**الجامعة المستنصرية -كلية الطب**

**المرحلة الرابعة**

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**Malabsorption syndrome**

conditions that affect the digestion or the absorption of nutrients.

1.Diarrhea: absence of diarrhea does not exclude malabsorption.

(acidic /Watery / Steatorrhea (pale, foul-smelling, bulky stools)

2.Abdominal distention.

3.Failure to gain weight.

4.Fall in growth chart percentiles.

**Classification:**

* CARBOHYDRATE MALABSORPTION
  + Lactose malabsorption
  + Congenital lactase deficiency
  + Secondary lactase deficiency
  + Glucose galactose malabsorption
* FAT MALABSORPTION
  + Cystic fibrosis
  + Shwachman-Diamond syndrome
  + Abetalipoproteinemia
* AMINO ACID MALABSORPTION
  + Enterokinase deficiency
* MINERAL AND VITAMIN MALABSORPTION
  + Congenital chloride diarrhea
  + Acrodermatitis enteropathica (zinc malabsorption)
  + Menke disease (copper malabsorption)
  + Vitamin D–dependent rickets.
  + Folate malabsorption
  + Secondary to mucosal damage (celiac disease)
  + Vitamin B12 malabsorption
  + Terminal ileal disease (e.g., Crohn disease) or resection
* DRUG INDUCED
  + Sulfasalazine: folic acid malabsorption
  + Phenytoin: calcium malabsorption

**CLINICAL APPROACH TO A CHILD WITH SUSPECTED MALABSORPTION**

**History:**

* Onset: in congenital chloride diarrhea and microvillus inclusion disease, the stool is watery since birth and can be mistaken for urine.

Onset of symptoms after introduction of a particular food into a child's

diet may provide diagnostic clues, such as seen with gluten in gluten-

sensitive enteropathy

* Nature:

explosive watery diarrhea ---suggests carbohydrate malabsorption;

loose, bulky stools---- are associated with celiac disease;

pasty and yellowish offensive stool ---suggests an exocrine pancreatic insufficiency.

Stool color is usually not helpful; green stool with undigested “peas and carrots” may suggest rapid intestinal transit in toddler's diarrhea.

* Dietary history A common example is the child with chronic, nonspecific diarrhea (**toddler's diarrhea**) generally presents in well-appearing toddlers between 1 and 3 yr of age (toddler's diarrhea). The diarrhea is often brown and watery, at times containing undigested food particles. If the child's fluid intake is >150 mL/kg/24 hr, fluid intake should be reduced to no more than 90 mL/kg/24 hr.

* Appetite

very good appetites(voraceous) as in exocrine pancreatic insufficiency(cystic fibrosis)

anorexia 🡪celiac disease

Food avoidance 🡪CHO malabsorption due to abdominal distension &abdominal pain.

* Change in weight, then ↓ht. the OFC will be compromised when malnutrition become chronic.

**Physical findings:**

* signs of malnutrition: include the disappearance of the subcutaneous fat, muscle wasting, and the appearance of skin being too loose for the child.
* Specific findings may guide toward a particular disorder;
  + *edema* 🡪protein-losing enteropathy,
  + *digital clubbing* 🡪 cystic fibrosis and celiac disease,
  + *perianal excoriation* and *gaseous abdominal* distention 🡪 carbohydrate malabsorption
  + *perianal and circumoral rash* 🡪 acrodermatitis enteropathica
  + *abnormal hair*🡪 Menkes syndrome
  + Long-term *calcium* and *vitamin D* malabsorption can lead to reduced bone mineral density and metabolic bone disease with increased risk of bone fractures.
  + *Vitamin K* malabsorption, irrespective of the underlying mechanism (fat malabsorption, mucosal atrophy), can result in coagulopathy.
  + Other nutrient deficiencies include *iron malabsorption* causing microcytic anemia and low reticulocyte count,
  + low serum *folate* levels in conditions associated with mucosal atrophy,
  + low serum vitamin A and vitamin E concentration in fat malabsorption.

**Investigation**

* **stool examination** 
  1. stool occult blood and leukocytes to exclude inflammatory disorders,
  2. stool microscopy and antibody tests for parasites such as *Giardia,*
  3. stool pH and reducing substance for carbohydrate malabsorption, and
  4. quantitative stool fat examination to identify fat malabsorption.
* **A complete blood counts** 
  1. peripheral smear for microcytic anemia,
  2. Macrocytic anemia 🡪folate &B12
  3. lymphopenia (lymphangiectasia),
  4. neutropenia (Shwachman syndrome),
  5. and acanthocytosis (abetalipoproteinemia) is useful.
* **S. albumin.**
  1. Depending on the initial investigation results, more specific investigations can be planned.

**Fat malabsorption**

* a microscopic examination of stool for fat:

mixing a small amount of stool with several drops of water or Sudan red stain. Fat droplets separate and can be easily identified, especially with a Sudan III stain. The presence of more than six to eight droplets per low-power field is abnormal.

* A positive test should be confirmed with a 72-hr quantitative fecal fat test, which remains the gold standard for assessing steatorrhea. Excretion of more than 7% of the total fat intake is abnormal and suggests the presence of malabsorption, still it is expensive, unpleasant, procedure.
* The most reliable simple stool test is acid steatocrit Steatocrit acid test: stool sample diluted and mixed with perchloric acid to PH less than 1 and result centrifuged to notice 2 layers of fatty and fecal material , can be regarded as qualitative test for fat malabsorption.
* Exocrine pancreatic insufficiency and other fat malabsorption disorders are usually associated with deficiencies of fat-soluble vitamins A, D, E, and K. Serum concentrations of vitamins A, D, and E can be measured to indicate fat malabsorption.

**carbohydrate malabsorption**

* Clinitest reagent for reducing substances is a simple screening test and can be performed at the bedside. The test is easily performed by combining 10 drops of water with 5 drops of stool and then adding a Clinitest tablet. The color change can be quantified as trace to 4+ using a color sheet provided by the manufacturer. Only 2+ or higher should raise the possibility of sugar malabsorption. Sucrose is not a reducing sugar and requires hydrolysis with hydrochloric acid before analysis.
* Stool pH, obtained easily with pH paper, lower than 5.6 is also suggestive of carbohydrate malabsorption.
* The breath hydrogen test can also be used to evaluate carbohydrate malabsorption. The gas produced by bacterial degradation of carbohydrates is largely absorbed in the colon, enters the portal and systemic venous return, goes to the lung, and is then released in the breath.
* After an overnight fast, the suspected sugar (lactose, sucrose,fructose, or glucose) is administered as an oral solution (carbohydrate load up to 2 g/kg, maximum total of 25 g, depending on the specific carbohydrate type). In malabsorption, the sugar is not digested or absorbed in the small bowel; it passes on to the colon and is metabolized by the normal gut microflora. One of the products of this process is hydrogen gas, which is absorbed through the colon mucosa and excreted in the breath. Increased hydrogen concentration in the breath samples suggests carbohydrate malabsorption. A rise in breath hydrogen of 20 ppm above the baseline preferably with associated symptoms is considered a positive test. The child should not be on antibiotics at the time of the test, because colonic flora is essential for fermenting the sugar.
* Small bowel mucosal biopsies can measure mucosal disaccharidase (lactase,

sucrase, maltase) concentrations directly. In primary enzyme

deficiencies the mucosal enzyme levels are low and small bowel mucosal

morphology is normal. Primary enzymatic deficiencies can be diagnosed by

genetic testing .Partial or total villous atrophy due to disorders such as CD, or following acute rotavirus gastroenteritis can result in secondary disaccharidase deficiency and transient lactose intolerance the disaccharidase levels revert to normal after mucosal healing.

**Protein malabsorption**

* Dietary and endogenous proteins secreted into the bowel are almost completely absorbed and minimal amounts of protein from these sources passes into the colon. Protein loss cannot be evaluated directly because bacterial protein accounts for such a large proportion of the stool nitrogen.
* Excessive bowel protein loss usually manifests as hypoalbuminemia. Because the most common cause of hypoalbuminemia in children is a renal disorder, urinary protein excretion must be determined. Other potential causes of hypoalbuminemia include acute infection, liver disease (reduced production) and inadequate protein intake.
* Measurement of spot stool α1 -antitrypsin levels is helpful in establishing a diagnosis of protein-losing enteropathy. This serum protein is resistant to digestion and therefore can be measured in stool in contrast to albumin.

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**Lactase Deficiency**

*Congenital lactase deficiency* is rare and is associated with symptoms occurring

on exposure to lactose in milk. Fewer than 50 cases have been reported

worldwide.

*Primary adult type-hypolactasia* is caused by a physiologic decline in lactase

actively that occurs following weaning in most mammals. The brush-border

lactase is expressed at low levels during fetal life; activity increases in late fetal

life and peaks from term to 3 yr, after which levels gradually decrease with age.

This decline in lactase levels varies between ethnic groups. Lactase deficiency

occurs in approximately 15% of white adults, 40% of Asian adults, and 85% of

African-American adults in the United States.

*Secondary lactose intolerance* follows small bowel mucosal damage (CD,

acute severe gastroenteritis) and is usually transient, improving with mucosal healing. Lactase deficiency can be diagnosed by H2 -breath test (2 g/kg up to 25 g) or by measurement of lactase activity in mucosal tissue retrieved by small bowel biopsy. Diagnostic testing is not mandatory, and often simple dietary changes that reduce or eliminate lactose from the diet relieve symptoms.

Treatment of lactase deficiency consists of a milk-free diet. A lactose-free formula (based on either soy or cow's milk) can be used in infants. In older children, low-lactose milk can be consumed. The addition of lactase to dairy products usually abbreviates the symptoms. Live-culture yogurt contains bacteria that produce lactase enzymes and is therefore tolerated in most patients with lactase deficiency. Hard cheeses and cottage cheeses have a small amount of lactose and are generally well tolerated.

**Gluten-Sensitive Enteropathy (Celiac Disease)**

* Celiac disease is an immune-mediated enteropathy caused by permanent sensitivity to gluten in genetically susceptible individuals which lead to mucosal damage.

**Etiology and Epidemiology**

CD is an immune-mediated systemic disorder elicited by gluten in wheat and

related prolamines from rye and barley in genetically susceptible individuals,

and is characterized by the presence of a variable combination of gluten dependent

clinical manifestations, CD–specific antibodies, human leukocyte

antigen (HLA)-DQ2 or DQ8 haplotypes, and enteropathy. CD–specific

antibodies comprise autoantibodies against TG2 including endomysial

antibodies (EMAs), and antibodies against deamidated forms of gliadin peptides.

Although CD develops in genetically susceptible individuals, environmental factors might affect the risk of developing CD or the timing of its presentation. Neither breastfeeding during gluten introduction nor any breastfeeding has been shown to reduce the risk of CD. The earlier introduction of gluten is associated with the earlier development of CD autoimmunity (positive serology) and CD, but the cumulative incidence of each in later childhood is not affected. It is advised to introduce gluten into the infant's diet anytime between 4 and 12 mo of age. Infectious agents have been hypothesized to play a causative role as frequent rotavirus infections were shown to be associated with an increased risk of developing CD. It is plausible that the contact with gliadin at a time when there is an ongoing intestinal inflammation alters intestinal permeability, and the enhanced antigen presentation can increase the risk of developing CD, at least in a subset of

persons.

**PATHOGENESIS.**

* develops only after dietary exposure to the protein gluten, which is found in (wheat, rye, oat and barley).The activity of gluten resides in the gliadin fraction
* A genetic predisposition
  + monozygotic twins approaching 100%.
  + 2 to 5% of first-degree relatives have symptomatic gluten-sensitive enteropathy
* Individuals with HLA-DQ2 and –DQ8 tissue type are at higher risk. Such a DQ molecule has been found to be present in more than 90% of CD patients, while the data available on DQ2-negative CD patients indicate that they almost invariably are HLA-DQ8–positive
* Celiac disease occurs at a higher frequency in children with
  + type 1 diabetes and is 50 times more common
  + Down syndrome.
  + selective IgA deficiency.
  + Turner syndrome,
  + thyroiditis.
* Environmental factors such as viruses may also play a role

**The inflammatory response results in:**

* + Total or subtotal villus atrophy,
  + crypt hyperplasia,
  + increased number of intraepithelial lymphocytes,
  + damage to the surface epithelium in the small bowel.
  + The injury is greatest in the proximal small bowel and extends distally for a variable distance.

**Clinical Presentation**

Clinical features of CD vary considerably. Intestinal symptoms are more

common in children whose disease is diagnosed *within the first 2 yr of life* ;

failure to thrive, chronic diarrhea, vomiting, abdominal distention, muscle

wasting, anorexia, and irritability are present in most cases .

Occasionally there is constipation, with cases presenting with intussusception.

As the age at presentation of the disease shifts to later in childhood, and with the more extensive use of serologic screening tests, extraintestinal manifestations, without any accompanying digestive symptoms, have increasingly become

recognized, affecting almost all organs .

One of the most common extraintestinal manifestation of CD is iron-deficiency anemia, which is usually unresponsive to iron therapy. Osteoporosis may be present; in contrast to adults, it can be reversed by a gluten-free diet, with restoration of normal peak bone densitometric values. Other extraintestinal manifestations include short stature, delayed puberty, arthritis and arthralgia, epilepsy with bilateral occipital calcifications, peripheral neuropathies, isolated hypertransaminasemia, dental enamel hypoplasia, and aphthous stomatitis.

Silent CD is recognized, mainly in asymptomatic first-degree relatives of CD patients and in subjects affected by diseases associated with CD .Small bowel biopsy in silent/subclinical CD reveals severe mucosal damage consistent with

CD. Potential CD is defined when patients have positive CD–specific antibodies, but without documented small bowel damage .

Non gastrointestinal Manifestations of Celiac Disease

1. Dermatitis herpetiforms
2. Dental enamel hypoplasia
3. Osteopenia/osteoporosis
4. Short stature
5. Delayed puberty
6. Anemia (nonresponsive to iron therapy, seen in adults only)
7. Hepatitis
8. Arthritis
9. Brain calcifications
10. Neurologic symptoms

CELIAC TESTING SHOULD BE CONSIDERED

• Metabolic bone disorders (reduced bone mineral density or osteomalacia)

• Unexplained neurological symptoms (particularly peripheral neuropathy or ataxia)

• Unexplained subfertility or recurrent miscarriage

• Persistently increased concentrations of liver enzymes with unknown cause

• Dental enamel defects

• Down syndrome

• Turner syndrome

• William syndrome

• Selective IgA deficiency

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An 18 mo old boy with active celiac disease. Note the loose skinfolds,

marked proximal muscle wasting, and distended abdomen. The child looks ill.

**Clinical Spectrum of Celiac Disease**

**SYMPTOMATIC CD**

Frank malabsorption symptoms and signs (e.g., chronic diarrhea, failure to thrive, weight loss)

Extraintestinal symptoms and signs (e.g., anemia, fatigue, hypertransaminasemia, neurologic disorders, short stature, dental enamel defects, arthralgia, aphthous stomatitis)

**SILENT CD**

No apparent symptoms in spite of histologic evidence of villous atrophy

In most cases identified by serologic screening in at-risk groups

**LATENT CD**

Subjects who have a normal intestinal histology, but at some other time have shown a gluten-dependent enteropathy

**POTENTIAL CD**

Subjects with positive celiac disease serology but without evidence of altered intestinal histology. Patients may or may not have symptoms and signs of disease and may or may not develop a gluten-dependent enteropathy later

**LABORATORY FINDINGS**

* 1.increase Fat content of stools—A 3-day collection of stools usually reveals excessive fecal fat.
* 2. Impaired carbohydrate absorption
* 3. Hypoproteinemia —Hypoalbuminemia

**SEROLOGIC TESTS**

* Anti-gliadin and anti-reticulin antibodies are often present in celiac disease. However, there is a 10% false-positive rate for the IgG antigliadin antibody among healthy individuals.
* Endomysial or tissue transglutaminase antibody assays are the most sensitive and specific screening tests for celiac disease. As both of these antibodies are of the IgA class, screening for them in a patient who is IgA deficient may yield a falsely negative screen result.
* The best available serologic screening test, therefore, is a quantitative IgA level with a transglutaminase or Endomysial antibody assay.
* The deamidated gliadin peptide DGP test , of both IgG,IgA, had high sensitivity and specificity comparable to TTG,Endomycial Ab test, it is the result of deamidation of unmodified gliadin by Ttg that activate the T-cell mediated immune response leading to Ab production and development of villous atrophy which is characterstic of CD.

**Genetic tests**

have an increasing role in the diagnosis

* Less than 2% of celiac patients lack both HLA specificities;
* approximately one third of the “normal” population has one or the other marker; that means that the measurement of HLA DQ2 and/or DQ8 has
* a (strong negative predictive value) but a (very weak positive predictive value) for the diagnosis of celiac disease.

With these limitations the test can prove useful to exclude celiac disease when the genetic studies are negative in subjects on a gluten-free diet or in subjects belonging to an at-risk group (e.g., 1st-degree relatives, insulin-dependent diabetics, patients with Down syndrome) to avoid long-term follow-up.

**D. BIOPSY FINDINGS**

* + Total or subtotal villus atrophy,
* crypt hyperplasia,
  + increased number of intraepithelial lymphocytes,
  + damage to the surface epithelium in the small bowel.

-The ultimate diagnosis of celiac disease relies on the demonstration of specific, though not pathognomonic, histopathologic abnormalities in the small bowel mucosa.

-According to The European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) current criteria, the 2 requirements mandatory for the diagnosis of celiac disease are:

\*\*the finding of villous atrophy with hyperplasia of the crypts and abnormal surface epithelium, while the patient is eating adequate amounts of gluten,

\*\*and a full clinical remission after withdrawal of gluten from the diet.

* The finding of circulating IgA celiac disease–associated antibodies at the time of diagnosis and their disappearance on a gluten-free diet adds weight to the diagnosis.
* Gluten challenge is not considered mandatory except in situations where there is doubt about the initial diagnosis, for example, when an initial biopsy was not performed or when the biopsy specimen was inadequate or atypical of celiac disease.

**Diagnosis**

The diagnosis of CD is based on a combination of symptoms, antibodies, HLA

status, and duodenal histology.

The initial approach to symptomatic patients is to test for anti-TG2 IgA antibodies and for total IgA in serum to exclude IgA deficiency. If IgA anti-TG2 antibodies are negative, and serum total IgA is normal for age, CD is unlikely to be the cause of the symptoms.

If anti-TG2 antibody testing is positive the patients should be referred to a pediatric gastroenterologist for further diagnostic workup, which depends on the serum antibody levels.

IgA anti-TG2 decline if the patient is on a gluten free diet. In patients with selective IgA deficiency, testing is recommended with IgG antibodies to TG2.

Patients with positive anti-TG2 antibody levels <10 times the upper limit of normal should undergo upper endoscopy with multiple biopsies.

In patients with positive anti-TG2 antibody levels at or >10 times the upper limit of normal, blood should be drawn for HLA and EMA testing. If the patient is positive for EMA antibodies and positive for DQ2 or DQ8 HLA testing, the diagnosis of CD is confirmed, a life-long gluten-free diet is started and the patient is followed for the improvement of symptoms and the decline of antibodies.

HLA testing is almost always positive; thus, it is possible that HLA testing will not be necessary in the future to establish diagnosis.

In the rare case of negative results for HLAand/or anti-EMA in a child with TG2 antibody titers >10 times the upper limits of normal, the diagnostic workup should be extended, including repeated testing and duodenal biopsies .

In asymptomatic persons belonging to high risk groups, CD should always be diagnosed using duodenal biopsies .

When biopsies are indicated, at least 4 fragments should be obtained from the descending part of the duodenum and at least 1 from the duodenal bulb. The diagnosis is confirmed by an antibody decline and preferably a clinical response to a gluten-free diet. CD is not the only cause for villous atrophy .

**other causes of flat mucosa/villous atrophy**

Autoimmune enteropathy

Tropical sprue

Giardiasis

HIV enteropathy

Bacterial overgrowth

Crohn disease

Eosinophilic gastroenteritis

Cow's milk enteropathy

Food allergy

Primary immunodeficiency

Graft-versus-host disease

Chemotherapy and radiation

Protein energy malnutrition

**Treatment**

A. DIET

* Treatment consists of dietary gluten restriction for life. All sources of wheat, rye, barley, and oat gluten must be eliminated during the initial treatment.
* Clinical improvement is usually evident within a week, and
* histologic repair is complete after 3–12 months.
* Tissue transglutaminase titers may decrease on a gluten free diet, but usually do not disappear.
* **Principles of Initial Dietary Therapy for Patients With Celiac Disease**
* Avoid all foods containing wheat, rye, and barley gluten (**pure** oats usually safe).
* Avoid malt unless clearly labeled as derived from corn.
* Use only rice, corn, maize, buckwheat, millet, quinoa, sorghum, potato or potato starch, soybean, tapioca, bean, and nut flours.
* Read all labels and study ingredients of processed foods.
* Beware of gluten in medications, supplements, food additives, emulsifiers, or stabilizers.
* Limit milk and milk products initially if there is evidence of lactose intolerance.

B. CORTICOSTEROIDS

* are indicated only in very ill patients with signs and symptoms of celiac crisis (profound malnutrition, diarrhea, edema, abdominal distention, and hypokalemia).

**Nonresponsive celiac disease** :

may be defined as persistent symptoms and signs despite 6-12 mo of dietary gluten avoidance.

Positive serologic testing for celiac disease despite 12 mo of treatment with a GFD (gluten free diet) suggest that there may be ongoing gluten ingestion.

***Refractory* *celiac disease (RCD****)*

is defined as persistent or recurrent malabsorptive symptoms and signs, with small intestinal villus atrophy despite a strict GFD for more than 12 mo and in the absence of other disorders including overt lymphoma.

**Prognosis**

* Clinical and histologic recovery is the rule but may be slow.
* Malignant lymphoma of the small bowel occurs with increased frequency in adults with long-standing disease.
* Dietary treatment seems to decrease the risk of this complication.

**Cystic Fibrosis**

Cystic fibrosis (CF) is an inherited multisystem disorder of children and adults; it is the most common life-limiting recessive genetic trait among whites. Dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) protein, the primary defect, leads to a wide and variable array of presenting manifestations and complications.

CF is responsible for most cases of exocrine pancreatic insufficiency in early life and is the major cause of severe chronic lung disease in children. It is also responsible for many cases of hyponatremic salt depletion, nasal polyposis, pansinusitis, rectal prolapse, pancreatitis, cholelithiasis, and nonautoimmune insulin-dependent hyperglycemia. Because CF may manifest as failure to thrive and hepatic dysfunction, including cirrhosis, this disorder enters into the

differential diagnosis of many pediatric conditions.

Genetics

CF occurs most frequently in white populations of northern Europe, North America, and Australia/New Zealand. The prevalence in these populations varies but approximates 1 in 3,500 live births .

*CFTR* is the deletion of a single phenylalanine residue at amino acid 508(F508del). This mutation is responsible for the high incidence of CF in northern European populations and is considerably less frequent in other populations, such as those of southern Europe.

The relationship between CFTR genotype and clinical phenotype is highly complex. CFTR mutation class is strongly associated with pancreatic dysfunction and will usually predict this manifestation in any given patient.

Respiratory complications and lung function decline are also correlated with mutation class severity but with greater variation due to the influence of non- CFTR modifier gene polymorphisms and environmental influences on the manifestations of lung disease in any one individual.

**ETIOLOGY AND EPIDEMIOLOGY**

* CF, an autosomal recessive disorder, In the U.S., 1 in 3200 white newborns is born with CF
* The gene for CF, localized to the long arm of chromosome 7, termed cystic fibrosis transmembrane regulator (*CFTR*) The secretory and absorptive characteristics of epithelial cells are affected.
* the respiratory epithelium exhibits marked impermeability to chloride and an excessive reabsorption of sodium. These lead to a relative dehydration of the airway secretions, resulting in impaired mucociliary transport and airway obstruction

**Pathogenesis**

failure to clear mucous secretions, a paucity of water in mucous secretions, an elevated salt content of sweat and other serous secretions, and chronic infection limited to the respiratory tract. In addition, there is a greater negative potential difference across the respiratory

epithelia of patients with CF than across the respiratory epithelia of control subjects. Aberrant electrical properties are also demonstrated for CF sweat gland duct and rectal epithelia. The membranes of CF epithelial cells are unable to secrete chloride or bicarbonate in response to cyclic adenosine monophosphate– mediated signals, and at least in the respiratory epithelial cells, excessive amounts of sodium are absorbed through these membranes. These defects can be

traced to a dysfunction of CFTR.

Many hypotheses have been postulated to explain how CFTR dysfunction

results in the clinical phenotype .It is likely that no one hypothesis explains the full spectrum of disease. One model is that airway hydration homeostasis requires both CFTR and P2Y2 -regulated calcium-activated chloride secretion. When extracellular ATP is depleted such as after viral infections,calcium-activated chloride secretion is not activated and the failure of mutant

CFTR chloride secretion results in dehydrated airway secretions, increased concentration of mucin solids, and more viscoelastic mucus that is not cleared by normal mucociliary transport. Another mechanism is that mutant CFTR causes failure of HCO3 − secretion and a more acidic airway surface liquid, which increases mucous viscoelasticity resulting in poor mucociliary

clearance. Mucous secretions are tethered to submucosal gland ducts and are retained and obstruct airways, starting with those of the smallest caliber, the bronchioles. Airflow obstruction at the level of small airways is the earliest observable physiologic abnormality of the respiratory system.

CFTR dysfunction in airway smooth muscle has been implicated in tracheal and airway

abnormalities in humans and in animal models of the disease

These data suggest that CFTR expression in this non epithelial tissue contributes

to airway constriction.

It has similar pathophysiologic events take place in the pancreatic and biliary ducts (and in the vas deferens), leading to desiccation of proteinaceous secretions and obstruction. Because the function of sweat gland duct cells is to absorb rather than secrete chloride, salt is not retrieved from the isotonic primary sweat as it is transported to the skin surface; chloride and sodium levels are consequently elevated.

**Chronic infection** in CF is limited to the airways. One explanation for

infection is a sequence of events starting with failure to clear inhaled bacteria

promptly and then proceeding to persistent infection and an inflammatory

response in airway walls. Another explanation for early infection is the failure of

innate immune proteins to kill bacteria in an abnormally acidic airway milieu. In

addition, it has been proposed that abnormal CFTR creates a proinflammatory

state or amplifies the inflammatory response to initial infections (viral or

bacterial).

It appears that inflammatory events occur first in small airways, perhaps because it is more difficult to clear altered secretions and microorganisms from these regions. The agents of airway injury include neutrophil products, such as oxidative radicals

and proteases, and immune reaction products. These inflammatory products

further aggravate airway obstruction by increasing mucin secretion and altering

mucin structure to promote both intramolecular and intermolecular interactions.

Excessive inflammatory cell polymers in CF sputum, including DNA, filamentous actin, and glycosaminoglycans, further contribute to abnormal

mucous viscoelastic properties and airway obstruction. Chronic bronchiolitis and

bronchitis are the initial lung manifestations ,but after months to years, structural changes in airway walls produce bronchiolectasis and **bronchiectasis** . With advanced lung disease, infection may extend to peribronchial lung parenchyma.

A central feature of lung disease in patients with CF is the high prevalence of

airway infection with ***Staphylococcus aureus*** ,***Pseudomonas aeruginosa*** ,and ***Burkholderia cepacia*** **complex** organisms that rarely infect the lungs of other

individuals.

It has been postulated that the CF airway epithelial cells or surface liquids may provide a favorable environment for harboring these organisms. CF airway epithelium may be compromised in its innate defenses against these organisms, through either acquired or genetic alterations. Antimicrobial activity is diminished in CF secretions; this diminution may be related to hyperacidic surface liquids or other effects on innate immunity.

Another puzzle is the propensity for *P. aeruginosa* to undergo mucoid transformation in the CF airways. The complex polysaccharide produced by these organisms generates a biofilm that provides a hypoxic environment and thereby protects *Pseudomonas* against antimicrobial agents.

Altered lipid homeostasis has been implicated as a predisposing factor for respiratory tract infection and inflammation. Concentrations of lipoxins—

molecules that suppress neutrophilic inflammation—are suppressed in CF

airways. There is an imbalance of lipids with increased arachidonic acid and

decreased docosahexaenoic acid, which promotes inflammation. There is also an

imbalance of ceramide in the CF airway that is proinflammatory. Supporting the

idea that altered lipid uptake affects infection and inflammation is the

observation that the 10–15% of individuals with CF who retain substantial

exocrine pancreatic function have delayed acquisition of *P. aeruginosa* and

slower deterioration of lung function.

Exposure to environmental tobacco smoke and outdoor air pollutants, and early acquisition of respiratory virus infections, as well as pathogenic organisms like *P. aeruginosa* and methicillin-resistant *S. aureus,* have been implicated as causes of worsening disease.

Sex/gender disparities also seem to exist, with females having a poorer prognosis.

Socioeconomic status has been shown to be a strong predictor of mortality, as well as both nutritional status and lung function .

**Pathology**

1.The earliest pathologic lesion in the lung is that of **bronchiolitis** (mucous

plugging and an inflammatory response in the walls of the small airways); with

time, mucous accumulation and inflammation extend to the larger airways

(**bronchitis** ) .

2.Goblet cell hyperplasia and submucosal gland hypertrophy become prominent pathologic findings, which is most likely a response to chronic airway infection. 3.Organisms appear to be confined to the endobronchial space; invasive bacterial infection is not characteristic. With longstanding disease, evidence of airway destruction such as **bronchiolar** **obliteration, bronchiolectasis ,**and**bronchiectasis** becomes prominent.

4.Bronchiectatic cysts and emphysematous bullae or subpleural blebs are frequent

with advanced lung disease, the upper lobes being most commonly involved.

These enlarged air spaces may rupture and cause pneumothorax. Interstitial

disease is not a prominent feature, although areas of fibrosis appear eventually.

5.Bronchial arteries are enlarged and tortuous, contributing to a propensity for

hemoptysis in bronchiectatic airways. Small pulmonary arteries eventually

display medial hypertrophy, which would be expected in secondary pulmonary

hypertension.

6.The **paranasal sinuses** are uniformly filled with secretions containing inflammatory products, and the epithelial lining displays hyperplastic and

hypertrophied secretory elements.

7.The nasal mucosa may form large or multiple **polyps** , usually from a base surrounding the ostia of the maxillary and ethmoidal sinuses.

8.The **pancreas** is usually small, occasionally cystic, and often difficult to find

at postmortem examination. The extent of involvement varies at birth. In infants,

the acini and ducts are often distended and filled with eosinophilic material. In

85–90% of patients, the lesion progresses to complete or almost complete

disruption of acini and replacement with fibrous tissue and fat. Infrequently, foci

of calcification may be seen on radiographs of the abdomen. The islets of

Langerhans contain normal-appearing β cells, although they may begin to show

architectural disruption by fibrous tissue in the 2nd decade of life.

9.The **intestinal tract** shows only minimal changes. Esophageal and duodenal

glands are often distended with mucous secretions. Concretions may form in the

appendiceal lumen or cecum. Crypts of the appendix and rectum may be dilated

and filled with secretions.

**10.Focal biliary cirrhosis** secondary to blockage of intrahepatic bile ducts is

uncommon in early life, although it is responsible for occasional cases of

prolonged neonatal jaundice. This lesion becomes much more prevalent and

extensive with age and is found in 70% of patients at postmortem examination.

This process can proceed to symptomatic multilobular biliary cirrhosis that has a

distinctive pattern of large irregular parenchymal nodules and interspersed bands

of fibrous tissue. Approximately 30–70% of patients have fatty infiltration of the

liver, in some cases despite apparently adequate nutrition.

11.The **gallbladder** may be hypoplastic and filled with mucoid material and often contains stones.Atresia of the cystic duct and stenosis of the distal common bile duct have been observed.

12.Glands of the **uterine cervix** are distended with mucus, copious amounts of

which collect in the cervical canal.

13. In >95% of males, the body and tail of the epididymis, the vas deferens, and the seminal vesicles are obliterated or atretic, resulting in male infertility.

**Clinical Manifestations**

**Respiratory Tract**

Infants diagnosed by CF newborn screening are generally asymptomatic from a

respiratory standpoint. Nonetheless, the majority are infected with *S. aureus* ,

*Haemophilus influenza* , or even *P. aeruginosa* within the 1st mo of life, and

chest CT scans show characteristic heterogeneous air trapping in 1/3 of infants by

their first birthday, and bronchiectasis is found in more than 10% of 1 yr olds and ∼60% of 5 yr olds.

The earliest symptom is usually cough that may begin with a viral respiratory tract infection but then persists unless treated with antibiotics. With treatment, the generally realized goal is for patients to remain asymptomatic throughout childhood, except for the periodic development of cough, chest congestion, sputum production, and/or wheezing that define a *pulmonary exacerbation* .

Cor pulmonale, respiratory failure, and death eventually supervene unless lung transplantation is accomplished; this has become increasingly uncommon in childhood. Infection with certain strains of *B. cepacia* and other multidrugresistant organisms may be associated with particularly rapid pulmonary deterioration and death.

Eventual physical findings include increased anteroposterior diameter of the chest, generalized hyperresonance, scattered or localized coarse crackles, and digital clubbing. Expiratory wheezes may be heard, a manifestation of airway inflammation and edema that may or may not be associated with bronchodilator responsiveness. Cyanosis is a late sign. Common pulmonary complications include atelectasis, hemoptysis, pneumothorax, and cor pulmonale; these usually

appear in late adolescence or beyond.

Even though the paranasal sinuses are virtually always opacified radiographically, acute sinusitis is infrequent. Nasal obstruction and rhinorrhea are common, caused by inflamed, swollen mucous membranes or, in some cases,nasal polyposis. Nasal polyps are most troublesome between 5 and 20 yr of age.

**Intestinal Tract**

In 15–20% of newborn infants with CF, the ileum is completely obstructed by meconium (**meconium ileus** ).

Abdominal distention, emesis, and failure to pass meconium appear in the first 24-48 hr of life and often requires surgical intervention. Abdominal radiographs show dilated loops of bowel with air-fluid levels and, frequently, a collection of granular,”ground-glass” material in the lower central abdomen. Rarely, **meconium** **peritonitis** results from intrauterine rupture of the bowel wall and can be detected radiographically as the presence of peritoneal or scrotal calcifications.

Ileal obstruction with fecal material (**distal intestinal obstruction syndrome [DIOS]** ) occurs in older children, causing cramping abdominal pain, abdominaldistention, and obstruction that can be treated with medical approaches to bowe evacuation.

More than 85% of children with CF have *exocrine* pancreatic insufficiency, causing protein and fat malabsorption. Symptoms, if untreated, include frequent, bulky, greasy stools and failure to gain weight even when food intake appears to be large. Weight gain can be challenging, but attainment of normal growth and development is an expectation of treatment. A protuberant abdomen, decreased muscle mass, poor growth, and delayed maturation are classic and rarely seen physical signs. Excessive flatus may be a problem. Supplementation with fat soluble vitamin preparations has made deficiencies of vitamin A, E, and K unusual, but vitamin D deficiency continues to be prevalent and, although rickets is rare, osteoporosis is common, especially in older patients and those with more severe lung disease. Historically a relatively common event, **rectal prolapse** occurs much less frequently as the result of earlier diagnosis and initiation of pancreatic enzyme replacement therapy.



**A** and **B,** Contrast enema study in a newborn infant with abdominal distention and failure to pass meconium. Notice the small diameter of the sigmoid and ascending colon and dilated, air-filled loops of small intestine. Several air-fluid levels in the small bowel are visible on the upright lateral view.

**Biliary Tract**

Infants may occasionally present with **neonatal jaundice** suggestive of biliary obstruction. Evidence for liver dysfunction is most often detected in the first 15 yr of life and can be found in up to 30% of individuals. **Biliary cirrhosis** becomes symptomatic in only 5–7% of patients. Manifestations can include icterus, ascites, hematemesis from esophageal varices, and evidence of hypersplenism. Biliary colic secondary to cholelithiasis may occur in the 2nd decade or later.

**Cystic Fibrosis–Related Diabetes and Pancreatitis**

*Endocrine* pancreatic insufficiency tends to develop in the 2nd decade and beyond and is more common in patients with a family history of type II diabetes mellitus.

Ketoacidosis usually does not occur, but eye, kidney, and other vascular complications have been noted in patients living ≥10 yr after the onset of hyperglycemia. Recurrent, acute pancreatitis occurs occasionally in individuals who have residual exocrine pancreatic function and may be the sole manifestation of homozygotic *CFTR* mutations.

**Genitourinary Tract**

Virtually all males are **azoospermic** because of failure of development of wolffian duct structures, but sexual function is generally unimpaired. The female fertility rate is diminished, especially in women who have poor nutrition or advanced lung disease.

**Sweat Glands**

Excessive loss of salt in the sweat predisposes young children to salt depletion episodes, especially during episodes of gastroenteritis and during warm weather. These children may present with **hypochloremic alkalosis.** Hyponatremia is a risk particularly in warm climates. Frequently, parents notice salt *frosting* of the skin or a salty taste when they kiss the child. A few genotypes are associated with normal sweat chloride values.

**Diagnosis and Assessment**

The diagnosis of CF has been based on a positive quantitative sweat test (Cl− ≥ 60 mEq/L) in conjunction with one or more of the following features:

identification of 2 CFTR mutations, typical chronic obstructive pulmonary disease, documented exocrine pancreatic insufficiency, and a positive family history. With newborn screening, diagnosis is often made prior to obvious clinical manifestations such as failure to thrive and chronic cough.



**Sweat Testing**

The sweat test, which involves using pilocarpine iontophoresis to collect sweat and performing chemical analysis of its chloride content, is the standard approach to diagnosis of CF.

The procedure requires care and accuracy. Anelectric current is used to carry pilocarpine into the skin of the forearm and locally stimulate the sweat glands. If an adequate amount of sweat is collected, the specimens are analyzed for chloride concentration.

Infants with a positive newborn screen for CF should have the sweat chloride testing performed after 36-wk corrected gestational age and at a weight greater than 2 kg and at age greater than 10 days to increase the likelihood of sufficient sweat collection for an accurate study.

Positive results should be confirmed; for a negative result, the test should be repeated if suspicion of the diagnosis remains.

More than 60 mmol/L of chloride in sweat is diagnostic of CF when one or more other criteria are present. In individuals with a positive newborn screen, a sweat chloride level less than 30 mmol/L indicates that CF is unlikely.

Borderline (or intermediate) values of 30-59 mmol/L have been reported in patients of all ages who have CF with atypical involvement and require further testing.

Non-CF conditions associated with elevated concentrations of sweat electrolytes (false +ve) include

**WITH FALSE-POSITIVE RESULTS**

Eczema (atopic dermatitis)

Ectodermal dysplasia

Malnutrition/failure to thrive/deprivation

Anorexia nervosa

Congenital adrenal hyperplasia

Adrenal insufficiency

Glucose-6-phosphatase deficiency

Mauriac syndrome

Familial hypoparathyroidism

Hypothyroidism

Nephrogenic diabetes insipidus

Pseudohypoaldosteronism

Klinefelter syndrome

Familial cholestasis syndrome

Autonomic dysfunction

Prostaglandin E infusions

Munchausen syndrome by proxy

**WITH FALSE-NEGATIVE RESULTS**

Dilution

Malnutrition

Edema

Insufficient sweat quantity

Hyponatremia

Cystic fibrosis transmembrane conductance regulator mutations with preserved sweat duct function

**DNA Testing**

Several commercial laboratories test for 30-96 of the most common *CFTR*

mutations. This testing identifies ≥90% of individuals who carry 2 CF mutations.

Some children with typical CF manifestations are found to have 1 or no

detectable mutations by this methodology. Some laboratories perform

comprehensive mutation analysis screening for all the >1,900 identified

mutations.

**Other Diagnostic Tests**

The finding of increased potential differences across nasal epithelium (nasal

potential difference) that is the increased voltage response to topical amiloride

application, followed by the absence of a voltage response to a β-adrenergic

agonist, has been used to confirm the diagnosis of CF in patients with equivocal

or frankly normal sweat chloride values.

**Pancreatic Function**

The diagnosis of pancreatic malabsorption can be made by the quantification of

*elastase-1 activity* in a fresh stool sample by an enzyme-linked immunosorbent

assay specific for human elastase. The quantification of fat malabsorption with a

72-hr stool collection is rarely necessary in the clinical setting. CF-related

diabetes affects approximately 20% of adolescents and 40–50% of adults, and

clinical guidelines recommend yearly oral glucose tolerance testing (OGTT)

after age 10. Spot testing of blood and urine glucose levels and glycosylated hemoglobin levels are not sufficiently sensitive.

**Radiology**

* Hyperinflation of lungs occurs early and is often accompanied by nonspecific peribronchial thickening .
* Bronchial thickening and plugging and ring shadows suggesting bronchiectasis usually appear first in the upper lobes.Nodular densities, patchy atelectasis, and confluent infiltrate follow. Hilar lymph nodes may be prominent.
* With advanced disease, impressive hyperinflation with markedly depressed diaphragms, anterior bowing of the sternum, and a narrow

cardiac shadow are noted.

* Cyst formation, extensive bronchiectasis, dilated pulmonary artery segments, and segmental or lobar atelectasis is often apparent with advanced disease.
* Most CF centers obtain chest radiographs (posteroanterior [PA] and lateral) at least annually.
* CT of the chest can detect heterogeneous hyperinflation and localized thickening of bronchial airway walls, mucous plugging, focal hyperinflation, and early bronchiectasis.CT abnormalities are commonly seen at a young age, even in asymptomatic children with normal lung function.
* Radiographs of paranasal sinuses reveal panopacification and, often, failure of frontal sinus development. CT provides better resolution of sinus changes if this information is required clinically.
* Fetal ultrasonography may show pancreatic changes indicative of CF and suggest ileal obstruction with meconium early in the second trimester, but this finding is not predictive of meconium ileus at birth.

****Serial radiographs in a boy show the changing appearance of cystic fibrosis over 6 yr. A, At 9 yr, frontal radiograph shows minimal peribronchial thickening and hyperaerated lungs indistinguishable from asthma. B, Nineteen mo later, the radiographic picture has worsened considerably. Extensive peribronchial thickening is now noted. Mucoid

impaction of the bronchus is seen in the left upper lobe and hilar shadows have become abnormally prominent. C, Ten mo later, further deterioration is obvious. Widespread typical changes of cystic fibrosis (CF) are noted

throughout both lungs. D, Follow-up studies show considerable improvement, which suggested that some of the changes evident on C were from superimposed infection. E, One yr later, note the progressive changes of CF—most severe in the upper lobes bilaterally.

**Pulmonary Function**

Standard pulmonary function studies are usually obtained starting at about 4

yr of age and are routinely done by age 6. Forced expiratory volume in 1 sec

(FEV1 ) is the measurement that has been shown to correlate most closely with

mortality and shows a gradual decline averaging 2–3% per year throughout

childhood.

Restrictive changes, characterized by declining total lung capacity and vital capacity, correlate with extensive lung injury and fibrosis and are a late finding.

**Microbiologic Studies**

*H. influenza* and *S. aureus* are the most common organisms recovered in young

children .

*Pseudomonas* may be acquired early and is eventually an organism of key significance. Once *P. aeruginosa* develops a mucoid phenotype, it is extremely difficult to eradicate from the airway. A wide range of

other organisms are frequently recovered, particularly in advanced lung disease;

they include a variety of Gram-negative rods including the *Burkholderia cepacia*

complex, *Aspergillus fumigatus* , which is most important due todevelopment of **allergic bronchopulmonary****aspergillosis** ; and nontuberculous mycobacterial species, especially *Mycobacterium avium* complex and *Mycobacterium abscessus* . Airway culturesare obtained regularly, most typically using oropharyngeal swabs in youngchildren, and then sputum (which may be induced) in older children capable ofexpectoration.

**Newborn Screening**

Newborn screening for CF is the most common way that CF is diagnosed.

use a combination of immunoreactive trypsinogen (IRT) results and limited DNA testing on blood spots; because not all mutations can be found using this approach, babies with an elevated IRT and a single detected mutation are considered a positive screen, and all positive screens are followed by a confirmatory sweat analysis.

about 10–15% of infants with a positive screen based on the finding of only 1 CF mutation will be found to have CF.

This screening test is ≈95% sensitive and should result in a median age at diagnosis of less than 1mo.

Importantly, good nutritional status (50 percentile weight for length or 50 percentile body mass index) is associated with better lung function at 6 yr of age.

**Treatment**

**General Approach to Care**

Initial efforts after diagnosis should be intensive and should include baseline

assessment, initiation of treatment to prevent pulmonary involvement in young

infants or reverse it in those diagnosed later, nutritional maintenance or

remediation, and education of the patient and parents. Follow-up evaluations are

scheduled every 1-3 mo, depending on the age at diagnosis, because many

aspects of the condition require careful monitoring.

An interval history and physical examination should be obtained at each visit. A sputum sample or, if that is not available, a lower pharyngeal swab taken during or after a forced cough is obtained for culture and antibiotic susceptibility studies.

A nurse, physical therapist, respiratory therapist, social worker, and dietitian, as members of the multidisciplinary care team, should evaluate children regularly and contribute to the development of a comprehensive daily care plan.

**Symptoms and Signs Associated With Exacerbation of Pulmonary Infection in Patients With Cystic Fibrosis**

**SYMPTOMS**

Increased frequency and duration of cough

Increased sputum production

Change in appearance of sputum

Increased shortness of breath

Decreased exercise tolerance

Decreased appetite

Feeling of increased congestion in the chest

**SIGNS**

Increased respiratory rate

Use of accessory muscles for breathing

Intercostal retractions

Change in results of auscultatory examination of chest

Decline in measures of pulmonary function consistent with the presence of obstructive airway disease

Fever and leukocytosis

Weight loss

New infiltrate on chest radiograph

Because secretions of CF patients are not adequately hydrated, attention in

early childhood to oral hydration, especially during warm weather or with acute

gastroenteritis, may minimize complications associated with impaired mucous

clearance. Intravenous therapy for dehydration should be initiated early.

The goal of therapy is to maintain a stable condition for prolonged periods.

This can be accomplished for most patients by interval evaluation and

adjustments of the home treatment program.

Intravenous antibiotics may be required infrequently or as often as every 2-3 mo. The goal of treatment is to return patients to their previous pulmonary and functional status.

**Pulmonary Therapy**

The object of pulmonary therapy is to clear secretions from airways and to

control infection.

**Inhalation Therapy**

Human recombinant DNase (2.5 mg) enzymatically dissolves extracellular DNA

released by neutrophils, a major contributor to the characteristically sticky and

viscous CF airway secretions. It is usually given as a single daily aerosol dose,

improves pulmonary function, decreases the number of pulmonary exacerbations, and promotes a sense of well-being. Improvement is sustained for 12 mo or longer with continuous therapy.

Nebulized hypertonic saline, acting as a hyperosmolar agent, is believed to

draw water into the airway and rehydrate mucus and the periciliary fluid layer,

resulting in improved mucociliary clearance. 7% hypertonic saline

nebulized 2-4 times daily increases mucous clearance and reduces pulmonary

exacerbation, with only a slight short-term improvement in pulmonary function.

**Airway Clearance Therapy**

Airway clearance treatment begins in infancy with chest percussion (with or

without postural drainage) and derives its rationale from the idea that cough

clears mucus from large airways, but chest vibrations are required to shear

secretions for the airway wall and move secretions from small airways, where

expiratory flow rates are low.

**Chest PT(phsiotherapy)** can be particularly useful for patients with CF because they accumulate secretions in small airways first, even before the onset of symptoms.. Airway clearance therapy is recommended 2-4 times a day, depending on the severity of lung dysfunction, and usually increased during acute exacerbations. Cough, huffing, or forced expirations are encouraged intermittently throughout the session. Vest-type mechanical percussors *(high-frequency chest wall oscillation)* are commonly

used past infancy due to their convenience, as are a variety of oscillatory positive

expiratory pressure devices (such as Acapella and Aerobika) and other

controlled breathing techniques (e.g., *autogenic drainage* ). Routine aerobic

exercise appears to slow the rate of decline of pulmonary function, and benefit

has also been documented with weight training. No one airway clearance

technique can be shown to be superior to any other, so all modes should be

considered in the development of an airway clearance prescription.

**Antibiotic Therapy**

Antibiotics are the mainstay of therapy designed to control progression of lung

infection. The goal is to reduce the intensity of endobronchial infection and to

delay progressive lung damage. The usual guidelines for acute chest infections,

such as fever, tachypnea, or chest pain, are often absent.

Antibiotic treatment varies from intermittent short courses of 1 antibiotic to nearly continuous treatment with 1 or more antibiotics. Dosages for some antibiotics are often 2-3 times the amount recommended for minor infections because patients with CF have proportionately more lean body mass and higher clearance rates for many antibiotics than other individuals.

**Oral Antibiotic Therapy**

Indications for oral antibiotic therapy in a patient with CF include the presence

of respiratory tract symptoms, physical signs, or changes in pulmonary function

testing or chest x-ray.

Common organisms, including *S. aureus (MRSA or MSSA),* nontypeable *H. influenzae, P.aeruginosa; B. cepacia* and other Gram-negative rods, are encountered with increasing frequency. The usual course of therapy is 2 wk, and maximal doses are recommended. The quinolones are the only broadly effective oral antibiotics for *Pseudomonas* infection, but resistance against these agents may emerge. Macrolides may reduce the virulence properties of *P. aeruginosa,* such as biofilm production, and contribute anti-inflammatory effects. Long-term therapy with azithromycin 3 times a week improves lung function in patients with chronic *P. aeruginosa* infection.

**Aerosolized Antibiotic Therapy**

Aerosolized antibiotics are often used as part of daily therapy when the airways

are infected with *P. aeruginosa* . Aerosolized tobramycin inhalation solution or

powder, or aztreonam inhalation solution used as a suppressive therapy (on 1

mo, off 1 mo), may reduce symptoms, improve pulmonary function, and

decrease the occurrence of pulmonary exacerbations.

Another important indication for aerosolized antibiotic therapy is to eradicate

*P. aeruginosa* in the airways after initial detection. Early infection may be

cleared for mo to several yr in this way, although eventual reinfection is

common. Other antibiotics have been used via inhalation, including liposomal

amikacin and levofloxacin for *P. aeruginosa* .

**Intravenous Antibiotic Therapy**

For the patient who has not responded to oral antibiotics and intensive home

measures with return of signs, symptoms, and FEV1 to baseline, intravenous

antibiotic therapy is indicated.

The ideal duration of treatment is unknown; although many patients show improvement within 7 days, many CF physicians believe that it is usually advisable to extend the period of treatment to at least 14 days. Permanent intravenous access can be provided for long-term or frequent courses of therapy in the hospital or at home.

Thrombophilia screening should be considered before the use of totally implantable intravenous devices or for recurring problems with venous catheters.

In general, treatment of *Pseudomonas* infection is thought to require 2-drug therapy. A 3rd agent may be given for optimal coverage of *S. aureus* or other organisms.

Changes in therapy should be guided by lack of improvement more than by

culture results; sensitivities do not always predict response to therapy, and this

may be due to the presence of other organisms that are not detected by culture

methods. If patients do not show improvement, complications such as right heart

failure, asthma, or infection with viruses, *A. fumigatus* (especially ABPA) nontuberculous mycobacteria or other unusual organisms should be considered. *B. cepacia* complex and acinetobacter are Gram-negative rods that may be particularly refractory to antimicrobial therapy.

**Bronchodilator Therapy**

Reversible airway obstruction occurs in many children with CF, sometimes in

conjunction with frank asthma or allergic bronchopulmonary aspergillosis.

Reversible obstruction is conventionally defined as improvement of ≥12% in

FEV1 or FVC after inhalation of a bronchodilator. In many patients with CF,

these may improve by only 5–10% (physiologic response), but subjects may

report subjective benefit.

**Antiinflammatory Agents**

Corticosteroids are useful for the treatment of allergic bronchopulmonary

aspergillosis and severe asthma occasionally encountered in children with CF.

Prolonged systemic corticosteroid treatment of CF lung disease reduces the

decline in lung function modestly but causes predictably prohibitive side effects.

Inhaled corticosteroids have theoretical appeal, but there are contradictory and

weak data regarding efficacy unless the patient has clinically diagnosable

asthma. Ibuprofen, given chronically in high doses adjusted to achieve a peak

serum concentration of 50-100 μg/mL, is associated with a slowing of disease

progression, particularly in younger patients with mild lung disease. However,

there are concerns regarding side effects of nonsteroidal antiinflammatory drugs,

so this therapy has not gained broad acceptance. Macrolide antibiotics have an

antiinflammatory effect, and 3 days/wk azithromycin has been shown to reduce

the likelihood of development of pulmonary exacerbations, especially in patients

with chronic *Pseudomonas* airway infection, so this is a commonly used therapy.

**Cystic Fibrosis Transmembrane Conductance Regulator**

**Modulator Therapies**

A major breakthrough in CF therapy is ivacaftor, a small molecule potentiator of

the CFTR mutation, G551D (present in ∼5% of patients). Ivacaftor activates the

CFTR-G551D mutant protein, a class III CFTR mutation that results in protein

localized to the plasma membrane but loss of chloride channel function .

Ivacaftor therapy resulted in improvement in FEV1 by an average of 10.6%, decreased the frequency of pulmonary exacerbations by 55%, decreased

sweat chloride by an average of 48 mEq/L, and increased weight gain by an

average of 2.7 kg. **Ivacaftor is approved for patients older than 2 yr of age with**

**class III and class IV mutations**.

The combination of ivacaftor with lumacaftor, a corrector that stabilizes

misfolded F508del and enables trafficking of the mutant molecule to the apical

cell membrane where it is potentiated by ivacaftor, is available for patients older

than 6 yr of age who are homozygous for the F508del mutation .

This medication is associated with smaller increments in pulmonary and

nutritional outcomes but is an important proof-of-concept treatment.

Tezacaftor and ivacaftor is another combination indicated for patients ≥ 12 yr

with 1 or 2 Phe508del alleles. This combination improves predicted FEV1 and

overall well-being.

**Other Therapies**

Expectorants such as iodides and guaifenesin do not effectively assist with the removal of secretions from the respiratory tract.

Inspiratory muscle training can enhance maximum oxygen consumption during

exercise, as well as FEV1

**Nutritional Therapy**

Up to 90% of patients with CF have loss of exocrine pancreatic function leading

to inadequate digestion and absorption of fats and proteins. They require dietary

adjustment and augmentation, pancreatic enzyme replacement, and

supplementary vitamins. In general, children with CF need to exceed the usual

required daily caloric intake to grow. Daily supplements of the fat-soluble

vitamins are required.

**Diet**

Most children with CF have a higher-than-normal caloric need because of

malabsorption despite the use of pancreatic enzyme supplementation.

Encouragement to eat high-calorie foods is important and often begins with

more concentrated, high-calorie formulas in the 1st yr. Even so, most mothers

can breastfeed successfully. It is vitally important to promote adequate weight

gain in the early years, both because of a clear relationship to later lung function

and also because early deficiencies make later catch up growth more difficult.

Maintenance of good weight gain and body mass index in the 1st yr of life

leads to better long-term preservation of lung function, but there is a strong

correlation between body mass index and FEV1 that persists through all ages in

people with CF. Better nutrition also leads to improved quality of life and

psychologic well-being and provides better reserves when weight loss occurs in

association with intermittent acute pulmonary exacerbations.

Malabsorption is an important contributor to nutritional deficiencies, and it is

important to ensure that pancreatic enzyme dosing is adequate and consistently

being taken correctly with all meals and feedings. Appetite stimulants when

cyproheptadine is not successful may include megestrol, oxandrolone,

dronabinol, antidepressants such as mirtazaoine, and even growth hormone. CFrelated diabetes needs to be ruled out.

When all these therapies fail, weight stabilization or gain can be achieved with

nocturnal feeding via nasogastric tube or gastrostomy tube.

**Pancreatic Enzyme Replacement**

Pancreatic exocrine replacement therapy given with ingested food reduces but

does not fully correct stool fat and nitrogen losses. Current products are entericcoated, pH-sensitive enzyme microspheres that come in capsules and given to children before they can swallow by opening the capsule and mixing the beads

in small amounts of acidic foods such as applesauce.

Administration of excessive doses has been linked to fibrosing colonopathy and **colonic strictures,** so recommendations are for enzyme dosing to stay below 2,500 lipase units/kg/meal in most circumstances. Snacks should also be covered. Some

individuals require proton pump inhibitor therapy to correct acid pH in the

duodenum which is due to lack of exocrine pancreatic secretions; neutralization

of duodenal pH permits activation of enteric-coated pancreatic exocrine

replacement therapy granules.

**Vitamin and Mineral Supplements**

Because pancreatic insufficiency results in malabsorption of fat-soluble vitamins

(A, D, E, K), vitamin supplementation is recommended.

They should be taken daily. Despite this supplementation, vitamin D deficiency is

common and should be treated with doses of cholecalciferol (vitamin D3) rather

than ergocalciferol (vitamin D2) in the range of 1,000 units/kg/wk. Salt

supplementation is also needed during infancy and is started at the time of

diagnosis.

**Salt Depletion**

Salt losses from sweat in patients with CF can be high, especially in warm arid

climates. Children should have free access to salt, especially when thirsty in hot

weather. Salt supplements are often prescribed to newborns and to children who

live in hot weather climates. Hypochloremic alkalosis should be suspected in any

patient who feels unwell in hot weather or who has had symptoms of

gastroenteritis, and prompt fluid and electrolyte therapy should be instituted as

needed.

**Treatment of Intestinal Complications**

**Meconium Ileus**

When meconium ileus is suspected, diatrizoate (Gastrografin) enemas with reflux of contrast material into the ileum not only confirm the diagnosis but may also result in the passage of meconium and clearing of the obstruction. Children in whom this procedure fails require operative intervention. Children who have had meconium ileus are at greater risk for nutritional deficiency and more likely to develop problems with DIOS when older. Infants with meconium ileus should be assumed to have CF unless proven otherwise.

**Distal Intestinal Obstruction Syndrome and Other Causes of Abdominal Symptoms**

Despite appropriate pancreatic enzyme replacement, a number of patients

accumulate fecal material in the terminal portion of the ileum and in the cecum,

which may result in partial or complete obstruction. For intermittent symptoms,

pancreatic enzyme replacement should be continued or even increased, and stool

hydrators such as polyethylene glycol (MiraLAX) should be given. If this fails

or symptoms are more severe, large-volume bowel lavage with a balanced salt

solution containing polyethylene glycol may be taken by mouth or by

nasogastric tube. When there is complete obstruction, a diatrizoate enema,

accompanied by large amounts of intravenous fluids, can be therapeutic.

**Prognosis**

CF remains a life-limiting disorder, although survival has dramatically improved

With exceptions, most children remain relatively healthy into adolescence or adulthood. The slow progression of lung disease eventually does reach disabling proportions. Life table data indicate a median cumulative survival of more than 40 yr, and the expectation is younger children with the disease have a life expectancy far in excess of this estimate.

Children with CF should not be restricted in their activities. A high percentage

eventually attend and graduate from college. Anxiety and depression are prevalent,

as in any other chronic disease, and impact quality of life and disease self management;