Emerging issues in Paediatric Respiratory Medicine

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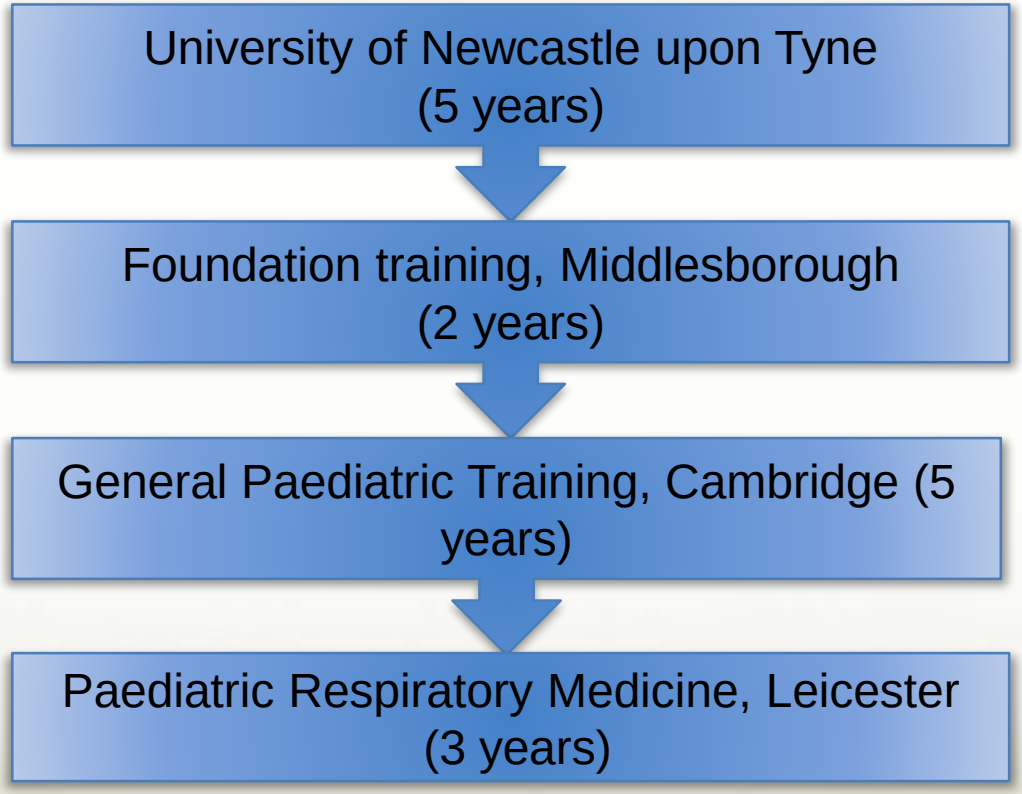
My career path



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

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Antibiotic resistance rise continues

By James Gallagher
Health editor, BBC News website

10 October 2014 | Health

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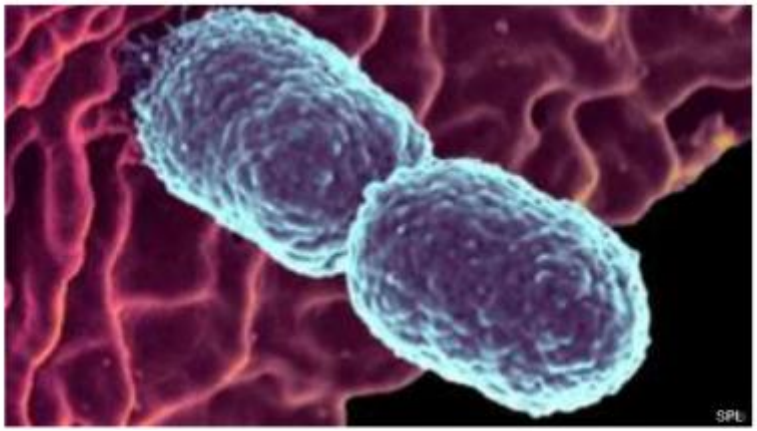

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Antibiotics are losing effectiveness in every country, says WHO

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

Mail Online

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. pneumonia*

Bacterial respiratory pathogens

Most prevalent

- Streptococcus *pneumoniae*
- Mycoplasma *pneumoniae*

Less prevalent

- Staphylococcus *aureus*
- Moraxella *catarrhalis*
- Group A *streptococci*
- Streptococcus *milleri*
- Haemophilus *influenzae*

Antibiotic resistance

Fundamental mechanisms

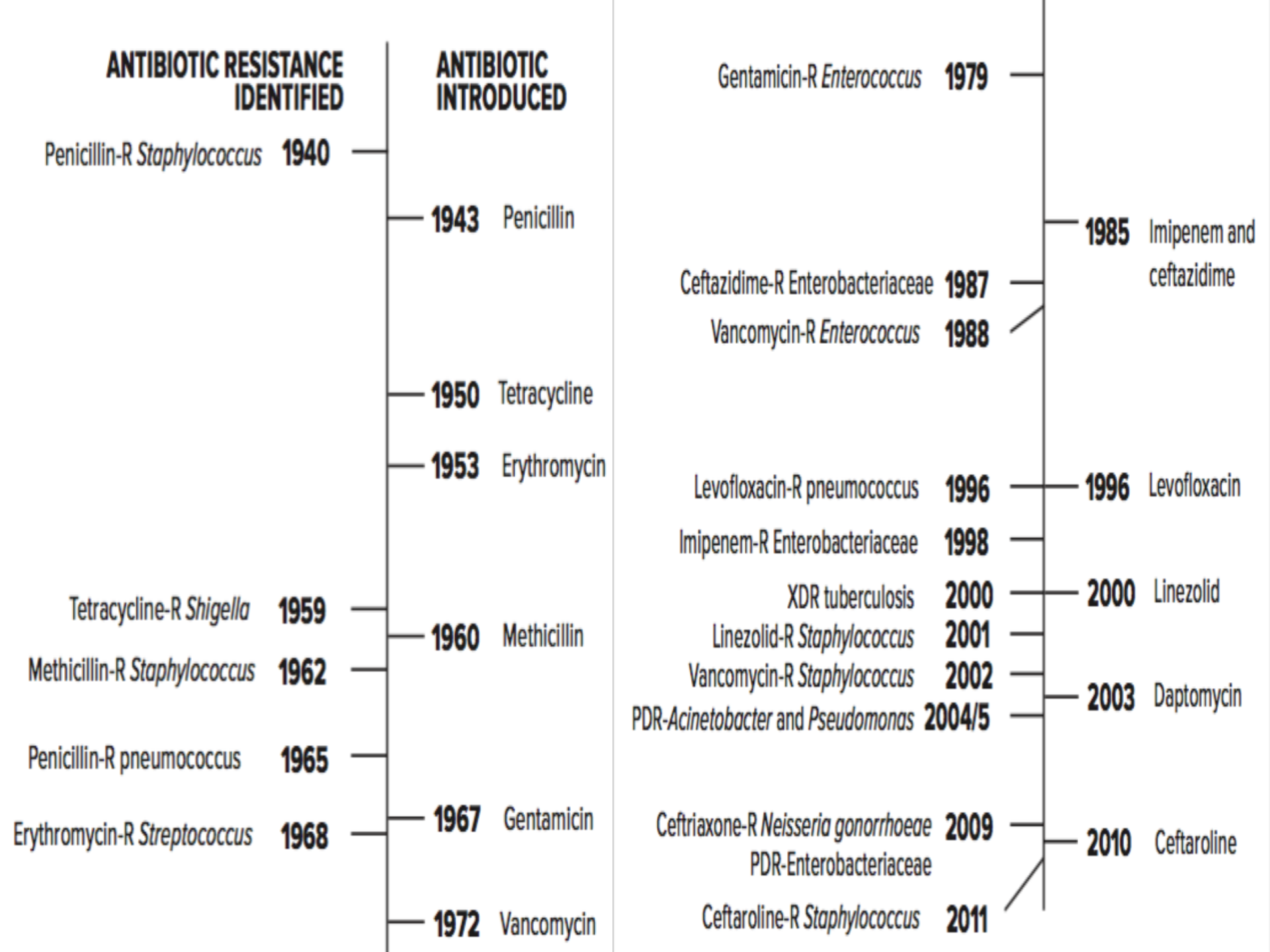
1. Enzymatic degradation of antibacterial drugs
2. Alteration of bacterial proteins that are antimicrobial targets
3. Changes in membrane permeability to antibiotics

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


ANTIBIOTIC RESISTANCE IDENTIFIED
ANTIBIOTIC INTRODUCED
Penicillin-R Staphylococcus 1940
1943 Penicillin
1950 Tetracycline
1953 Erythromycin
Tetracycline-R Shigella 1959
1960 Methicillin
Methicillin-R Staphylococcus 1962
Penicillin-R pneumococcus 1965
Erythromycin-R Streptococcus 1968
1967 Gentamicin
1972 Vancomycin
Gentamicin-R Enterococcus 1979
1985 Imipenem and ceftazidime
Ceftazidime-R Enterobacteriaceae 1987
Vancomycin-R Enterococcus 1988
Levofloxacin-R pneumococcus 1996
1996 Levofloxacin
Imipenem-R Enterobacteriaceae 1998
XDR tuberculosis 2000
2000 Linezolid
Linezolid-R Staphylococcus 2001
Vancomycin-R Staphylococcus 2002
2003 Daptomycin
PDR-Acinetobacter and Pseudomonas 2004/5
Ceftriaxone-R Neisseria gonorrhoeae 2009
PDR-Enterobacteriaceae
2010 Ceftaroline
Ceftaroline-R Staphylococcus 2011

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

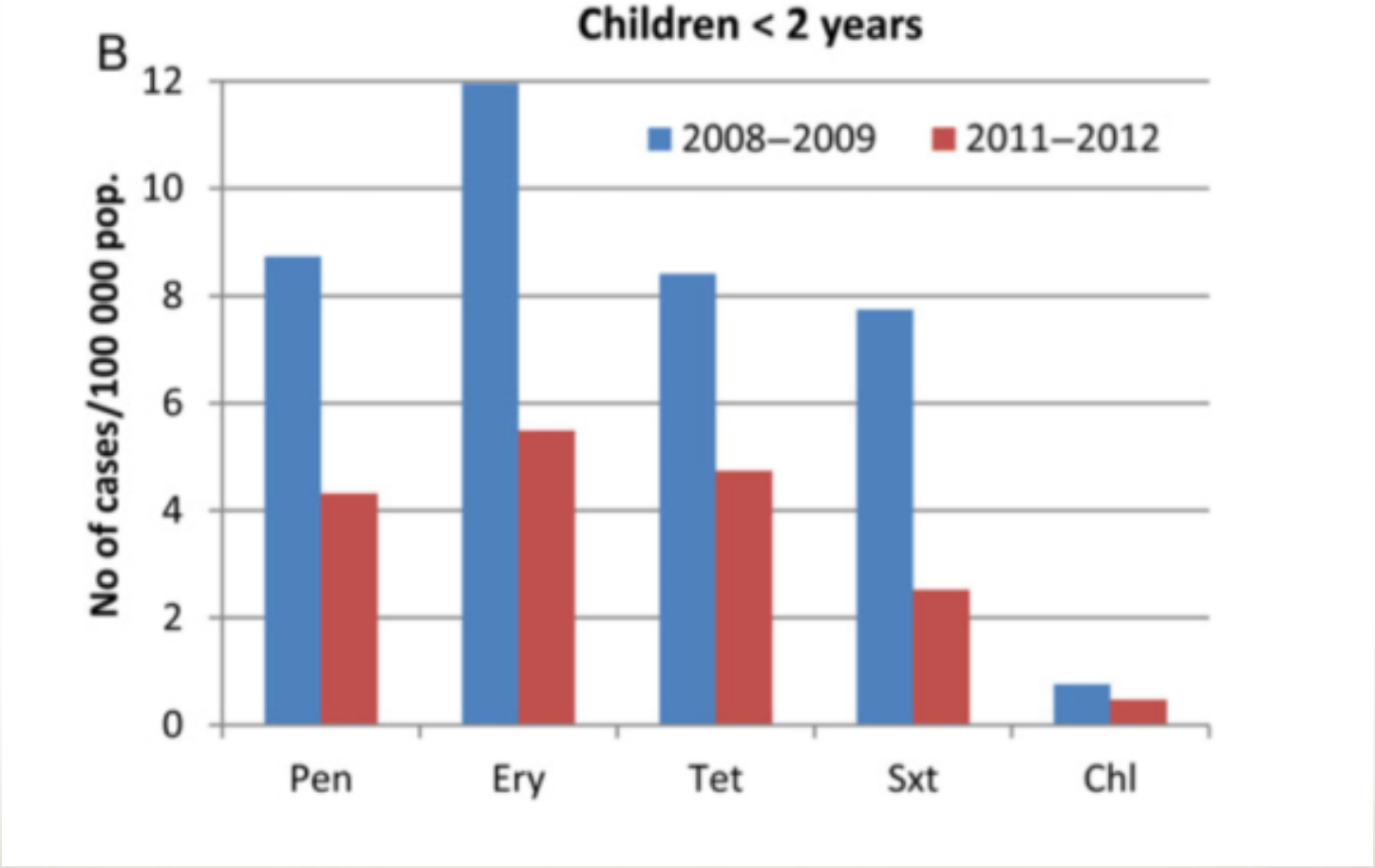
- No clinical benefits of low-doses azithromycin after one year of treatment in CF *(Samson, 2016)*
  - Selection for macrolide-resistant strains of bacteria occurred

- 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)

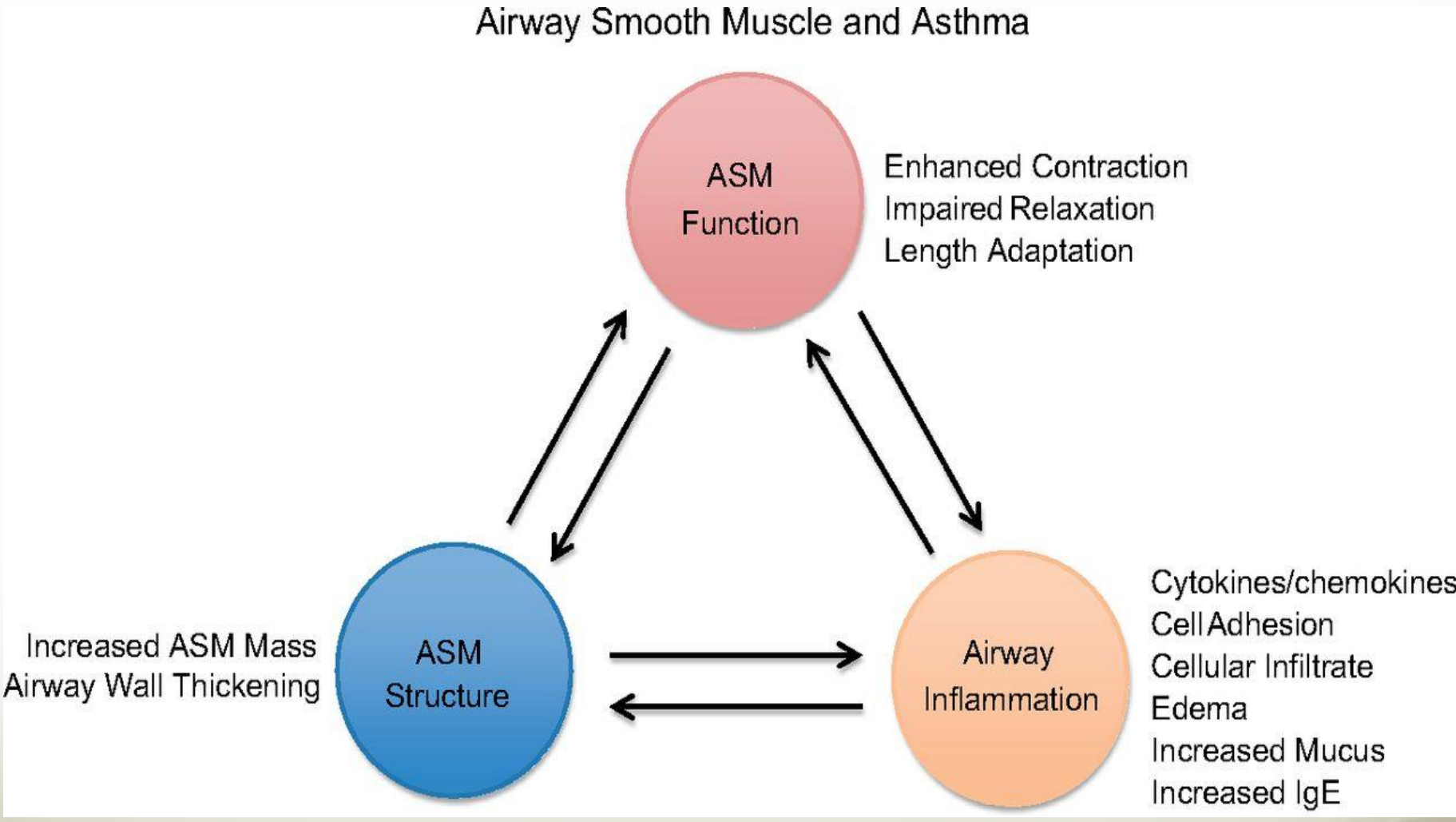
- Alteration in its pharmacological reactivity
  - increase in contraction or a decrease in relaxation
  - inflammatory mediators and cytokines

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

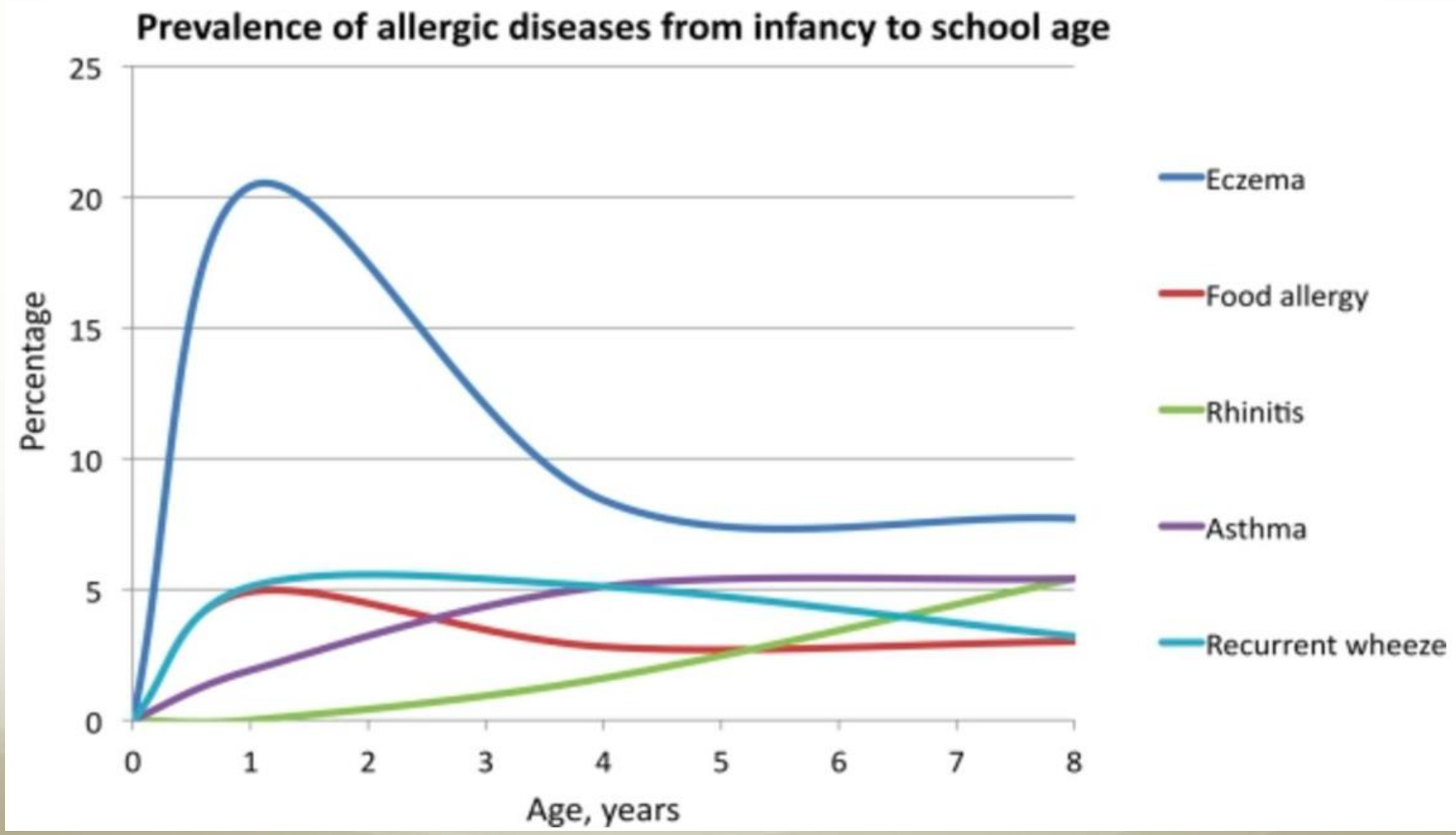

Airway Smooth Muscle and Asthma
ASM Function
Enhanced Contraction
Impaired Relaxation
Length Adaptation
Increased ASM Mass
Airway Wall Thickening
ASM Structure
Airway Inflammation
Cytokines/chemokines
Cell Adhesion
Cellular Infiltrate
Edema
Increased Mucus
Increased IgE

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

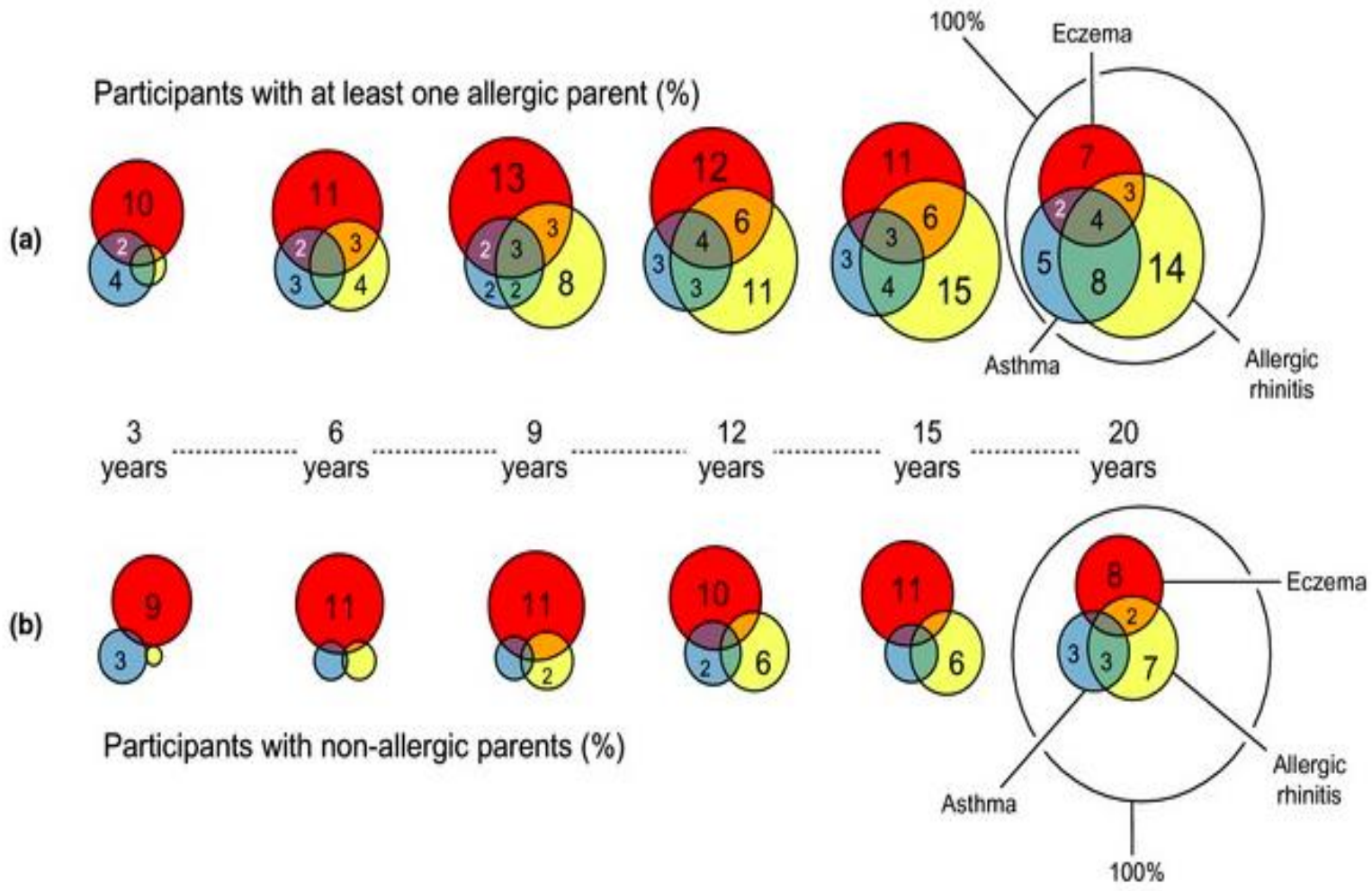
- Males-
  - an earlier age of presentation with asthma
  - higher prevalence of asthma in pre- and peri-pubertal males than females
- Due to a smaller peripheral airway calibre before puberty and an increased prevalence of atopy
- Later in childhood and towards puberty
  - gradual shift to an increased 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
  - Polysomonography(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!

References

- Bacharier LB,Guilbert TW,Mauger DT,et al. Early administration of azithromycin and prevention of severe lower respiratory tract illnesses in preschool children with a history of such illnesses: a randomized clinical trial. *JAMA.* 2015. doi:10.1001/jama.2015.13896.

- Flasche S, Van Hoek AJ, Sheasby E, Waight P, Andrews N, Sheppard C, et al. Effect of pneumococcal conjugate vaccination on serotype-specific carriage and invasive disease in England: a cross-sectional study. *PLoS Med.* 2011;*8*: e1001017.

- Gough H., Grabenhenrich L., Reich A., et al. Allergic multimorbidity of asthma, rhinitis and eczema over 20 years in the German birth cohort MAS. Pediatric Allergy and Immunology. 2015;26(5):431–437. doi: 10.1111/pai.12410.

- Gur M, Hakim F, Bentur L. Better understanding of childhood asthma, towards primary prevention – are we there yet? Consideration of pertinent literature. F1000Research. 2017;6:2152. doi:10.12688/f1000research.11601.1.

- Iber C, et al. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. Westchester, American Academy of Sleep Medicine, 2007.

- Janoir C, Lepoutre A, Gutmann L, Varon E. Insight Into Resistance Phenotypes of Emergent Non 13-valent Pneumococcal Conjugate Vaccine Type Pneumococci Isolated From Invasive Disease After 13-valent Pneumococcal Conjugate Vaccine Implementation in France. *Open Forum Infect Dis.* 2016 Feb 2;3(1):ofw020. doi:10.1093/ofid/ofw020.

- McCullers JA. Insights into the interaction between influenza virus and pneumococcus. *Clin Microbiol Rev.* 2006;19(3):571–82. doi: 10.1128/CMR.00058-05.