated with gestational age and birth weight
- Paradoxical breathing with a less stable baseline oxygen saturation in REM sleep
- Apnoeas occur more frequently in REM sleep than in quiet sleep
- Exacerbated by diseases such as infections, intracranial haemorrhage, hypoxic–ischaemic encephalopathy, seizures, patent ductus arteriosus, and glucose or electrolyte imbalances
Complications of sleep apnoea

- Cardiac
  - Pulmonary hypertension, systemic hypertension, cardiac arrhythmias

- Neurological
  - Hypoxic cerebral injury, seizures

- Growth
  - Failure to thrive

- Systemic
  - Daytime sleepiness, neurocognitive impairment, behavioural problems
Management of sleep apnoea

- Surgery - adenotonsillectomy
- Orthodontic therapy
- Supplementary oxygen
- Caffeine (apnoea of prematurity)
- Mechanical ventilation - CPAP/BiPAP
  - Facemasks
  - Tracheostomy
In summary

- Discussed about antibiotic overuse and antibiotic resistance
- Highlighted the increasing prevalence of atopic diseases, and their associations with asthma
- Outlined the physiology of sleep, and the aetiology of sleep disorders
I hope you did not sleep...

Thank you for listening!


