Respiratory

(Med I, Block 3, RS)
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Objectives:

1. To understand the pattern of normal lung development.
2. To recognize the embryological basis for certain congenital respiratory abnormalities encountered in infants and adults.
3. Order appropriate investigations to confirm the clinical diagnosis.
4. Outline a rational plan of management.

Reading:


1. **Normal development and growth of the lung**

   **I. EMBRYONIC DEVELOPMENT: first 5 weeks**

   A. Differentiation of ventral wall of embryonic foregut (~day 26)
   
   i. Mesodermal specification of respiratory endodermal morphogenesis
   
   ii. Formation of laryngotracheal groove and diverticulum

   B. Differentiation of laryngotracheal diverticulum
   
   i. Formation and division of lung bud
   
   ii. Separation from esophagus
   
   iii. Formation of larynx and trachea

   C. Development of bronchi
   
   i. Formation of primary - main (days 26-28), secondary - lobar (days 28-34), and tertiary - segmental bronchi
   
   ii. Organization of bronchopulmonary segments

   D. Development of pleural cavities
   
   i. Growth of lung buds into pericardioperitoneal canals
   
   ii. Extension ventrally into somatic mesoderm
   
   a. Formation of pleuropéricardial membranes with enclosed common cardinal veins and phrenic nerves
   
   b. Formation of thoracic wall
   
   iii. Division of pleural and pericardial cavities
   
   a. Fusion of pleuropéricardial membranes with mesoderm ventral to trachea and esophagus
   
   b. Formation of fibrous pericardium
   
   iv. Division of pleural and peritoneal cavities
   
   a. Formation of pleuropéritoneal membranes
   
   b. Closure of pleuropéritoneal opening
   
   v. Composite formation of diaphragm: (1) septum transversum, (2) pleuropéritoneal membranes, (3) dorsal mesentery of esophagus and (4) lateral body walls
II. FETAL DEVELOPMENT

A. Pseudoglandular period *weeks 5 - 17*
   i. Formation of "glandular" tubular airways - 65-75% of all bronchial branching has occurred by 10th-14th week
   ii. Completion of airway branching to terminal bronchioles

B. Canalicular period *weeks 13 - 25*
   i. Formation and capillary invasion of respiratory bronchioles and terminal sacs
   ii. Differentiation of epithelium and production of surfactant

C. Terminal sac period *weeks 24 - birth*
   i. Proliferation of terminal sacs (primordial alveoli) and capillary network
   ii. Differentiation of alveolar epithelium - Type I and Type II pneumocytes
   iii. Secretion of surfactant by Type II pneumocytes sufficient to permit survival of premature infant at ~25 weeks

III. POSTNATAL DEVELOPMENT

A. Alveolar period *birth - year 8*
   i. Respiratory bronchioles, terminal sacs, alveolar ducts and alveoli increase in number
      a. More than 85% of alveoli are formed after birth
      b. Lung volume increases about 23 times between birth and adulthood
      c. Pulmonary capillary network grows more than 20 times in surface area; more than 35 times in volume
      d. Gas exchange surface area increases linearly with body weight

2. Developmental Abnormalities - examples

I. Tracheoesophageal Fistula (TEF)

A. Most common anomaly of lower respiratory tract
B. ~1: 3000-4500 live births
C. Males > females
D. A result of incomplete division of cranial part of foregut into respiratory and esophageal parts during 4th week
E. Abnormal communication between trachea and esophagus can result from incomplete fusion of the tracheoesophageal folds
F. Four types of congenital TEF - in 90%, there is a proximal blind-ending esophagus and usually a connection between the distal esophagus and the trachea
G. Polyhydramnios often associated
H.
II. **Tracheal stenosis (narrowing) and atresia (obstruction) [uncommon]**
   A. Usually associated with TEF
   B. Sometimes there is a web of tissue obstructing airflow

III. **Tracheal diverticulum [extremely rare]**
   A. A blind, bronchus-like projection from the trachea
   B. Outgrowth may terminate in normal lung tissue resulting in a tracheal lobe of the lung

IV. **Pulmonary hypoplasia and oligohydramnios**
   A. Fluid in the lungs stimulates lung development
   B. Insufficient amniotic fluid (oligohydramnios) can retard lung development

V. **Lobe of Azygos Vein**
   A. Appears in right lung in ~1% of people

VI. **Congenital Lung Cysts**
   A. Dilatation of terminal bronchi form cysts, which can be filled with fluid or air
   B. Presence of several cysts give a honeycomb appearance on CXR
   C. Usually at the lung periphery

VII. **Unilateral pulmonary agenesis**
   A. Failure of a bronchial bud to develop
   B. Heart and other mediastinal structures are shifted to the affected side
   C. Existing lung is hyperexpanded

VIII. **Lung Hypoplasia**
   A. Associated with *congenital diaphragmatic hernia* or congenital heart disease
   B. The lung is unable to develop because of compression by the abnormally placed abdominal viscera
   C. Markedly reduced lung volume causes pulmonary insufficiency which may be incompatible with life

IX. **Pulmonary Sequestration [very uncommon]**
   A. Small accessory lung
   B. Usually at the base of the left lung
   C. Does not communicate with the tracheobronchial tree
   D. Blood supply is from systemic circulation instead of pulmonary
Case Discussions:

I. A woman is 36 weeks pregnant with her first child. Recently she has noticed rhythmic spasms of her abdomen that can last for several minutes at a time. She states these are different from the kicking movements of her baby. She tells you that she is worried that her baby is having convulsions.

A. What do you tell her?

II. Within the first 2 hours of life, a full term baby infant experiences severe respiratory distress. An x-ray of the chest/abdomen reveals coils of air-filled small bowel in the left hemithorax

A. What is the congenital problem?
B. What is the embryological abnormality?
C. What are the associated developmental problems?
D. How can you screen for this problem prenatally?
E. The parents would like to have more children. Is any counseling required?

III. A 24-year-old man with a suspected diagnosis of asthma complains of increasing cough when drinking and eating. He denies symptoms of gastroesophageal reflux and stomach ulcer. Pulmonary function studies show no airflow obstruction, normal lung volumes, normal gas transfer and a negative methacholine challenge.

A. What developmental abnormality might account for this patient's symptoms?
B. How would you investigate this problem?
C. What other symptoms might he have?
D. What pulmonary complications could he develop if untreated?
E. What are some acquired causes of this problem?

IV. An 18-year-old woman is admitted to hospital with recurrent left lower lobe pneumonia. She has had 2 previous episodes of pneumonia in the same location during the past 6 months.

A. What developmental abnormality might account for this recurrence?
B. What is the differential diagnosis?
C. What investigations will you order?
D. What treatment will help prevent another recurrence?
Objectives:

1. Describe the characteristics of fetal breathing
2. Describe the characteristics and the mechanisms of secretion and clearance of fetal lung fluid
3. Demonstrate understanding of the mechanics of the first post-natal breaths
4. Describe the events and the circulatory adjustments associated with the transition to extrauterine circulation

Introduction:

It is well known now that during fetal life the placenta and not the lungs serves as the organ for gas exchange. Because of this, the normal fetal circulatory pattern is arranged very differently from that observed after birth and is quite satisfactory for survival in the womb. The transition from the placenta to the lungs at birth is accomplished by three main cardiopulmonary processes: 1. Onset of breathing, resulting in lung expansion with concomitant decrease in pulmonary vascular resistance and increase pulmonary blood flow; 2. Increase blood oxygen content that further decreases pulmonary vascular resistance; and 3. Loss of the placental circulation with resultant increase in systemic vascular resistance leading to the closure of the fetal cardiovascular shunts and transition from fetal to neonatal circulation. Thus, to establish the lungs as the site of gas exchange after birth, significant changes in the cardiac and pulmonary circulation as well as the initiation of pulmonary ventilation must occur. Many abnormal maternal, placental and fetal conditions may interfere with this physiologic transition and compromise the newborn infant.

The establishment of effective pulmonary ventilation at birth requires that the lungs develop to a stage where the alveoli can be inflated to provide adequate gas exchange. It also requires the lowering of the pulmonary vascular resistance to allow for the increase in pulmonary blood flow to accommodate the entire cardiac output. The successful transition also requires that the lung liquid volume be removed from the alveolar spaces and that surfactant material be secreted into the acinus to allow for satisfactory physical expansion of the lungs after the initial postnatal breaths. Adequate neurologic drive to generate and maintain spontaneous continuous breathing is essential to maintain ventilation postnatally.

Respiratory Adaptation:

Fetal Breathing

Although of unknown purpose, since no gas exchange is involved, fetal breathing may represent preparation in utero for a vital function important in life.

The discovery of fetal breathing in the late 60's not only stimulated the development of the area of fetal assessment but it also brought a new dimension to the events occurring at birth. What has been traditionally called "the initiation of breathing at birth" must now be called "the establishment of continuous breathing at birth". Breathing begins long before birth. Fetal breathing is episodic in late gestation, primarily occurring during periods of low-voltage electrocortical activity (equivalent to REM sleep). During high-voltage electrocortical activity (equivalent to quiet sleep) there is no established breathing present.
Characteristics of fetal breathing movements:
1. normal feature of intrauterine life present in about 40% of the time during late pregnancy
2. occur almost exclusively during low-voltage electrocortical activity (REM sleep)
3. are important for lung development
4. are sensitive to variations in PaCO2, PaO2, and pH
5. are inhibited by hypoxia, adenosine, prostaglandins, GABA, opioids, and hypoglycemia
6. are stimulated by high PaCO2 and high PaO2, by cord occlusion, hyperglycemia, and indomethacin

II. Establishment of Continuous Breathing at Birth

So the question now is not what determines the appearance of breathing at birth, but what makes it continuous. From another angle, what makes fetal breathing episodic in late gestation and present only during low-voltage electrocortical activity? The answer to this question remains unknown. Although many stimuli interact to trigger the first breath (sound, air, gravity, light, temperature, etc.), the physiologic mechanisms responsible for the switch from episodic to continuous breathing at birth remains unknown. It has been debated whether the key factors in inducing these changes are intrinsic to the fetal brain or are in the placenta. Because placental separation at birth is associated with the onset of continuous breathing, many authors have hypothesized that placental factors might be responsible for the inhibition of fetal breathing. This is supported by experiments in fetal sheep showing that umbilical cord occlusion induces continuous breathing and wakefulness in utero as long as hypoxia is prevented by ventilating the fetal lungs. Breathing becomes intermittent immediately upon release of the umbilical cord. These experiments suggest the origin in the placenta of a compound which inhibits fetal breathing and fetal activity.

Pulmonary Adaptation:

a. Secretion of fetal lung fluid

During fetal life, the internal volume of the lungs is maintained by the secretion of liquid into the pulmonary lumen. This liquid expansion of potential air spaces is essential for the growth and the development of normal lung structure before birth, which in turn may influence lung function after birth.

We know now that the fetal lung fluid is neither a mere ultrafiltrate of plasma nor aspirated amniotic fluid. Compared to plasma this lung fluid is rich in chloride and potassium, is significantly lower in bicarbonate and has similar sodium concentration. It is also quite different from amniotic fluid having much higher osmolality, Na+ and Cl- concentrations, and significantly lower K+ and protein concentration. The high Cl- and the low protein content characteristics of the lung fluid result from active Cl- secretion and tight junctions between epithelial cells respectively. In fetal lambs, the volume of lung liquid increases from about 5ml/kg of body weight at mid-gestation to about 30 to 50 ml/kg at term.

This liquid secreted by the fetal lungs flows intermittently up the trachea with fetal breathing movements. Some of this fluid is swallowed and the remainder contributes directly to the formation of amniotic fluid production accounting for approximately 25 to 50% of the amniotic fluid turnover in the sheep fetus, with the rest being formed by the fetal urine. The larynx acts as a one-way valve preventing amniotic fluid to be aspirated into the lungs. The continuous secretion of liquid by the lungs creates an important positive intrapulmonary pressure, which is essential for normal growth and for the structural and biochemical maturation of the developing
lung. Thus, unimpeded leakage of tracheal liquid decreases lung size by arresting pulmonary tissue growth whereas prolonged obstruction of tracheal outflow leads to lung hyperplasia. Pulmonary hypoplasia in humans can be observed in pathological conditions such as diaphragmatic hernia, pleural effusion, or severe oligohydramnios (Potter’s syndrome) as a result of the compression of the fetal lungs and the decrease in their internal volume. Pulmonary hypoplasia in fetal sheep can be considerably improved by short-term obstruction at the tracheal level.

The production of fetal lung liquid depends on a system of active ion transport across the alveolar type II cells of the pulmonary epithelium. Lung liquid secretion is coupled with active transport of Cl- toward the pulmonary lumen, generating an electrical potential difference of -5mV (lumen negative). This chloride secretion generates an osmotic gradient that causes liquid to flow from the microcirculation through the interstitium into the potential air spaces. This chloride secretion occurs through chloride channels in the apical membrane (alveolar side) and depends largely on chloride influx at the Na+ -K+ -2Cl- (NKCC) cotransporter system in the basolateral membrane (interstitial side). Thus, Cl- enters the cell on a cotransporter linked with K+ and Na+ down the electrochemical potential gradient for Na+ generated by Na+ -K+ -ATPase in the basolateral membrane of the cell. Consequently, Cl- concentration increases inside the cell, above its equilibrium potential, which provides an electrochemical gradient for Cl- exit across the luminal membrane of the epithelial cell through Cl- permeant ion channels.

b. Clearance of lung fluid at birth

Pulmonary fluid, essential to fetal lung development, must be rapidly removed at birth in order to allow adequate postnatal gas exchange. Thus the transition from intra to extrauterine life requires the effective clearance of lung liquid to support air breathing and the conversion of the pulmonary epithelium in the distal air spaces from fluid secretion to fluid absorption. Disruption of this process has been implicated in several disease states, including transient tachypnea of the newborn (TTN) and hyaline membrane disease (HMD). Preterm delivery and cesarean section without prior labor result in excessive retention of lung fluid and may contribute to respiratory compromise in the newborn infant.

It is clear now that the traditional explanations for fluid reabsorption which relied on Starling forces, lymphatic uptake and vaginal squeeze at the time of birth, can only account for a very small fraction of the lung fluid clearance. The primary mechanism of lung liquid reabsorption is the change in ion transport induced by catecholamines during labor. Although the mechanisms responsible for lung liquid clearance at birth develop gradually during the last part of pregnancy, the removal of lung liquid and the switch from fluid secretion to fluid absorption, triggered by events at birth, are probably quite rapid because in the human the functional residual capacity (FRC) of the lungs rises to a near normal value of 25 to 30 ml/kg within 15 minutes after normal delivery. Thus, the vast bulk (>75%) of this liquid leaves the lung some time before normal term birth. This rapid decline in lung fluid volume occurs within labor and is mainly due to active reabsorption of fluid driven by active Na+ transport through the pulmonary epithelium. This process is stimulated by the catecholamine surge which occurs just before the onset of labor.

As explained before, chloride secretion across the distal lung epithelium results in the production of lung liquid which is necessary for proper lung development in fetal life. In contrast, sodium absorption allows for fluid reabsorption and is critical for efficient oxygenation in the newborn. This movement of sodium from the alveolar lumen to the interstitium with subsequent absorption into the vasculature can be considered a two-step process. In the first step sodium passively enters the apical membrane of the alveolar type II cell, through Na+ channels (ENaC). In the second step, sodium is actively pumped out of the cell into the interstitium through the
basolateral membrane by the Na⁺-K⁺-ATPase pump. To equilibrate the osmotic pressure, generated by the movement of Na⁺, water diffuses from the alveolar to the interstitial space either through specific water channels (aquaporins) or through the paracellular junctions.

At birth, epinephrine, oxygen, glucocorticoid and thyroid hormones interact to produce a permanent switch from secretion to absorption in the distal epithelium. Beside the switch from Cl⁻ secretion to sodium absorption, other passive factors play a role in clearing the residual liquid present in potential air spaces at birth. The first is transient and peaks early and relates to enlarged transepithelial pores produced by expansion of the lungs. This causes passive reabsorption down the transpulmonary pressure gradient, shifting residual liquid from the lung lumen into the interstitium around distensible perivascular spaces of large pulmonary blood vessels and airways. The second mechanism, is the transvascular protein gradient that facilitates the movement of fluid from the essentially protein-free lung fluid into the interstitium followed by passage of liquid into the bloodstream.

**Mechanics of the first postnatal breaths:**

Although the neural and chemical control mechanisms responsible for establishment of continuous breathing at birth are not completely understood, the mechanical processes responsible for inflating the lungs at birth are known in some detail.

Sufficient force (opening pressure) must be generated across the lungs with the first inspiration to overcome the viscosity of the fluid in the airways as well as the forces of surface tension and tissue resistance. The findings of a negative intra-pulmonary pressure near the end of labor may in part explain reports that the first inspiration in human infants does not require diaphragmatic contraction. The elastic recoil of the chest wall after delivery would tend to rebound to the resting position causing a small passive inspiration of air.

A pressure of about 60 cm H₂O is required to make this fluid flow through the airways with the first inspiration. However, a much higher opening pressure would be needed to overcome the high surface tension forces if the airways were not partially distended with this fluid. According to the Laplace equation for a cylinder state, the pressure required to overcome surface tension is directly proportional to the surface tension and indirectly proportional to the radius of curvature (P⁺t/r). If the airways were not partially distended by liquid, the opening pressure in the terminal airway would be very large because of the small radius of curvature. Thus, the normal fluid content of the lung at birth facilitates the first breath by lowering the opening pressure, and ensuring a more homogeneous filling of the lung with air.

The opening pressure of the lungs at birth also depends on the compliance of the alveolar tissue and the surface forces at air-fluid interface. During labor and birth, a massive release of surfactant in pulmonary fluid facilitates lung opening by lowering the opening pressure through the decrease in surface forces and the improvement of lung compliance. Thus, the first postnatal breath begins with no air volume in the lungs and no transpulmonary pressure gradient. As the chest wall expands, the transpulmonary pressure increases until it overcomes the surface tension of small airways and alveoli. At this point, actively inspired air begins to enter the lungs and according to the Laplace equation, as the radius increases, the distending pressure required to open up those units decreases.

Although the first inspiratory effort is extremely important for lung opening, the creation of FRC at the end of the first expiratory effort is essential for the normal pulmonary adaptation at birth. It is obvious that if all the air that entered the lung were to leave the lung, every breath would necessarily resemble the first breath. This FRC can only be created if the pulmonary surfactant is
present allowing for the stabilization of the peripheral air spaces. The near-zero surface tension and the bubble formation produced by surfactant allows for retention of large volumes of air at the end of the first expiration. When surfactant is deficient the consequences are a tendency to airlessness with each expiration and the application of high inspiratory pressures to maintain respiration. This leads to the marked retractions so commonly associated with atelectasis and HMD as seen in preterm infants with surfactant deficiency. Thus under normal conditions, the amount of air exhaled after the first breath is less than the inhaled volume representing the formation of the FRC. This FRC continues rising from about 10 ml/kg at birth to 30 ml/kg by the second day of life.

**Circulatory Adaptation:**

1. **Fetal circulation**

A combination of preferential flow and streaming through structural shunts in the liver (ductus venosus) and heart (foramen ovale and ductus arteriosus), allows the highest oxygen content blood coming from the placenta to be delivered to the heart, brain and upper torso. This relative parallel flow contrasts with the flow in series and without shunts of the adult circulation. Thus, the volume of blood in the fetal heart ventricles is not equal, with the right ventricle ejecting approximately two thirds of total fetal cardiac output (300 ml/kg/minute), whereas the left ventricle ejects only about one third (150 ml/kg/minute).

Placenta blood is delivered to the fetus through the umbilical vein. This umbilical blood flow passes through the ductus venosus directly into the inferior vena cava and mixes with the systemic venous drainage from the lower body. This highly oxygenated blood is directed across the foramen ovale into the left atrium and then the left ventricle and ascending aorta. The poorly oxygenated blood from the superior vena cava (which drains the head and upper body) and the coronary sinus (which delivers venous return from the myocardium) at the right atrium, is directed through the tricuspid valve into the right ventricle.

Since the placenta is responsible for gas exchange in utero, very little blood flow is sent to the lungs. The pulmonary circulation is a high-resistance, low-flow circuit that receives less than 10% of the ventricular output. Instead of entering the pulmonary arteries, most of the right ventricular blood is diverted away from the lungs through the widely patent ductus arteriosus to the descending aorta, reaching the placenta for oxygenation through the umbilical arteries. The high pulmonary resistance observed during fetal life is related to the mechanical compression of pulmonary vessels by the fluid-filled, atelectatic lungs and also by active vasoconstriction mainly maintained by the low fetal arterial PO₂.

The well-oxygenated blood coming across the foramen ovale joins the small amount of blood returning from the lungs via the pulmonary veins in the left atrium and traverses the mitral valve into the left ventricle. This blood is then ejected across the aortic valve into the ascending aorta bringing well-oxygenated blood to the myocardium, brain, and upper torso.

2. **Transition to extraterine circulation**

At birth, a number of complex events must take place so that the fetal circulation that depends on the placenta for gas exchange and intracardiac and extracardiac shunts to deliver oxygenated blood to the heart and brain, switch to the neonatal circulation in which the gas exchange is transferred to the lungs and the fetal shunts are eliminated. A rapid and sustained decrease in pulmonary vascular resistance during the first breaths facilitate this adaptation. Although this normal pulmonary vascular transition occurs spontaneously and quickly in most neonates, failure
of the pulmonary circulation to undergo this changes results in persistent pulmonary hypertension of the newborn (PPHN). This condition, which carries significant morbidity and mortality, develops when the pulmonary vascular resistance fails to decrease adequately during the transition to extrauterine life. Altered intrauterine environment producing structural changes in the pulmonary circulation or hypoxemia, acidosis and/or hypercarbia secondary to meconium aspiration, surfactant deficiency, or pneumonia abnormally constrict the pulmonary circulation at birth. In PPHN, right to left shunts at the atrial and ductus arteriosus levels continue secondary to the high pulmonary vascular resistance, producing significant hypoxemia which in turns causes more pulmonary vasoconstriction. Thus, two major hemodynamic events must occur at delivery to allow for a normal transition from fetal to neonatal circulation.

**A. Pulmonary vasodilatation:** At birth, pulmonary arterial blood flow increases 8 to 10 fold and pulmonary vascular resistance (PVR) decreases by 50% within the first 24 hours, as the lung assumes the function of gas exchange. This decrease in PVR is brought about by active vasodilation which is triggered by a number of birth-related stimuli. Three main factors contribute to the increase in pulmonary blood flow during this transition: 1. ventilation of the lungs, 2. increased oxygenation, and 3. hemodynamic forces, such as increased shear stress. The effects of these factors on pulmonary circulation at birth appears to be mediated primarily by the release of nitric oxide from the vascular endothelium.

**B. Loss of the placental circulation and closure of the fetal shunts:** The removal of the low-resistance vascular bed of the placenta produces much of the increase in systemic vascular resistance at birth. Without umbilical venous flow, the constriction of the ductus venosus begins and its closure is complete by the end of the first week of life. The reasons for closure of the foramen ovale after birth are twofold. First, the occlusion of the umbilical cord decreases the volume of blood flowing up the inferior vena cava decreasing the right-left atrial pressure difference. Secondly, the increase in pulmonary venous return to the left atrium in response to the marked increase in pulmonary blood flow increases left atrial pressure. The reverse pressure-difference across the foramen ovale pushes the foramen ovale flap against the atrial septum closing the shunt. The closure of the third fetal shunt, the ductus arteriosus, is triggered by increase oxygenation and the rapid fall in circulating prostaglandins caused by increased lung metabolism (from increased pulmonary blood flow) and the loss of placental prostaglandins. Although functional closure of the ductus arteriosus occurs in the first 72 hours of life, permanent or anatomical closure takes several days and weeks and is achieved by subintimal proliferation and connective tissue formation. When the ductus arteriosus fails to close or reopens in the first days of life, as frequently observed in preterm infants, a significant left to right shunt may occur. The closure of the patent ductus arteriosus effectively separates the pulmonary and systemic circulations and establishes the normal postnatal circulatory pattern.

**Conclusion:** The transition from fetal to neonatal life represents one of the most dynamic and difficult periods in human life cycle. Dramatic neurohormonal, metabolic, and cardiorespiratory adjustments must occur over hours to days around the time of delivery to insure the smooth and successful transition to extrauterine life. These changes are invoked by a variety of processes including perinatal surges in hormones, labor, delivery, gaseous ventilation and oxygenation of the lungs, cord occlusion and decrease in environmental temperature. This transitional period is characterized by removal of the lung liquid volume from the alveolar spaces and by the secretion of surfactant material into the acinus for satisfactory physical expansion of the lungs after the initial postnatal breaths. To maintain adequate ventilation and oxygenation the newborn infant must also switch from intermittent fetal breathing to continuous breathing at birth. The switch from placental to pulmonary gas exchange also requires the elimination of the fetal shunts and a rapid and sustained decrease in pulmonary vascular resistance to allow a significant increase in pulmonary blood flow. Thus, the circulation changes from one characterized by a
relatively low combined ventricular output, right ventricular dominance, and pulmonary vasoconstriction, to a circulation in series with a high cardiac output equally divided between the two ventricles, and a greatly dilated pulmonary vascular bed. Many factors can disrupt this physiologic process causing significant morbidity and mortality.

**Fetal breathing movements (FBM)**

FBM are a normal feature of intrauterine life.

FBM are important for lung development they maintain a high level of lung expansion.

FBM occur in episodes related to fetal CNS activity (e.g., REM sleep).

Normally, there is an efflux of lung liquid during FBM.

Influx of amniotic fluid may occur during vigorous FBM.

FBM are sensitive to variations in PaO$_2$, PaCO$_2$ and pH.

Central chemoreceptors are functional in the fetus.

Nutrient availability can have a major influence on FBM.

Common drugs taken by the mother can greatly affect FBM. Examples: alcohol, narcotics, analgesics, nicotine, caffeine, indomethacin.

Factors that attenuate or abolish FBM over a long time are likely to impair growth and structural maturation of the lungs.

**The first breath**

Many stimuli interact to trigger the first breath; light, sound, air, gravity, temperature.

The role and function of peripheral chemoreceptors at birth is not entirely clear.

Various central nervous system factors are involved:

- Inhibitory impulses from higher centers, neurohumoral substances or neural modulators (e.g., catecholamines, serotonin, opioids, GABA, noradrenaline, adenosine, prostaglandins, hypoxia).

Possibility of inhibitory humoral substances from the mother (placental factor).

**Mechanics of the first breath**

Lung fluid (approx. 30% of TLC, 50 to 100 mL) has to be removed at birth.

Large negative intrapleural pressures are needed to overcome:

1. extremely low compliance of the lung.
2. increased airway resistance from obstructing liquid
3. viscous resistance of the fluid filled airways
4. high surface-tension of the air-liquid interface

**Mechanics of the first breath**

The pleural pressure during the first inspiration may reach - 100 cm H₂O (esophageal pressure - 50 cm H₂O on average)

Large negative pleural pressures persist for several breaths

Compliance of the lung during the first breaths is <1/3 of that in older children

TLC of a full-term infant is 85-90 mL/kg (275 mL for a 3.2 kg infant)

Average tidal volume of the first breath is 40 mL (11 mL/kg)

The volume of the first expiration is considerably less than inspiration, contributing to establish a residual volume

Pressures as high as 124 cm H₂O have been measured during the first expiration (71 cm H₂O on average)

Expiratory duration is highly variable during the first breaths and becomes progressively shorter over the first hour of life

FRC is 15% of final size after the first breath, 40% at 15 min, and approx. 100 mL (30 mL/kg) at 2 days of age

With the first breaths, pulmonary blood flow increases from ~50 mL/kg to 400 mL/kg
Factors: rise in \( \text{PO}_2 \), change in surface tension, vasodilators

**Fetal lung liquid and its removal near birth**

Lung epithelial cells actively produce liquid that is different in composition than plasma or amniotic fluid

The pulmonary circulation (not the bronchial) is the major source of lung liquid

The volume of lung liquid (in the lamb) increases from 4-6 mL/kg at mid-gestation to >20 mL/kg at term

The hourly flow of tracheal liquid increases from ~2 mL/kg at mid-gestation to ~5 mL/kg at term

Transepithelial chloride movement is the major driving force

Before birth, lung liquid decreases to ~6 mL/kg factors: labor, epinephrine, plasma protein, hormones
The distal respiratory tract epithelium switches from chloride secretion to sodium absorption before birth.

Clearance of lung liquid involves transepithelial flow into the interstitium, followed by flow into the bloodstream directly or through lymphatics.

Lung water content does not decrease until ~30 to 60 min after birth. Perivascular fluid cuffs max. at ~30 min, gone by 6 hours.

**Fetal and neonatal pulmonary circulation**

The fetal lung receives <4% of combined ventricular output at mid-gestation, increasing to ~10% at birth.

With the first inspiration, the pulmonary circulation must accommodate the total cardiac output.

The factors that allow this rapid transition at birth are still not fully understood.

The important steps are:

a. Establishment of an air-liquid interface in the alveoli
b. Change in arterial oxygen tension
c. Reduction in arterial CO₂ tension

A variety of endogenous amines and peptides influence the pulmonary circulation, e.g., histamine, bradykinin, angiotensin II.

Other mediators currently under study are endothelins, eicosanoids and endothelium-derived nitric oxide.
Objectives:
1. Define hyaline membrane disease and its clinical and physiologic presentation.
2. Outline the major differential diagnosis.
3. Outline briefly two or three other pulmonary disorders that may not be part of the differential diagnosis of hyaline membrane disease, but, because of the frequency, are relevant clinical problems.

REQUIRED READING*
1. Excerpt from the Neonatal Resuscitation Protocol, Women’s Hospital, “Endotracheal Intubation”
2. Cochrane Library Review “Endotracheal Intubation at Birth for Preventing Morbidity and Mortality in Vigorous, Meconium-stained Infants Born at Term”

CASE 1: Baby AS was born by precipitous vaginal delivery to a 17-year-old gravida 2 para 1 mother at 30 weeks of gestation. Mrs. S. received little prenatal care during pregnancy and had arrived at a hospital in active labor. A physical examination at the time revealed a completely dilated cervix and fully effaced. Delivery occurred within 45 minutes of arrival at the hospital. Apgar scores for this infant were 4 and 7 at one and five minutes respectively. Birth weight was 1400 grams. Shortly after birth the infant started grunting, became somewhat cyanotic, and the respiratory rate was 75.

Questions:
1. What is the most likely diagnosis for this infant?
2. What is the differential diagnosis?
3. How would you investigate this infant?
4. What would be your strategy for management?

CASE 2: This infant was born of a 23-year-old gravida 2 para 1 aborted 1 mother at 41 weeks of gestation. Labor was somewhat slow, with a prolonged second stage. At rupture of the membranes it was noticed that the amniotic fluid was meconium stained. The infant was born with Apgars 1 and 3 at one and five minutes respectively. Birth weight was 3560 grams. Because of poor color the infant needed to be intubated and bagged with 100% oxygen. An umbilical arterial catheter was placed and the arterial blood showed a P02 of 45 mmHg, a PCO2 of 59 mmHg and a pH of 7.22. The baby was then placed on the ventilator and transferred to the Intensive Care Unit.
Questions:

1. What is the most likely diagnosis for this infant?
2. List other important diagnoses to be considered?
3. What laboratory tests would you order at this time?
4. Suppose that the initial work up of this patient reveals the following:

Chest x-ray: Gross patchy infiltrates spread throughout both lungs.

Complete Blood Count: Hemoglobin 154 grams/L,
White blood cell count 10,000/mm³ with normal differential
Platelets - normal

Blood Culture: Pending

What would be your strategy for the management of this infant?

Note: Complete details and a map is provided on the website.

*Important Note: To access the website for the Required Reading, go to:

<http://www.umanitoba.ca/faculties/medicine/education/undergraduate/preclerkship/notes_references.html>

Username is: medguest
Password is: medguest
Objectives:

1. You should become familiar with the most common acute diseases of the upper and lower airways presenting as respiratory emergencies in children.
2. You should understand the etiology, pathogenesis, clinical presentation, diagnosis, treatment, complications, and prognosis of viral laryngotracheitis (croup), epiglottitis, infectious bronchiolitis, and foreign body aspiration.
3. You should gather information on asthma and on pertussis (whooping cough) in infants and young children.

Suggested Reading:

Objectives:

1. Recognize and understand the complexity of diagnosis and management of Cystic Fibrosis, the most common lethal chronic lung disease in children.
2. Outline the long-term effects of congenital and/or neonatal pulmonary disease on lung health in children.

Suggested Reading:


CYSTIC FIBROSIS

Generalized disorder of exocrine glands inherited in an autosomal recessive manner. Multisystem disease with major clinical problems arising from damage to lung and pancreas.

**INCIDENCE:** Approximately 1:2000 to 1:2500 among North American Caucasians, gene frequency about 1 in 20 to 25 (4-5%). Cystic fibrosis gene located on the long arm of chromosome 7. Gene locus responsible for production of CFTR (cystic fibrosis transmembrane conductance regulator), a chloride channel. Deletion of phenylalanine at position 508 (ΔF508) is most common cause of CF in North America but more than 600 different gene defects have been described.

**PATHOPHYSIOLOGY:** Abnormal chemical content or physical properties of exocrine gland secretions. Defective chloride reabsorption in sweat glands causing high sweat NaCl concentrations.

**CLINICAL MANIFESTATIONS:**

Respiratory: Cough, airway obstruction and lung hyperinflation, infections (initial presentation often wrongly diagnosed as viral bronchiolitis, whooping cough or asthma); later - chronic changes, bronchiectasis, particularly severe in upper lobes. Complications are pneumonia, hemoptysis, pneumothorax, atelectasis, acute or chronic respiratory failure.

Cardiovascular: Cor pulmonale.

Gastrointestinal: Obstructive complications (meconium ileus, meconium ileus equivalent, rectal prolapse), pancreatic deficiency (malabsorption, pancreatitis, diabetes), hepatobiliary disease (obstructive jaundice, hepatic steatosis and cirrhosis, cholelithiasis).

Genitourinary: Male infertility in 98% (atresia of vas deferens), female subfertility.

Skin/musculoskeletal: Secondary chest deformities, digital clubbing, increased salt loss in sweat.

**DIAGNOSIS:** Sweat chloride over 60 mEq/l in children, over 70 mEq/l in adults. Pancreatic insufficiency (in about 85% of patients). Meconium ileus (in 5 to 15% of patients). Ancillary
findings (positive family history, aspermia, mucoid strain of Pseudomonas aeruginosa in sputum, radiographic evidence of pansinusitis, nasal polyps).

*TREATMENT:* In North America mainly in specialized centers, involving a team of health professionals. Focus on respiratory system (physiotherapy, inhalations, antibiotics) and gastrointestinal system (enzymes, vitamins, nutritional supplements).

*PROGNOSIS:* Significantly improved, 50% of patients in Canada survive to above 30 years of age.

Objectives

1. Explain the mechanisms underlying the allergen-induced development of acute asthma.
2. Describe the role of chemical mediators of inflammation in the generation of both acute and chronic asthma (and other acute allergic reactions).
3. Explain how nonspecific irritant stimuli may be responsible for aggravation of allergic asthma or may contribute to other clinical forms of asthma.
4. Describe the physiological alterations that occur in acute asthma and the persistence or reversal of such changes in treated asthma.
5. Recognize that the clinical presentation of asthma may vary and may appear in any age group.
6. Itemize the clinical and physiological approach to assessment of the acute asthma attack.
7. Explain the rationale of treatment of acute and chronic asthma.
8. Comment on the importance of supervised long-term follow-up of both acute and chronic asthma.

Definition: A universally accepted definition of asthma does not exist. Asthma is likely not a single disease but a syndrome that may have multiple precipitating mechanisms. The primary abnormality in asthma is reversible airway obstruction. This is related to underlying airway inflammation that is associated with increased mucous production and airway smooth muscle hyperreactivity. There may be overlap between features of asthma and other lung diseases that produce airways obstruction (such as chronic obstructive pulmonary disease), and sometimes it is difficult to categorize patients simply into one group or the other.

Prevalence: The estimated prevalence of asthma is 8.4% in Canada according to the 1998-1999 Population Health Survey. The incidence of asthma is increasing, as is the morbidity and mortality associated with the disease. Between 1982-1992 the annual age-adjusted prevalence of asthma increased by 42% in the United States. This increasing prevalence has been shown in many other countries as well. The cause of this is unclear, but may be related to changes in our environment caused by chemicals, air pollution and other features of industrialized society. At least some of the increase in asthma mortality is probably related to suboptimal treatment of asthma by physicians and patients.

Epidemiology: Asthma may occur at any age, and about 20% of asthmatics will develop their disease after the age of 65. The majority (60%) of children who wheeze in the first three years of life will no longer by the age of six years. These children mostly wheeze with respiratory tract infections in early life and have lower lung function than other infants. Whereas those children who wheeze after age 3-4 years and those who persistently wheeze in childhood, are more likely to be diagnosed with asthma. When asthma begins in childhood, it carries a better prognosis than when it occurs in adults. About one half of childhood asthmatics will “outgrow” their disease by adulthood, and another ¼ will only have minimal symptoms. The ¼ that will have persistent significant symptoms of asthma into adulthood tend to be the group with the most severe disease as children. The pattern of asthma in adulthood appears to parallel the course of asthma in childhood.

Other allergic conditions are associated with a higher, but still low risk of asthma. For example allergic rhinitis (hay fever), following the first year of diagnosis, is associated with about a 5 to 10% lifetime risk of developing asthma. The most common risk factors included gender, airway hyperreactivity, family history, atopy, allergens, infections, tobacco smoke,
obesity, perinatal infections and childhood wheezing. Childhood asthma is much more common in boys, however after adolescence asthma switches to becoming more prevalent in girls. The reasons for this are still unclear. Not all subjects with bronchial hyperreactivity have asthma, however they are at increased risk for developing asthma. Serum IgE level is also closely related to the development of asthma. Indoor allergens such as house dust mite, cat and dog allergen, cockroach allergen and endotoxin play a role in the development of asthma, however studies are still conflicting with regard to the nature of the relationships. Some observational suggest that respiratory infections in early life may prevent allergic diseases later in life, but again these results are controversial. Both active smoking and passive smoking have been associated with asthma and wheezing illnesses. Other factors that have been associated in some studies with an increased risk of asthma include: young maternal age, prematurity, not breastfeeding, obesity, and antibiotic use in early life.

Genetics: Asthma is a complex disease which likely results from the interactions between multiple genetic and environmental factors. Twin studies have shown that asthma is a heritable trait. Linkage analysis studies have shown association of areas on chromosome 5q with the development of asthma. This area of chromosome 5 contains the genes for the beta-2-adrenergic receptor as well as multiple cytokine genes including, interleukin (IL)-4, IL-5, IL-19 and many others. Other areas on chromosome 11q and 12 q have been inconsistently linked to asthma phenotypes. Genetics variations in the beta-2 adrenergic receptor have also yielded differing responses to beta-agonist stimulation in vitro.

Pathology: The narrowing of the airways which lead to reduce airflow can be induced by smooth muscle contraction, thickening of the airway wall and the presence of secretions within the airway lumen. Airway inflammation, cellular infiltration, and subsequent cytokine production are the predominant causes of airway obstruction in asthma. Airway inflammation is a hallmark of asthma. This involves varying degrees of basement membrane thickening, infiltration of eosinophils, desquamation of epithelium, hypertrophy of airway smooth muscle, and mucous plugging of airways. The inflammatory cascade in asthma is incompletely understood, but involves mast cells, eosinophils, neutrophils, T-lymphocytes, macrophages, and a number of cytokines.

Clinical evaluation: Symptoms in the typical patient with asthma include cough, wheeze, shortness of breath and chest tightness. The cough is typically non-productive, but some asthmatics may produce sputum chronically or intermittently. Symptoms are usually intermittent and precipitated by irritants such as upper respiratory tract infections, smoke, dust, exercise, perfumes, or cats. A careful environmental and occupational history looking for precipitants for asthma is therefore essential. Occupational asthma is a subject unto itself, but a distinction should be made between occupational exposures that worsen preexisting asthma (for example working in a bar with exposure to second hand smoke) and occupational exposures that may actually cause asthma in a previously non-asthmatic individual (for example exposure to isocyanates in auto body painting). Asthma symptoms are typically worse at night, and may also display a seasonal pattern, usually being worse in the spring and fall in response to pollens, flowers, weeds and grasses. Certain foods and medications (especially β-blockers and aspirin) may also precipitate asthmatic symptoms.

The clinical examination is often normal, especially if the patient is between attacks. In some patients, one may hear wheezing, and a prolonged expiratory phase to respiration. Some patients with severe asthma or those in the middle of an acute attack may simply demonstrate decreased breath sounds and no wheezing, because there is insufficient airflow to generate wheezing. These patients also may demonstrate tachycardia, signs of hyperinflation, a rapid respiratory
rate, and use of accessory muscles of respiration, the latter two signifying severe respiratory distress.

The differential diagnosis includes many causes of dyspnea and cough, including infection, pulmonary embolus, chronic obstructive pulmonary disease and congestive heart failure. Two special syndromes necessary to be aware of when evaluating patients for asthma include, vocal cord dysfunction and upper airway obstruction. The former syndrome may present with dyspnea and wheezing, and is due to adduction of the vocal cords throughout the respiratory cycle. It may be difficult to distinguish from asthma, but typically is associated with inspiratory stridor audible at the mouth, does not improve with therapy for asthma, and may show diagnostic abnormalities on pulmonary function testing and on laryngoscopy (visualization of the vocal cords). Upper airway obstruction may present with dyspnea, may also be associated with stridor, and has a characteristic flow-volume loop on pulmonary function testing that is different from that seen in asthma.

Asthma may range from a mild disease with only occasional annoying symptoms to a life threatening problem. It is essential to assess the severity of asthma in each patient, in order to guide rational therapy. Auscultation of the chest is often not helpful in assessing asthma severity, although certain signs point to severe asthma, as mentioned above. History and pulmonary function testing are usually more informative in assessing asthma severity. On history, features that suggest more severe asthma include: previous intubations or admissions to the intensive care unit, previous hospitalizations, frequent emergency room visits, the need for oral or intravenous corticosteroid therapy to control symptoms, and the presence of frequent symptoms despite appropriate use of prescribed medications.

History alone is not sufficient for assessing asthma severity or the success in controlling the disease activity however. Symptoms and signs of asthma may disappear when the lung function is only 40 to 70 % of normal. Therefore, patients may still have ongoing disease without obvious clinical signs. A subset of asthmatics may develop life-threatening airflow obstruction before they actually perceive a significant deterioration in their breathing. This highlights the importance of pulmonary function testing in asthma.

**Investigations:**

**Pulmonary function testing (PFTs):** PFTs are used both to diagnose asthma and to assess asthma severity. Commonly performed measurements include: 1. peak flows; 2. spirometry; 3. the flow volume loop; 4. lung volumes; and 5. tests used to detect increased bronchial reactivity. You will learn more about pulmonary function testing in other lectures and tutorials, and as a result only a brief overview will be presented here.

1. Peak flow monitoring is done by having the patient inhale to total lung capacity (a maximal breath in) and then exhale forcefully into a small plastic tube that registers peak expiratory airflow. The advantage of this technique is that it is simple and can be done by the patient at home at frequent intervals, allowing them to monitor their own disease.

2. Spirometry involves a similar maneuver by the patient, but provides more information about expiratory flows. It graphs expiratory volume against time, and allows one to calculate the FEV1 (maximal expired volume in 1 second), the FVC (maximal forced expired volume) and the ratio of FEV1 to FVC. With asthma of moderate severity, the FEV1 is usually below 80 % of the normal value, and the FEV1 to FVC ratio is usually decreased. In mild asthma, or in asthma that is quiescent, spirometric values may be normal. Spirometry requires a spirometer, specialized equipment that is usually only found in physician offices or hospitals.

3. The flow-volume loop graphs expiratory flows against volume rather than time. It allows one to detect decreased expiratory flows at low lung volumes, which is a more sensitive measure of expiratory airflow obstruction than simple spirometry with measurement of only the FEV1.
and FVC. (Note: with simple calculations, similar information about flows at low lung volumes can be derived from spirometry as well.) 4. Measurement of lung volumes allows one to detect gas trapping from incomplete lung emptying (an increased “residual volume”) and hyperinflation of the lung (an increased “total lung capacity”), both of which are signs of significant airflow obstruction. Measurement of the flow-volume loop and lung volumes, and tests for increased bronchial reactivity (described below) are usually only available in a specialized pulmonary function laboratory.

5. In many patients with mild asthma, all 4 of the above described tests can be normal, particularly at a time where their asthma is not active. Tests of increased bronchial reactivity to irritants (bronchial challenge tests) are more sensitive detectors of asthma, and may allow a more conclusive diagnosis of asthma to be made in such patients. Common tests performed include exposure to inhalation of methacholine, cold air, or histamine, or performance of exercise. Spirometry is measured before and after exposure, and a significant fall in the FEV1 (usually 20% from baseline) is consistent with increased bronchial reactivity, which in turn is characteristic, (although not specific for) asthma. There is overlap between mild asthma and normal subjects in the extent to which they display bronchial hyperreactivity, at times making diagnosis of mild asthma difficult with these tests. As well, treatment of asthma may result in negative bronchial challenge tests.

The chest x-ray may be helpful to exclude other conditions such as pneumonia, or to demonstrate complications from asthma such as pneumothorax, hyperinflation, or mucous plugging. However it is not particularly helpful in either diagnosing asthma or assessing its severity.

The arterial blood gas in asthma may be normal in mild cases. The first abnormality that becomes apparent as asthma severity increases is often a fall in carbon dioxide levels, due to dyspnea and hyperventilation. A normal carbon dioxide level may actually be the first sign of impending respiratory failure.

Eosinophilia can be seen on the peripheral blood count, but is often absent. Serum IgE level maybe elevated as a marker of atopy and many patients may have positive skin tests to allergens.

**Treatment:**

**Goals of treatment:** the goals of treatment include: 1. maximizing bronchodilation and minimizing airway inflammation; 2. minimizing symptoms; 3. minimizing the need for short acting bronchodilator agents; and 4. educating the patient so they can participate in the management of their disease through irritant avoidance, and proper compliance and dosing of medication. In order to achieve these goals, we must look at multiple factors: monitoring of symptoms and lung function, control triggers, pharmacologic therapy and patient education.

**Monitoring:** Peak expiratory flow monitoring (PEFR) should be encouraged by all patients with moderate to severe asthma. It is useful for monitoring an individual’s change or trend. Sputum eosinophilia can also be used as a guide to therapy, however this is not widely available. Additionally, exhaled nitric oxide is a newer method to predict airway inflammation, however its role is still being elucidated.

**Education:** Education about their disease is essential for all asthma patients. This allows patients to participate in managing their disease (environmental modifications, adjustment of medications), ensures compliance and proper use of medication, and ensures recognition of warning symptoms or signs that may signal the need to seek urgent medical attention.
Environmental modification: Avoiding triggers is obviously desirable, but may not always be possible or acceptable to patients (e.g., getting rid of pets, changing carpets to hardwood or vinyl flooring in the home to reduce dust). Suggested measures include minimizing dust and molds in the home, regular cleaning of heating and ventilation ducts, washing bed sheets in hot water and plastic mattress covers to decrease the burden of house dust mites, avoidance of second hand smoke (and obviously cessation of smoking for the patient), and staying indoors with windows closed during times of seasonal outdoor irritants. Modification of occupational conditions, or even changing jobs may also be necessary.

Pharmacotherapy:

Drug therapy for asthma follows a step care approach, with progressively more intensive therapy necessary, depending on the severity of the asthma. The major drugs used will be described below, followed by a description of what their role is in asthma of varying degrees of severity.

1. Bronchodilators: These medications primarily act to relax the smooth muscle tone of the airway, thereby treating bronchoconstriction and allowing bronchodilation.

   a) β-adrenergic agents (“β-agonists”): Stimulation of beta receptors activates adenyl cyclase, which increases intracellular cyclic AMP. This in turn causes compartmental shifts in calcium, leading to bronchial smooth muscle relaxation and bronchodilation. Beta-2 receptors in the airways mediate bronchodilation, whereas beta-1 receptors mediate increased heart rate and contractility. It is therefore advantageous in terms of avoiding side effects to utilized β-agonists that are relatively selective for β-2-receptors. Salbutamol (Ventolin) is the prototypical β-2-agonist, and the most commonly utilized at present. It is available in oral, intravenous and inhalational forms, but the oral and intravenous forms have fallen into disuse in the past number of years, particularly for adults, due to the rapid onset of action, potency, and favorable side effect profile of the inhaled forms of salbutamol. β-agonists are available in short (salbutamol) and long (for example, salmeterol) acting forms. The short acting forms are generally used for quick short term relief from symptoms of asthma. They begin acting within minutes, and last 2 to 6 hours. The long-acting β-agonists can be given on a twice daily schedule. They are particularly helpful for asthmatics who have nocturnal symptoms and are used for asthmatics with symptoms despite a moderate dose of inhaled corticosteroid. As with all inhaled bronchodilators, when delivered by a metered dose inhaler (MDI), the medication should be administered with a spacer device. This promotes greater drug deposition in the airways, with resulting improved efficacy. There is currently a controversy over the question of whether β-agonist treatment, if used regularly, can actually make asthma symptoms worse. The issue is complex, but it is clear that excessive reliance on β-agonist therapy, without combined anti-inflammatory therapy may result in poor asthma control. Conversely, however, asthmatics should never avoid taking β-agonists when they are necessary for the immediate relief of acute symptoms.

   b) Methylxanthines: The most frequently prescribed methylxanthines are theophylline (generally given orally) and aminophylline (for intravenous use). Theophylline is now considered a 3rd or 4th line agent in the treatment of asthma, due to the emergence of newer more effective medications such as long acting β-agonists and the leukotriene modifiers. The exact mechanism of how theophylline works is unknown. It is only a weak bronchodilator, and can have serious side effects at higher blood levels, necessitating monitoring of blood levels when initiating treatment or adjusting doses. The sustained duration of theophylline (12 to 24 hours depending on the preparation) makes it useful for treating nocturnal symptoms, and it may also have a role in patients not adequately controlled on β-agonists and inhaled steroids. However, that being said this medications is rarely used at this time.
c) Anticholinergic agents: Anticholinergic bronchodilators such as ipratropium are weaker bronchodilators in asthma than are β-agonists. They are generally not used in the treatment of most asthmatics, although a subsegment of asthmatics may benefit from them. Specifically, those with a component of chronic obstructive pulmonary disease, those with psychogenic asthma, and those with severe asthma not responding to conventional medications may benefit from therapy with ipratropium. In the acute setting it can be used in combination with β-agonists to provide further bronchodilation than that provided by β-agonists alone. Additionally, it can reduce the amount of β-agonist needed and therefore any side-effects.

2. Anti-inflammatory agents:

a) Inhaled corticosteroids: The central role of airway inflammation in the pathogenesis of asthma makes anti-inflammatory medications essential in the control of all but the mildest of asthmatic patients with intermittent symptoms only. The most effective and commonly prescribed inhaled anti-inflammatory agents are the inhaled corticosteroids. They have been shown to reduce asthmatic symptoms, reduce reliance on bronchodilator medications, reduce airway inflammation, and reduce the need for systemic steroid treatment to control symptoms. They can generally be given on a twice a day schedule for all but the most severe asthmatics. At higher doses, these medications may begin to have side effects similar to systemic steroids (see below), although at lower doses that are conventionally used in the treatment of asthma, side effects are minimal.

Oral or intravenous steroids are sometimes necessary in the treatment of asthma, either for the treatment of acute exacerbations or in the chronic treatment of severe asthma. Although very effective medications in asthma, they have significant side effects when used long-term or in high doses, including hyperglycemia, hypertension, fluid retention, weight gain, poor wound healing, myopathy, osteoporosis, adrenal suppression, immunosuppression, cataracts, and avascular necrosis of bone. They are best used in short courses at the minimal dose necessary to control symptoms, although at times the need to effectively treat severe asthma necessitates treatment that will cause some of the side effects listed above.

b) Mast cell stabilizing agents (Nedocromil sodium and sodium chromoglycate): Sodium chromoglycate when administered prior to allergen exposure blocks both the early and late asthmatic response following antigen inhalation. It probably acts by inhibiting mediator release from mast cells, and does not act specifically as a relaxant of bronchial smooth muscle. Nedocromil sodium is structurally different but has similar pharmacological properties. Although both have been shown to be of benefit to patients when added to bronchodilators alone, they are less effective than inhaled corticosteroids, and are used much less frequently. The drugs are most effective when administered before a challenge such as exercise, allergen, or cold air.

c) Leukotriene modifiers: These include agents that inhibit the action of the cysteinyl leukotrienes (for example montelukast, zafirlukast) or inhibit the action of the enzyme 5-lipoxygenase. They are given orally. They are the first new class of anti-asthma medications in the past 20 years. They are more effective than placebo in decreasing asthma symptoms and reducing the need for bronchodilators, but have not yet been proven as effective as inhaled steroids as anti-inflammatory medications, although studies are ongoing. They may improve compliance in that some patients prefer to take a pill as opposed to an inhaler. At present, they have a role in treating asthmatics who remain symptomatic despite optimizing treatment with bronchodilators and inhaled steroids and in patients with severe asthma in order to decrease their dependence on oral steroids, and in patients who will not or cannot use inhaled medications. Patients with aspirin-induced asthma seem to respond well to leukotriene modifying agents and they may also have a role in exercise induced bronchoconstriction.
3. Novel therapies

Anti IgE therapy (Omalizumab): A recombinant humanized antibody that binds IgE with high affinity. Many asthmatics have an allergic component and elevated serum IgE. The binding of IgE to its receptors on mast cells, eosinophils, basophils and other cell types results in activation of these cells and their inflammatory mediators. Therefore binding IgE will prevent its downstream effects. It is administered subcutaneously or IV every 2-4 weeks in a dose determined by weight and the serum IgE level. Treatment has resulted in a reduction in steroid usage (both oral and inhaled), decreased hospitalization and improved quality of life. Omalizumab is approved as an add-on therapy for patients with moderately-severe asthma who are still symptomatic despite therapy with inhaled corticosteroids +/- long acting beta agonist. In addition, patients must have sensitivity to a perennial aeroallergen and an elevated serum IgE level as well as being older than the age of 12 years to qualify for use of this medication.

Treating associated aggravating conditions: Post nasal drip/sinusitis and gastroesophageal reflux can aggravate asthma, making it more difficult to control. These conditions should ideally be treated when associated with asthma.

**Classification of asthma according to severity and implications for treatment:**

Some patients with asthma have only mild symptoms that are infrequent or associated with a single known precipitant such as exercise. In such patients, as needed bronchodilator treatment with short acting β-agonists is acceptable.

In all other asthmatics, who experience regular symptoms or need frequent bronchodilator therapy (ie more than 3 to 4 times per week), anti-inflammatory treatment with low dose inhaled steroids (200 to 800 μg) should be initiated, along with as needed treatment with short acting β-agonists.

In asthmatics who either remain symptomatic on this regime, need frequent bronchodilator therapy, or have persistent significant airflow obstruction on pulmonary function testing, options include using high dose inhaled steroids (1000 to 2000 μg), adding a long-acting β-agonist, or adding a leukotriene modifier. Adding long-acting β-agonists have been shown to be somewhat more efficacious in controlling symptoms in this situation than increasing the dose of inhaled steroids, although results will vary in individual patients. For more severe asthmatics, all 3 modifications may be necessary.

For asthmatics who are not controlled adequately even after initiation of the above measures, (ie treatment with high dose inhaled steroids, long-acting β-agonist, and leukotriene modifiers), options include adding theophylline, adding ipratropium, starting systemic steroids, or for those who are allergic and have an elevated IgE level, Omalizumab.

It is essential that before medication is added or doses increased, the physician confirms that a) the patient is in fact suffering from symptoms of asthma and not some other disease; b) the medication is being taken as prescribed on a regular basis; and c) that environmental irritants have been reduced as much as possible.

The below figure is from the Canadian Asthma Consensus Guidelines (2003) and outlines the steps in management of asthma depending on the severity of disease.
CASE 1

A 6-month-old boy presents to the Emergency Department with a brief history of cough and wheezing. He is restless and irritable, and he has not been eating well. On examination, his weight is 7 kg, axillary temperature 38.5 °C. Respiratory rate (RR) 90 per min, heart rate (HR) 160 per min. You observe suprasternal and intercostal retractions and a paradoxical movement of chest and abdomen. The skin appears pale. On auscultation, you hear low breath sound intensity over both sides, with wheezing and occasional crackles both during inspiration and expiration. The chest x-ray shows hyperlucent lung fields and flattened diaphragms bilaterally, and there are patchy perihilar infiltrates. An arterial blood gas shows pH 7.24, PO₂ 53 mmHg, PCO₂ 43 mmHg.

1. What is your working diagnosis/differential diagnosis?
2. Is the PCO₂ normal in this infant?
3. For immediate treatment, which one is the most important:
   i. air humidification
   ii. fluids IV
   iii. antibiotics IV
   iv. bronchodilator inhalation
   v. supplemental oxygen
4. Which additional information do you want from history and clinical investigations?
5. If this is viral bronchiolitis, what other treatment modalities are available?
6. What would you tell the parents about their son’s immediate and long-term prognosis?

CASE 2

A 1 ½-year-old boy has been coughing for several hours following an episode where he choked and turned blue during play at home. You see him in your office. He is upset and clings to his mother, and physical examination is difficult. His color is normal, RR is 50 to 60 per min. You hear decreased breath sound intensity on the right side with expiratory wheezing that appears louder on the right than on the left side.

1. What is your working diagnosis?
2. What is your next diagnostic test?
   i. arterial blood gas
   ii. chest radiograph
   iii. chest computer tomogram
   iv. chest fluoroscopy
   v. endoscopy
3. If your working diagnosis is confirmed, what is the treatment of choice?
4. What are the potential acute and long-term complications?

CASE 3

A 3-year-old girl is seen at the Emergency Department who during the day has developed a sore throat, fever and cough. Her breathing has become more noisy, with a low-pitched inspiratory
stridor. On physical exam, she appears anxious and agitated. Her RR is 45 per mm, pulse 135 per mm, axillary temperature 39.3 °C. She is leaning forward and drooling. Her face looks flushed, but her skin color is otherwise normal. You notice suprasternal retractions. The girl appears unable to swallow water.

1. What is your next step?
   i. administer oxygen at 3 L/min via face mask
   ii. obtain a blood culture and start antibiotics IV
   iii. perform arterial puncture for blood gas analysis
   iv. give nebulized racemic epinephrine via face mask
   v. give dexamethasone IV or IM
   vi. carefully inspect the oropharynx
   vii. obtain lateral neck radiograph
   viii. alert colleagues in intensive care and anaesthesia

2. If this girl has a bacterial infection, what would be the most likely organism(s)?
3. Which signs would you look for on a lateral neck radiograph?
4. How do you explain to the parents the severity of this illness as well as the short and long-term prognosis?
5. How would you deal with this situation during a locum in a small northern community?

CASE 4

A five-year-old boy has been rescued from a trailer home that he set on fire when playing with matches. He is brought to the Emergency Room 20 minutes later where you find him to be in a confused state, hallucinating, heart rate regular 130 bpm, respiratory rate 45 per minute, some intercostal and suprasternal retractions. His skin color is pink but he shows some burn injury of the face, involving mouth and nose, with erythema and mild swelling.

You want some additional information. What questions do you ask the paramedics? You consider the following tests. How do you rank their diagnostic value?

- chest x-ray
- arterial blood gas analysis
- pulse oximetry
- carboxyhemoglobin level
- endoscopy

How do you interpret these results from arterial blood gas analysis and pulse oximetry in this patient?

SaO₂  94%
PaO₂  85 mmHg
pH  7.30
PCO₂  30 mmHg
HCO₃⁻  15 mEq/L

You realized that the following complications are likely to occur. Describe their pathophysiology, the diagnostic test that you order to identify them, and your choice of therapies.

1. airway obstruction
2. worsening respiratory failure
3. coma
Objectives:

The objectives for the lecture, assigned study & tutorial are the same:

1. Describe at least four (4) major clinical features that one could expect to see in the throats of patients with infectious pharyngitis syndromes (sore throats).
2. Differentiate the clinical presentation of infectious pharyngitis from non-infectious sore throat.
3. List the commonest and the more unusual specific causes of infectious sore throat.
4. Develop a cost-effective management strategy for any patient who seeks medical attention for a sore throat.
5. Define nasopharyngitis, cold, rhinitis, diphtheria, pseudomembrane, herpangina, hand-foot-and-mouth disease, coryza.
6. Name at least four major secondary bacterial infections which are complications of viral and/or bacterial U.R.I.
7. Name, and describe the pathogenesis of, the two major non-suppurative, immunologic complications of group A streptococcal sore throat and outline the strategies to prevent their occurrence.
8. Differentiate the signs & symptoms of influenza-like illness (ILI), infectious mononucleosis syndrome (IM), colds, acute pharyngitis syndrome, measles, rubella, varicella (chickenpox) and severe acute respiratory syndrome (SARS).

References:

1. Cecil Essentials of Medicine - Chapter on “Infections of the Head and Neck”.
2. Medical Microbiology & Immunology, 4th Ed.: see chapters dealing with Streptococci (Group A, C & G), Corynebacterium diphtheriae, measles, rubella, chickenpox.
Be prepared to discuss examples of patients presenting with sore throat &/or other respiratory symptoms in order to help you achieve the objectives.

URI include infections of the mucosal surfaces of the nose, nasopharynx, pharynx, epiglottis* and larynx*. Infections of the mucosa of the middle ear and Eustachian tube and the conjunctiva also may be considered “URI” since the microbes which frequently cause infections in these sense organs often, but not always, colonize the nasopharynx; or the conjunctiva acts as a portal of entry to the URT via the naso-lacrimal duct. Infections involving the tonsils and soft palate are also categorized as URI, but infections of the tongue, gingiva, teeth, buccal mucosa, parotid glands and hard palate, etc. are categorized as oral (mouth) infections and as such really belong to the gastrointestinal (alimentary) system. The indigenous microbial inhabitants of the URT and mouth differ substantially and there are numerous niches with very unique microorganisms. The gingiva, for instance, are colonized mainly be anaerobic bacteria of enormous variety (cocci, bacilli and spirochetes) and quantity. The nasopharynx is generally colonized by very small numbers comprising relatively few species of bacteria. However, nasopharyngeal colonization by virulent bacteria is often a harbinger of more serious systemic infections (e.g. community-acquired bacterial pneumonia, acute bacterial meningitis), although this colonization is generally not recognized clinically (i.e. it is asymptomatic colonization). * on the borderline between upper and lower respiratory tract.

Family physicians (CMAJ 1998; 158(1):75-83) have attempted to design an algorithm to determine which patients require investigation and treatment for pharyngitis. Premise: is the sore throat due to GAS or not? It is a ‘point-score system’ as follows:

<table>
<thead>
<tr>
<th>Clinical Finding</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature &gt;38C</td>
<td>1</td>
</tr>
<tr>
<td>No cough</td>
<td>1</td>
</tr>
<tr>
<td>Tonsillar swelling/exudate</td>
<td>1</td>
</tr>
<tr>
<td>Tender anterior cervical adenopathy</td>
<td>1</td>
</tr>
<tr>
<td>Age 3-14 years</td>
<td>1</td>
</tr>
<tr>
<td>Age 15-44 years</td>
<td>0</td>
</tr>
<tr>
<td>Age &gt;44</td>
<td>-1</td>
</tr>
</tbody>
</table>

Total Score =

**Interpretation and Action**
<table>
<thead>
<tr>
<th>Total Score</th>
<th>Chance of GAS infection in community with usual levels of infection (%)</th>
<th>Suggest/recommended management</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2-3</td>
<td>No throat swab culture/BAD &amp; no antibiotic</td>
</tr>
<tr>
<td>1</td>
<td>4-6</td>
<td>Do throat swab culture/BAD, wait for result. Give antibiotic only if positive for GAS</td>
</tr>
<tr>
<td>23</td>
<td>10-12</td>
<td>Do throat swab culture/BAD, wait for result. Give antibiotic only if positive for GAS</td>
</tr>
<tr>
<td>4</td>
<td>38-63</td>
<td>As above or if quite sick give antibiotic without doing test</td>
</tr>
</tbody>
</table>
Objectives:

1. Compare and contrast lower respiratory tract infections in terms of frequency, clinical syndromes, etiology of both community-acquired and hospital-acquired infections and characteristic signs and symptoms, by age group as follows: <1 year old; 1 to <6 years old; >6 years old.

2. *Bordetella pertussis*, Respiratory Syncytial Virus (RSV) and Parainfluenza Virus are three major pathogens that cause severe respiratory tract infection in infants and children. For each describe: pathogenesis of disease, associated clinical syndrome(s) and mode of spread of infection. (See: Levinson+Jawetz; Behrman+Kleigman's Nelson).

3. For each of the following age groups, identify two common and two less common causes of community-acquired pneumonia: newborn infants (<1 month old); 1-3-month-olds; 4 months to 4 years, 5-15 years. (see below).

4. Formulate an approach to the diagnosis and management of lower respiratory tract infections during childhood.

Suggested Reading:

Available on reserve at the library:


Introduction:

Respiratory infections are important in children because they occur frequently, cause significant morbidity and are among the most common causes of death in children, especially in developing countries.

Site of Infection:

Clinical respiratory infection syndromes are often divided into upper (URI) and lower (LRI) respiratory tract infections. In children this division is artificial since viruses, which are the major respiratory pathogens, target the ciliated respiratory epithelial cells, which extend from the nasal mucosa to the peripheral small airways. Thus, most viral infections as well as pertussis start out with a typical cold (nasopharyngitis) and may progress to cause LRI symptoms over time. Most viral respiratory pathogens can cause all of the various clinical syndromes although some have predilection for a specific site as indicated below:
<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Nasopharyngitis</th>
<th>Croup</th>
<th>Bronchiolitis</th>
<th>Pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinovirus</td>
<td>+++</td>
<td>+</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>RSV</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Parainfluenza</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Influenza</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Mycoplasma</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Pyogenic bacteria*</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+++</td>
</tr>
</tbody>
</table>

*(Pneumococcus, H. influenzae, S. aureus)*

Age often determines the nature of the presenting features of a respiratory infection with infants more likely to have severe disease than are older children and adults, irrespective of the specific viral pathogen. e.g. RSV causing pneumonia in a 2 month old, bronchiolitis in an 11 month old, croup in a 2-3 year old and a typical cold in older children and adults.

**AGE-RELATED ETIOLOGY OF PNEUMONIA IN PEDIATRICS:** (most common at each age are bolded & underlined)

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Newborn</th>
<th>1-3 months</th>
<th>4 months-4 years</th>
<th>&gt;5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial</td>
<td>Group B</td>
<td>B. pertussis</td>
<td>B. pertussis</td>
<td>Pneumococcus</td>
</tr>
<tr>
<td></td>
<td>Streptococcus (S. agalactiae)</td>
<td>Chlamydia</td>
<td>H. influenzae</td>
<td>(S. pneumoniae)</td>
</tr>
<tr>
<td></td>
<td>Enterobacteriaceae</td>
<td>Mycoplasma</td>
<td>Pneumococcus</td>
<td>Mycoplasma</td>
</tr>
<tr>
<td></td>
<td>Listeria</td>
<td>Ureaplasma</td>
<td>Meningococcus</td>
<td>Group A strep</td>
</tr>
<tr>
<td></td>
<td>S. aureus</td>
<td>S. aureus</td>
<td>Mycoplasma</td>
<td>(S. pyrogenes)</td>
</tr>
<tr>
<td>Viral</td>
<td>Cytomegalovirus (CMV)</td>
<td>RSV (Respiratory Syncytial Virus)</td>
<td>RSV</td>
<td>Influenza</td>
</tr>
<tr>
<td></td>
<td>RSV</td>
<td>CMV</td>
<td>Influenza</td>
<td>Adenovirus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Parainfluenza</td>
<td>Measles</td>
</tr>
<tr>
<td>Parasitic</td>
<td>Toxoplasmosis</td>
<td>P. carinii</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Objectives:

1. Outline how the family history contributes to the assessment of a patient with a respiratory illness.
2. Describe the variability of the “genetic respiratory diseases” including Cystic Fibrosis and Alpha-1-antitrypsin deficiency.
3. Discuss the implications of genetic testing for these conditions.

References:

1. Genetic Testing for Cystic Fibrosis - NIH Consensus Statement  

Lecture Notes:

Asthma

• Major locus regulating IgE on 5q31-5q33
• ? Bronchial hyperresponsiveness gene nearby

<table>
<thead>
<tr>
<th>Who Affected</th>
<th>Chance of Developing</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 parents</td>
<td>6.5%</td>
</tr>
<tr>
<td>1 parent</td>
<td>19.7%</td>
</tr>
<tr>
<td>2 parents</td>
<td>63.3%</td>
</tr>
<tr>
<td>MZ twin</td>
<td>19%</td>
</tr>
<tr>
<td>DZ twin</td>
<td>4.8%</td>
</tr>
</tbody>
</table>
Lung Cancer
- Male twins born 1917-1927, twin registry
- 5933 MZ pairs, 7544 DZ pairs
- MZ twins more likely concordant for smoking

Kartagener Syndrome
- Autosomal recessive, situs inversus (50%)
- Chronic sinusitis, nasal polyps, chronic bronchitis, males sterile
- DX nasal mucosa brushing for EM and light photometry for measurements of cilia beat frequency

Alpha-1-Antitrypsin Deficiency
- Autosomal co-dominant
- Protease inhibitor (target=elastase)
- >75 known forms of A1AT protein, most differ by 1 aa
- <40% A1AT- > increased risk emphysema
  2% of all emphysema
  Panacinar and predominantly lower lung regions
  smoking major factor
  70% ZZ smokers die of lung disease age 50
  ?20% ZZ nonsmokers
  Diagnosis: Measure A1AT levels, PI typing (protein electrophoresis), DNA
  TEST ALL 1ST DEGREE RELATIVES

<table>
<thead>
<tr>
<th>Genotype</th>
<th>%A1AT</th>
<th>POP Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM</td>
<td>100</td>
<td>90%</td>
</tr>
<tr>
<td>MS</td>
<td>75</td>
<td>6%</td>
</tr>
<tr>
<td>MZ</td>
<td>57</td>
<td>3%</td>
</tr>
<tr>
<td>SS</td>
<td>52</td>
<td>1%</td>
</tr>
<tr>
<td>SZ</td>
<td>37</td>
<td>1/800</td>
</tr>
<tr>
<td>ZZ</td>
<td>16</td>
<td>1/3500</td>
</tr>
</tbody>
</table>

- Neonatal Hepatitis
  ? In 10% of deficiency (28% died of cirrhosis, 28% had cirrhosis, 21% biochem liver abnormalities, 22% normal), increased risk liver disease if previous liver disease
- Adult cirrhosis, hepatoma, increased in ZZ
- Null/Null: very high risk emphysema, no liver disease

Case Presentation 1
Meconium ileus at birth, recurrent lung infections since infancy, pancreatic insufficiency, salty taste, sweat chloride 120, Pseudomonas infections, severe obstructive lung disease, clubbing, DEATH at age 12.

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Case Presentation 2
Meconium ileus at birth, pancreatic insufficiency, sweat chloride 115, minimal clubbing, mild lung disease at age 21, no hospitalizations for lung infections, normal physical activity, FEV1 82%, almost normal chest x-ray (23/25).

Case Presentation 3
50-year-old female, chronic cough, purulent sputum, several pneumonias in hospital since age 3, since age 12 prescribed antibiotics twice/year, age 33 hemoptysis, FEV1 78%, sweat chloride 49-69, no meconium ileus, no pancreatic disease.

Case Presentation 4
30-year-old male, no lung disease, no pancreatic disease, normal sweat chloride, infertile azoospermia, congenital absence of vas deferens

Genetics of Cystic Fibrosis
- 1/25 carriers, 1/2500 affected (1/25 x 1/25 x 1/4)
- CFTR (CF transmembrane conductance regulator) on 7q
- Mutations
  - defective chloride transport in epithelial cells
  - secondary decreased Na, Water transport
  - dehydrated viscous secretions
  - luminal obstruction

CFTR gene
- ΔF508 = most common mutation (70%)
  - 3 bp deletion in exon 10
  - loss of one aa (phenylalanine) at codon 508
- >450 mutations identified
- Mutations correlated with pancreatic status
  - ΔF508/ΔF508 - > insufficient, R117H/DF508 - > sufficient
- Usually not correlated with lung disease
  - few exceptions, e.g. A455E (Alanine to glutamine E) mild lung disease

CF and congenital absence of the Vas Deferens

(Rigot et al. NEJM 1991)
- 18 azoospermic men with CAV
- 8 heterozygous for D508
- 7 have chronic sinusitis, 2 have sweat chloride near 100

(Maddelena et al. AJHG 1992)
- 18 males with CAV
- 6 heterozygotes for D508, 2 W1282X heterozygotes, 1 R117H heterozygotes, 2 D508/R117H compound
<table>
<thead>
<tr>
<th>CFTR Genotype</th>
<th>Poly T Genotype</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF/CF*</td>
<td>non 5T/non 5T</td>
<td>19</td>
</tr>
<tr>
<td>CF/N</td>
<td>non 5T/5T</td>
<td>33</td>
</tr>
<tr>
<td>CF/N</td>
<td>non 5T/non 5T</td>
<td>20</td>
</tr>
<tr>
<td>N/N</td>
<td>non 5T/5T</td>
<td>7</td>
</tr>
<tr>
<td>N/N</td>
<td>non 5T/non 5T</td>
<td>22</td>
</tr>
</tbody>
</table>

CF Screening

- before screening
  \[
  \frac{1}{25} \times \frac{1}{25} \times \frac{1}{4} = \frac{1}{2500}
  \]
- wife positive
  \[
  1 \times \frac{1}{25} \times \frac{1}{4} = \frac{1}{100}
  \]
- husband negative for D508
  \[
  1 \times \frac{3}{243} \times \frac{1}{4} = \frac{1}{324}
  \]
  (250 people -> 240 noncarriers, 7 positive carriers, 3 negative carriers)

CF Screening in Ashkenazi Jewish Population

- 94 CF Patients
  - Ashkenazi Jews in Israel
  - 5 mutations > 97% of CF alleles
    - DF508 30%, G542X 12%, W1282X 48%, N1303K 3%, 3849 + 10kb C >T 4%
- Carrier frequency
  \[
  1/29, \text{ based on pilot study of 424}
  \]

Attitudes toward Prenatal Diagnosis of CF

- 227 families attending CF clinic
  - 69% sterile, widowed, divorced
  - 31% (70 couples) fertile and at risk
  - 44% intended to have more children
  - 77% would consider CF prenatal Dx
  - 28% would terminate of CF
  - 44% would carry fetus to term
  - 28% undecided

CF Gene Therapy

- cDNA cloned
- insertion into epithelial cells corrects chloride channel defect
- Best target? Resp epithelial cells
- Adenovirus vectors
  - Given to >60 CF adults
  - Low level (<1%) gene transfer by measuring nasal transepithelial potential difference
  - No increase in chloride or sodium transport
- Cationic liposome delivery
  - 15 men with CF
nasal potential diff normal on Day 3
baseline by Day 7
• both had local and systemic inflammatory responses

Summary:
Be aware of atypical/mild presentations
Family history of more than just lungs
Other family members at risk