Crohn_Disease_UlcerativeColitis_Chole.doc

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Crohn Disease

Background
Crohn disease (CD) is a chronic inflammatory bowel disease. Once considered rare in the pediatric population, CD is recognized with increasing frequency among children of all ages. Approximately 20-30% of all patients with CD present when they are younger than 20 years. With its increasing recognition, CD has become one of the most important chronic diseases that affect children and adolescents.

In addition to the common GI symptoms of diarrhea, rectal bleeding, and abdominal pain, children often experience growth failure, malnutrition, pubertal delay, and bone demineralization. Other problems unique to the pediatric population include the paucity of controlled clinical trials and the psychological issues that occur in children and adolescents with CD. The unique problems encountered in the pediatric population necessitate a medical approach that promotes clinical improvement and reverses growth failure with minimal toxicity.

Causes
The etiology of CD is multifactorial. An interaction between the predisposing genetic factors, environmental factors, host factors, and triggering event is necessary for the disease to develop.

A high rate of concordance for CD between monozygotic twins (44.4%) compared with dizygotic twins (3.8%) was reported in a Swedish study of an unselected twin registry.3 Because monozygotic twins share identical genomic material and yet may be discordant for CD, the genetic component is necessary but not sufficient, as in all multifactorial diseases. About 30% of patients whose disease is diagnosed when they are younger than 20 years have a positive family history. The percentage decreases to 18% for patients whose disease is diagnosed at age 20-39 years and to 13% after age 40 years.

The first and best described disease-associated mutations for CD were found on the NOD2/CARD15 gene, which is found on chromosome 16 and regulates intracellular immune response to bacterial products. Strictures disease requiring early surgery, ileal involvement, and younger age at diagnosis are phenotypic characteristics that have been associated with recognized CARD15 mutations. Approximately 25% of white children have a CARD15 mutation compared with only 2% of black and Hispanic children.

Multiple additional genes associated with CD have been recently discovered. An association between mutations in the IL23R gene and inflammatory bowel disease has recently been confirmed, suggesting a major protective effect on susceptibility to CD. A predisposition to CD, specifically with ileal involvement, has been associated with a single nucleotide polymorphism (SNP) in the ATG16L1 gene, which is involved in autophagocytosis, an essential component of the innate immune response targeted towards pathogen-derived proteins.

Pathophysiology
The pathogenesis of CD is multifactorial. After a triggering event occurs in a genetically susceptible individual, an altered immune response leads to chronic inflammation of the intestine. Although the etiology of the precipitating event is unknown, luminal bacteria or specific antigens are thought to be involved.

Chronic inflammation from T-cell activation leading to tissue injury is implicated. After activation by antigen presentation, unrestrained responses of helper lymphocytes type 1 (Th1) predominate in CD because of defective regulation. Th1 cytokines, such as interleukin (IL)-12 and tumor necrosis factor (TNF)-alpha stimulate the inflammatory response. Inflammatory cells recruited by these cytokines release nonspecific inflammatory substances, including arachidonic acid metabolites, proteases, platelet activating factor, and free radicals, which result in direct injury to the intestine.

The macroscopic findings at the time of endoscopy and/or colonoscopy or surgery include various degrees of edema, erythema, ulceration, friability, thickening of the bowel wall and mesentery, and extension of fat over the serosal surface of the intestine (see Media file 1). Skipped areas of inflammation anywhere in the upper or lower GI tract are characteristic of CD, in contrast to the

- Crohn Disease
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continuous diffuse colonic inflammation found with ulcerative colitis (UC). Microscopic findings on intestinal mucosal biopsy consist of chronic inflammation with architectural distortion (see Media file 2). Granulomas (see Media file 3) are sometimes noted on biopsy findings in CD but never in UC; their presence can be useful in distinguishing between these 2 entities.

Frequency
The rate of CD in Europe is 2.1-3.7 cases per 100,000 population, and rates are somewhat higher in northern regions than southern regions. CD is rare in Africa, Asia, and South America.

Mortality/Morbidity
Death from CD is extremely rare in children and adolescents. Severe and complicated CD may result in prolonged hospitalizations, surgeries, growth failure, malnutrition, pubertal delay, and poor quality of life.

Race
CD is more common in whites than in blacks and is rare in Asian and Hispanic children. Rates are higher in people of Jewish descent, particularly Ashkenazi Jews and Jews of middle Eastern origin compared with Sephardic or eastern European Jews.

Sex
The rate of CD in women is 1.1-1.8 times higher than that in men.

Age
The rate of CD reaches its first peak in the second and third decade of life. The second, smaller peak occurs in adults aged 60-80 years.

Approximately 25% of all cases of inflammatory bowel disease are diagnosed before age 20 years.

Clinical History
Patients with suspected Crohn disease (CD) should initially be evaluated by their primary care physician. The patients' symptoms should be elicited in detail. A medical history, detailed review of systems, and family history should be obtained, and growth parameters should be documented.

In a large series of pediatric patients with CD from the Hospital for Sick Children in Toronto (n = 386), the distribution of presenting symptoms was as follows: abdominal pain in 86%, weight loss in 80%, diarrhea in 78%, blood in the stool in 49%, perianal lesions in 44%, and fever in 38%.²

The location and extent of the disease primarily determines the patient's clinical presentation. The terminal ileum is involved in 50-70% of children. More than half of these patients also have inflammation in various segments of the colon, usually the ascending colon. Overall, children seem to be more likely than adults to have colonic involvement; approximately 10-20% have isolated colonic disease. Gastric inflammation, duodenal inflammation, or both may be observed in as many as 30-40% of children with CD.

CD of the small intestine: Children with CD of the small intestine usually present with evidence of malabsorption, including diarrhea, abdominal pain, growth deceleration, weight loss, and anorexia. Initially, these symptoms may be quite subtle. The onset of growth failure is usually insidious, and any child or adolescent with persistent alterations in growth should undergo appropriate diagnostic evaluation for CD. Growth failure may precede GI symptoms by years.

Colonic CD: This may be clinically indistinguishable from ulcerative colitis (UC), with symptoms of bloody mucopurulent diarrhea, cramping abdominal pain, and urgency to defecate.

Perianal CD: Perianal involvement includes simple skin tags, fissures, abscesses, and fistulae. Symptoms of painful defecation, bright red rectal bleeding, and perirectal pain, erythema, or discharge may signal perianal disease and may occur without symptomatic involvement in any other area of the GI tract. The perineum should be inspected in all patients who present with signs and symptoms of CD because abnormalities detectable in this region substantially increase the clinical suspicion of inflammatory bowel disease.

Upper GI CD: Patients with this condition may experience nausea, vomiting, and abdominal pain as dominating presenting symptoms.

Physical
Findings on physical examination depend on the duration and extent of the disease and on the extraintestinal manifestations.

A careful assessment of growth and development is an important part of evaluating the pediatric patient. Growth abnormalities may be detected by evaluating several parameters: height and weight, percentage height and weight for the patient's age and percentage weight for the patient's height, growth velocity, body composition on anthropology, and skeletal bone age. The most sensitive indicator of growth abnormalities is a decrease in growth velocity, which may be observed before the major percentile lines on standard growth curves are crossed.

Growth failure and delayed sexual development are common in adolescents and children with CD. From studies of the growth of children with CD, impairment of linear growth was common before diagnosis and in subsequent years. Decrease in height velocity before the onset of intestinal symptoms
can be observed in as many as 46% of patients with Tanner stage 1 or 2. Height at maturity is often compromised. The etiology of growth failure is multifactorial, with nutritional, hormonal, and disease-related factors all contributing.

Vital signs are usually normal, although tachycardia may be present with anemic patients. Chronic intermittent fever is a common presenting sign.

Body weight and height may reveal weight loss and growth delay.

Abdominal findings may vary from normal to those of an acute abdomen. Diffuse abdominal tenderness is often present. Fullness or a discrete mass may be appreciated, typically in the right lower quadrant of the abdomen, which may represent a palpable thickened loop of bowel.

Perianal disease (eg, skin tags, abscesses, fistulae, fissures) is present in approximately 45% of patients.

Pubertal delay may precede the onset of intestinal symptoms, and accurate Tanner staging should be a part of routine physical examination.

The most common cutaneous manifestations of CD are erythema nodosum and pyoderma gangrenosum. Skin examination may also reveal pallor in patients with anemia or jaundice in those with concomitant liver disease. The most common skin manifestation of CD is erythema nodosum. Erythema nodosum is more common in CD than in UC and usually follows the course of the disease. Erythema nodosum affects 3% of pediatric patients with CD, less frequent than in adults. Approximately 75% of patients with erythema nodosum ultimately develop arthritis. The lesions of erythema nodosum are raised, red, tender nodules that appear primarily on the anterior surfaces of the lower leg.

Pyoderma gangrenosum is another skin manifestation, though it is uncommon in CD. Pyoderma gangrenosum is often an indolent chronic ulcer, which may occur even when the disease is in remission. Therefore, medical therapy for the underlying bowel disease is not always successful.

Aphthous ulceration in the mouth is the most common oral manifestation of CD. This ulceration is commonly associated with skin and joint lesions. Oral lesions appear to parallel intestinal disease in most cases, but they may also occur before any GI symptoms occur.

In CD, ophthalmologic manifestations most frequently occur when the disease is active. The rate is 4% in the adult population but is lower in children and adolescents. The most common ocular findings are episcleritis and anterior uveitis. The uveitis is usually symptomatic, causing pain or decreased visual acuity. Increased intraocular pressure and cataracts may be observed in children who receive corticosteroid therapy. All patients with CD require ophthalmologic examination at regular intervals.

The most common extraintestinal manifestations of CD are arthritis and arthralgia. The large joints (eg, hips, knees, ankles) are typically involved.

The most common extraintestinal manifestation in children and adolescents is arthritis (7-25% of pediatric patients). The arthritis is usually transient, nondeforming, asymmetric in distribution, and involves the large joints of the lower extremities. In adults, the arthritis occurs when the disease is active, but in children, the arthritis may occur years before any GI symptoms develop.

Urologic manifestations of CD include nephrolithiasis, hydrenephrosis, and enterovesical fistulae. Nephrolithiasis occurs in less than 5% of children with CD. Nephrolithiasis is usually the result of fat malabsorption that occurs with small bowel CD. Dietary calcium binds to malabsorbed fatty acids in the colonic lumen; therefore, free oxalate is absorbed. The absorption of free oxalate results in hyperoxaluria and oxalate stones. In patients with an ileostomy, increased fluid and electrolyte losses may lead to concentrated acidic urine and the formation of uric acid stones. External compression of the ureter by an inflammatory mass or abscess may lead to hydrenephrosis. Enterovesical fistulae may present with recurrent urinary tract infections or pneumaturia.

Hepatobiliary disease is one of the most common extraintestinal manifestations of CD and its therapies.

Abnormal serum aminotransferases are common during the course of CD in children. Most aminotransferase elevations are transient and appear to relate to medications or disease activity. Persistent aminotransferase elevations (>6 mo) should be investigated because the likelihood of serious liver disease is increased.

Both intrahepatic and extrahepatic manifestations of liver disease occur in children with CD. Intrahepatic manifestations include chronic active hepatitis, granulomatous hepatitis, amyloidosis, fatty liver, and pericholangitis. Extrahepatic manifestations include cholelithiasis and obstruction. Chronic active hepatitis and sclerosing cholangitis develops in fewer than 1% of children with CD.

Thromboembolic disease is considered the result of a hypercoagulable state that parallels disease activity and is manifested by thrombocytosis, elevated plasma fibrinogen, factor V, factor VIII, and decreased plasma antithrombin III. This may lead to deep vein thrombosis, pulmonary emboli, and neurovascular disease.

Differential Diagnoses: Behcet Syndrome, Tuberculosis, Ulcerative Colitis, Henoch-Schoenlein Purpura, Irritable Bowel Syndrome, Protein Intolerance, Infection, Celiac disease, Immunodeficiency, Chronic granulomatous disease, Radiation enteritis, Ischemic enterocolitis.
### Characteristics Differentiating CD and UC

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<thead>
<tr>
<th>Characteristic</th>
<th>CD</th>
<th>UC</th>
</tr>
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<tbody>
<tr>
<td>Distribution</td>
<td>Entire GI tract</td>
<td>Colon only, although gastritis recognized</td>
</tr>
<tr>
<td></td>
<td>Skip lesions</td>
<td>Granulomas (30%)</td>
</tr>
<tr>
<td></td>
<td>Full thickness</td>
<td>Entire GI tract</td>
</tr>
<tr>
<td>Pathology</td>
<td>Fistulas, abscesses, fibrotic strictures</td>
<td>Continuous involvement proximally from rectum</td>
</tr>
<tr>
<td>Cancer risk</td>
<td>Increased</td>
<td>Estimated 1% per year starting 10 years after diagnosis</td>
</tr>
<tr>
<td>Presentation</td>
<td>CD</td>
<td>UC</td>
</tr>
<tr>
<td>Bleeding</td>
<td>Common</td>
<td>Very common</td>
</tr>
<tr>
<td>Obstruction</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Fistula</td>
<td>Common</td>
<td>None</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Perianal disease</td>
<td>Common</td>
<td>Rare</td>
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### Laboratory Studies

Laboratory data are nonspecific. The CBC count may reveal evidence of hypochromic microcytic anemia due to the iron deficiency anemia secondary to GI blood loss, or it may reveal normocytic anemia due to the anemia of chronic disease.

Levels of acute-phase reactants, the erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels are often elevated in patients with Crohn disease (CD). However, a normal ESR or CRP level should not deter further evaluation in a suspicious case.

Hypoalbuminemia is a common laboratory finding in patients with CD. Additional common deficiencies include iron and micronutrients (eg, folic acid, vitamin B-12, serum iron, total iron binding capacity, calcium, magnesium). Stool studies should be obtained to rule out bacterial or parasitic infection.

Serologic testing for inflammatory bowel disease is available. Immunoglobulin A (IgA) and immunoglobulin G (IgG) antibodies to anti-Saccharomyces cerevisiae (ASCA) have been associated with CD, whereas perinuclear antineutrophil cytoplasmic antibody (p-ANCA) has been associated with ulcerative colitis (UC). Although these tests might assist in differentiating between CD and UC, they are not good screening tests. A retrospective review reported that serologic screening that included ASCA, perinuclear antineutrophil cytoplasmic antibody (pANCA), and antibody to Escherichia coli outer membrane porin (anti-OmpC) demonstrated a sensitivity of 60%, a specificity of 91%, and a positive predictive value of 60%.

Excretion of fecal calprotectin, a protein derived from neutrophils, is increased with colorectal inflammation. Enzyme-linked immunosorbent assay for fecal calprotectin is available; the cutoff level is more than 50 mcg/g feces.

### Imaging Studies

A single-contrast upper-GI tract radiologic series with small-bowel follow-through (SBFT) can be used to evaluate the small intestine, which cannot be reached during endoscopy.

In older children, double-contrast radiography (enteroclysis) is used to examine fine mucosal details. CT scanning is useful in the assessment of abscess and phlegmon.

Radionuclide-tagged WBC scanning can be helpful. However, upper-GI involvement cannot be assessed with WBC scanning, and agreement with endoscopic findings is poor for topographic localization of lower-GI disease.

MRI is becoming a standard diagnostic tool for the detection of inflammation in the intestine. MRI is especially useful in the evaluation of pelvic and perianal disease.

Abdominal ultrasonography can be used to investigate intestinal disease and to rule out gallbladder and kidney stones.

Positron emission tomography can be an experimental diagnostic tool.

### Procedures

The development of flexible, small-caliber endoscopes has allowed for colonoscopic evaluation of pediatric patients of all ages, including infants.
Colonoscopy with several colonic and terminal ileal biopsies is invaluable and considered a standard in the diagnosis of CD.

Upper endoscopy, or esophagogastroduodenoscopy (EGD), should be part of the first-line investigation in all new cases of suspected CD. It is useful in planning therapy and in differentiating between CD and UC, especially if granulomas are present. Clinically significant upper-tract inflammation can be present in the absence of upper-GI symptoms.

Video capsule endoscopy is being increasingly used to evaluate for small-bowel CD in children. A dissolvable patency capsule or upper GI with SBFT should be performed first to ensure that no area of narrowing at which the capsule could obstruct is present.

Histologic Findings
The microscopic findings of intestinal biopsy samples consist of edema, inflammation (mononuclear and polymorphonuclear), cryptitis and crypt abscesses, architectural crypt changes, and transmural extension of the inflammation. The presence of granulomas may be helpful in differentiating between UC and CD, but granulomas are present in only about 30% of biopsy specimens obtained from patients with CD.

Treatment
Diet
Patients are advised to avoid food that is difficult to digest because it is rich in insoluble fiber (eg, uncooked vegetables, popcorn, seeds, nuts) in order to prevent intestinal obstruction. The obstruction may be due to narrowing or stricture secondary to the inflammation in the small intestine. No other empiric dietary restrictions are recommended, although patients are advised to avoid any foods that tend to exacerbate their disease.

Nutritional therapies are used for treatment of mild and moderate-to-severe disease, maintenance of remission, and nutritional rehabilitation. In addition to the beneficial nutritional effect, the formula is thought to have anti-inflammatory properties.

Activity
The goal of the therapy is to allow normal unrestricted activity. Patients with osteoporosis secondary to prolonged corticosteroid therapy should avoid high speed and high impact contact sports to minimize the risk of fracture.

Medical Care
The general goals of treatment for children with CD are (1) to achieve the best possible clinical, laboratory, and histologic control of the inflammatory disease with the least adverse effects from medication; (2) to promote growth with adequate nutrition; and (3) to permit the patient to function as normally as possible (eg, in terms of school attendance, participation in activities). Treatment has changed over the past few years, reflecting the development of new agents that can target specific locations in the GI tract and specific cytokines.

1. Typically, therapy for pediatric CD is administered in a step-up approach. Patients with mild disease are treated with preparations of 5-aminosalicylic acid (5-ASA), antibiotics, and nutritional therapy. If no response occurs or if disease is more severe than initially thought, corticosteroid and immunomodulatory therapy with 6-mercaptopurine (6-MP) or methotrexate (MTX) is attempted. Finally, biologic and surgical therapies, at the tip of the treatment pyramid, are used.
2. -ASA preparations
3. Although commonly used, recent adult meta-analyses have suggested that oral-ASA preparations do not demonstrate clinically important treatment effect for active Crohn disease (CD) and are not superior to placebo for the maintenance of remission in CD.
4. Topical-ASA therapy is available in suppository and enema forms for the treatment of distal colitis.

Nutritional therapy
Nutritional therapy is another important modality for the treatment of disease, malnutrition, and growth failure observed in CD. A dramatic reversal of malnutrition and a change in growth velocity can be expected in all children treated with adequate nutrition in conjunction with medical therapy to control symptoms of CD. Additionally, exclusive enteral nutrition has been shown to be as effective as corticosteroids for the induction of remission and might promote better GI tract mucosal healing.

Because most patients have appetite suppression, overnight nasogastric feeds are often used. Although the exact mechanism of action is unknown, beneficial effects could be due to alteration of the intestinal flora, decrease in the antigen load, and decrease in inflammatory cytokine levels.

Corticosteroids
These are the mainstay of therapy for acute exacerbations because they suppress acute inflammation, thereby providing rapid symptomatic relief. Systemic corticosteroids are not indicated for maintenance therapy. Enteric coated ileal-release preparations have been developed for the treatment of ileal and cecal CD with decreased systemic effects.

Immunomodulators
Immunomodulators have been used to induce and maintain long-term remission in chronically active,
steroid-dependent or steroid-refractory, moderate-to-severe pediatric CD.

6-mercaptopurine (6-MP) and its prodrug, azathioprine, are effective for the induction and maintenance of remission and reduction of corticosteroid exposure in pediatric CD. Three months is often required to achieve therapeutic efficacy, although the onset of action varies.

Thiopurine methyltransferase (TPMT) activity should be measured prior to initiation of therapy to identify patients predisposed to altered drug metabolism, increasing the risk of leukopenia.

Measurement of 6-thioguanine nucleotide (6-TG) metabolites are helpful in assessing compliance and adjusting therapy.

Methotrexate (MTX) is effective in inducing and maintaining remission in chronic CD in adults, and retrospective studies have suggested good efficacy and safety profile in pediatrics. The onset of action is shorter for MTX than for 6-MP, and the once-weekly dosing is sometimes preferred. Whether oral therapy is as effective as parenteral administration is unclear.

Antibodies to TNF-alpha

Infliximab, a chimeric monoclonal antibody to TNF-alpha, is effective in patients who have an inadequate response to conventional therapy and for the treatment of fistulizing CD. Infliximab has been approved for the treatment of pediatric CD. Current clinical practice is to use it as an intravenous (IV) infusion of 5 mg/kg at 0, 2, and 6 weeks, followed by maintenance IV infusions every 8 weeks.

Adalimumab, a fully humanized anti-TNF-alpha antibody, is a safe and effective substitute for patients who are allergic to infliximab or develop high titers of human antichimeric antibodies (HACA).

Antibiotics: A few, small studies have shown the usefulness of antibiotic therapy in the treatment of CD. Metronidazole, as well as the combination of metronidazole and ciprofloxacin, is useful in both the management of perianal disease and small bowel and colonic disease.

Alternative and complimentary therapies: Patients and their families frequently use alternative and complimentary therapies. A potential beneficial effect has been observed with omega-3 fatty acids found in fish oil. Probiotics might provide some treatment benefit, although studies have provided inconsistent results.

Surgical Care

Surgery is considered when medical therapy fails. Indications include intractable disease with growth failure, obstruction or severe stenosis, abscess requiring drainage, perianal fistulae, intractable hemorrhage, and perforation. Recurrence of disease at the anastomotic site is common after resection. Surgical treatment for CD, unlike that for ulcerative colitis (UC), is not curative. Laparoscopic techniques have shown promising results in children with CD, speeding recovery and shortening hospital stays.

Complications

The major intestinal complications of CD are due to the transmural nature of the disease. This leads to the formation of abscesses, fistulae, sinus tracts (incomplete fistulae ending in a "cul de sac"), strictures, and adhesions, which may also contribute to obstruction.

Frank perforation is one of the most serious complications of CD. Perforation typically occurs into other segments of bowel, leading to fistulae, or to areas such as the retroperitoneum, resulting in abscess formation. The presenting features of frank perforation are those of classic peritonitis, although high-dose corticosteroid therapy may mask these features.

Fistula and abscess formation is common in CD and is due to transmural bowel perforation. Perianal and perirectal fistulization are most common. Proper evaluation of perianal disease includes evaluation for perianal abscess or fistula.

Colonic malignancy is a clinically significant complication of CD in patients with pancolitis beginning in childhood.

Although the risk of malignancy in CD is not as high as that in ulcerative colitis (UC), the risk of adenocarcinoma of the colon in Crohn colitis is 4-20 times that of the general population. Small intestinal carcinoma is 50-100 times more likely to develop in patients with small intestinal CD but is still rare. The risk for children with an onset of disease in the first decade is unknown, but children who develop colitis when younger than 10 years should undergo colonoscopic screening during adolescence.

Epithelial dysplasia generally precedes carcinoma; therefore, yearly surveillance colonoscopy is recommended for patients with this condition, who are at high risk.

Approximately 25-35% of patients with CD have at least one extraintestinal manifestation, which may be diagnosed before, when, or after CD is diagnosed. Extraintestinal manifestations may carry prognostic importance and include the following:

**Dermatologic manifestations:** Erythema nodosum, Pyoderma gangrenosum, Orofacial granulomatosis, Angular and aphthous stomatitis, Acrodermatitis enteropathica, Alopecia, CD of the vulva and penis.

**Ophthalmologic manifestations:** Episcleritis, Uveitis, ritis, Conjunctivitis.

**Musculoskeletal manifestations:** Arthralgia, Arthritis, Ankylosing spondylitis, Sacroiliitis.

**Bone metabolic disorders:** Osteopenia, Osteoporosis.

**Hematologic manifestations:** Iron deficiency anemia, Vitamin B12 deficiency anemia, Folate deficiency.
Ulcerative colitis

Background
Ulcerative colitis (UC) is a disease characterized by remitting and relapsing inflammation of the large intestine. UC and Crohn disease (CD) account for the disorders that represent the inflammatory bowel diseases (IBDs). The hallmark symptoms of UC include abdominal cramping, diarrhea, and bloody stools. Many patterns of presentation are possible in the pediatric age group. UC is generally considered to always affect the rectum, with contiguous involvement that can include the entire large intestine.

Frequency
About 20% of patients with UC present before age 20 years. The incidence rate for UC in North Americans aged 10-19 years is approximately 2 cases per 100,000 persons. No simple Mendelian genetic mechanism explains the transmission of IBD, yet many familial occurrences are known in 15-20% of patients. Patients in whom disease is diagnosed before age 20 years appear to have an associated family history of the disease.

Race
Early studies tended to show a higher prevalence of UC in white Americans than in black Americans. Over time, this trend seems to be decreasing, with recent incidence rates nearly the same. Asian Americans appear to have low incidences. Several studies have shown that the incidence of IBD in white Americans is up to 4 times higher in Jewish people than among other racial or ethnic groups.

Sex
No sex predilection for UC is reported.

Age
In most studies, incidence of UC peaks between adolescence and early adulthood (ie, in people aged 15-30 y).
A smaller peak occurs in patients aged 60-80 years.
UC occurs less frequently in children younger than 5 years than in others.

Causes
UC is thought to be a multifactorial disease.
Data from genetic epidemiologic studies strongly support the role of genetic factors in UC. Concordance is higher among monozygotic twins than among dizygotic twins; however, the lack of perfect concordance in monozygotic twins suggests other factors in the etiology of UC as well.
Several environmental factors have been implicated in the pathogenesis of IBD.
Smoking influences the course of IBD (positively in UC, negatively in CD).
Certain infections have been implicated in IBD (eg, measles, atypical mycobacteria infection).
Patients with IBD have been shown to have different colonizing bacteria than people without IBD.

Pathophysiology
UC is characterized by accumulations of polymorphonuclear neutrophils in the crypts of the colon (crypt abscesses) with epithelial ulceration, edema, and hemorrhage. These changes may represent the final common pathway of a heterogeneous group of diseases relating to genetic and environmental
The mucosal immune system of the large intestine is continuously exposed to a wide array of antigens from ingested food products and from the billions of bacteria that live there. When activated, the cells of the mucosal immune system release cytokines that recruit inflammatory cells to the tissue and perpetuate the inflammatory response. In patients with IBD, the inflammatory response to luminal antigens may be exaggerated over that seen in healthy individuals or they may not respond normally to down-regulation. The patient's genetic background likely determines when and how the inflammatory cells of the mucosal immune system react to the environment.

Clinical History

Ulcerative colitis (UC) is a diffuse mucosal inflammation limited to the colon that affects the rectum and may extend proximally in a symmetric uninterrupted pattern to involve parts or all of the large intestine. Because UC is a mucosal disease limited to the colon, the most common presenting symptoms are rectal bleeding, diarrhea, and abdominal pain. Many patterns of presentation occur in the pediatric age group.

Mild disease is observed in 50-60% of patients. This presentation involves insidious onset of diarrhea, later associated with hematochezia. No systemic findings of fever, weight loss, or hypoalbuminemia are observed. UC is typically confined to the distal colon and responds well to therapy.

Moderate disease is observed in 30% of patients and is characterized by bloody diarrhea, cramps, urgency to defecate, and abdominal tenderness. Associated systemic findings, such as anorexia, weight loss, low-grade fever, and mild anemia, are present.

Severe colitis occurs in approximately 10% of patients. This presentation involves more than 6 bloody stools per day, abdominal tenderness, fever, anemia, leukocytosis, and hypoalbuminemia. Patients with severe colitis may experience life-threatening complications, including severe hemorrhage, toxic megacolon, or intestinal perforation.

Less than 5% of children with UC present with predominantly extraintestinal manifestations, such as growth failure, arthropathy, skin manifestations, or liver disease.

Recently, a clinical scoring system known as the Pediatric Ulcerative Colitis Activity Index (PUCAI) has been developed and validated. The PUCAI may be used more frequently to assess disease activity in clinical trials involving pediatric patients with UC.

Physical

The findings on physical examination in UC vary depending on the extent, duration, and severity of the disease. In addition to abdominal signs, many extraintestinal manifestations of UC may become evident during physical examination.

Vital signs may indicate fever.

Tachycardia may represent anemia or hypovolemia.

Tachypnea may be present because of abdominal splinting or as a compensatory mechanism for acidosis in cases of severe dehydration.

Comparison with growth charts may reveal delayed growth.

Cushingoid appearance is indicative of steroid use, usually over a long period. The patient may appear toxic in cases of fulminant disease.

Long-standing and severe disease may cause signs of malnutrition, such as muscle wasting.

Abdominal examination findings are sometimes normal, but examination is likely to reveal abdominal tenderness.

Voluntary or involuntary guarding may be present.

Bowel sounds may be normal, hyperactive, or hypoactive.

Rushes or high-pitched tinkling may be found in cases of obstruction.

Rebound tenderness indicates severe disease and possible perforation.

A palpable mass may indicate obstruction or megacolon.

An enlarged spleen may be indicative of portal hypertension from associated autoimmune hepatitis or primary sclerosing cholangitis.

Skin examination may reveal pallor in cases of anemia, decreased skin turgor in cases of dehydration, and jaundice, caput medusae, or spider angioma when associated liver involvement is present. Erythema nodosum may be evident on extensor surfaces (but more common in Crohn disease [CD] than UC); pyoderma gangrenosum affects approximately 1% of patients with UC. Patients with episcleritis can present with a painful erythematous eye.

Scleral icterus may be indicative of liver disease.

Joint pain (arthralgia) is a common finding in inflammatory bowel disease (IBD), although swollen or red joints (arthritis) occur less frequently. The large peripheral joints, such as the knees, ankles, wrists, and elbows, are most commonly involved, but any joint can be involved. Approximately 1% of patients with UC develop ankylosing spondylitis; most of these patients test positive for human leukocyte antigen (HLA) type B27.
Unlike what is seen in some patients with CD, perianal examination in patients with UC should not reveal any evidence of fistulae or abscesses; however, chronic diarrhea may lead to perianal erythema, fissuring, or hemorrhoids.

Sexual development may be delayed in patients with UC, but this finding is more common in patients with CD than in UC.


Other Problems to Be Considered: Pseudomembranous (Clostridium difficile) colitis, Infectious colitis (due to Escherichia coli or Yersinia, Salmonella, or Shigella species).

Laboratory Studies

- CBC count commonly reveals a mild anemia, which can be due to chronic blood loss (ie, microcytic, hypochromic) or may represent chronic disease (ie, normocytic). In cases of fulminant colitis, severe anemia may be present.
- Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level are frequently elevated during active disease.
- Result for antineutrophil cytoplasmic antibody with a perinuclear staining pattern (p-ANCA) are positive in up to 80% of patients with ulcerative colitis (UC) and in up to 20% of patients with Crohn disease (CD).
- Serum albumin levels may be low in fulminant colitis.
- Fecal calprotectin may be elevated during times of active inflammation.
- Calprotectin is a calcium-binding S-100 protein found in the neutrophil cytosol that is released with cell activation or death.

- An assay for calprotectin is now commercially available and may be useful to differentiate a disease flare from other causes of abdominal pain or diarrhea.
- Micronutrient and vitamin levels are typically low in CD but less commonly so in UC.
- Obtain stool cultures to rule out infectious colitis. Obtain an assay for E coli H7:0157 if the patient's symptoms are consistent with hemolytic uremic syndrome.
- Obtain a stool assay for C difficile toxins A and B because C difficile colitis can mimic UC or it may be responsible for a flare. Evaluation for toxin A or toxin B alone is inadequate for an accurate diagnosis of C difficile infection.
- Liver dysfunction may indicate sclerosing cholangitis or autoimmune hepatitis.

Imaging Studies

- An abdominal obstruction series (ie, supine and upright abdominal radiography) is useful to evaluate for air-fluid levels, dilated loops of bowel, evidence of obstruction, or possible toxic megacolon. No pathognomonic findings for UC on this type of study are reported.
- Barium enema study is useful to evaluate the colon for stricture and for mucosal abnormalities, especially when colonoscopy cannot be performed. Barium enema studies may also demonstrate source of bleeding other than UC, such as a polyp.
- An upper GI series with small-bowel follow-through is used to evaluate for small-bowel inflammation that would support a diagnosis of CD rather than UC.
- CT scanning of the abdomen is useful to evaluate for bowel-wall thickening and obstruction. If present, abscesses and fistulae imply a diagnosis of CD rather than UC.
- Radionuclide-tagged WBC scanning can be used to demonstrate small-bowel inflammation that differentiates CD from UC.
- MRI of the abdomen is increasingly used to evaluate the large and small bowel for inflammatory changes and to look for transmural versus mucosal inflammation.
- Wireless video capsule endoscopy, also known as the Pillcam, is an increasingly used imaging technology that may reveal small bowel involvement in inflammatory bowel disease (IBD) that differentiates CD from UC.

Procedures

- Colonoscopy with biopsy is the most valuable procedure in the evaluation of the patient with IBD.
- Typical findings in someone with UC are inflammation first evident in the rectum that proximally extends in a contiguous fashion. The mucosa typically appears erythematous, friable, and granular, and it has lost the normally visible vascular markings.
- Findings more consistent with CD than with UC are sparing of the rectal mucosa, aphthous ulceration, and noncontiguous or skip lesions.
- When possible, visualizing the entire colon and the last portion of the ileum (terminal ileum) is best because the terminal ileum is not actively involved in UC but is commonly involved in CD. However, patients with pancolitis occasionally have microscopic inflammation in the terminal ileum, which is thought to be secondary to reflux of colonic contents through an inflamed ileocecal valve (ie, backwash ileitis).

Histologic Findings

- Biopsy findings consistent with UC are polymorphonuclear leukocytes near the base of the crypts.
- Cryptitis describes aggregation of polys in the crypt epithelium, and the term crypt abscess is used
when polys have accumulated in the lumen of the crypt.

Lymphocytes, eosinophils, and mast cells may also be observed in the lamina propria in acute UC. However, no pathognomonic biopsy findings have been described for UC.

Noncaseating granulomas are diagnostic of CD.

Treatment

Diet

Patients with fulminant disease, possible obstruction, or possible toxic megacolon should ingest nothing by mouth (NPO) until their condition is stable.

Patients should avoid poorly digested foods, such as uncooked vegetables, seeds, nuts, and high roughage, especially patients with stricture or narrowing.

Activity

The goal of therapy is to allow normal, unrestricted activity.

Medical Care

The general goals for managing inflammatory bowel disease (IBD) in children are to achieve the best possible clinical and laboratory control of the disease with the least adverse effects while permitting the patient to function as normally as possible.

Most patients with ulcerative colitis (UC) can be treated on an outpatient basis. Hospitalization is necessary when maximal outpatient therapy is unsuccessful or when patients develop severe disease.

5-Aminosalicylate (5-ASA)

The mainstay of outpatient management is anti-inflammatory therapy with 5-ASA preparations. Sulfasalazine (Azulfidine) was the first 5-ASA preparation available for the treatment of UC. More recently, mesalamine (Pentasa, Asacol) was introduced. Mesalamine may have fewer adverse effects than sulfasalazine because the sulfa component has been removed. However, mesalamine is not available in a pediatric preparation.

Asacol tablets must be swallowed whole, which limits its use in young children.

Pentasa capsules may be opened so that the granules can be swallowed from a spoon (eg, mixed with applesauce), but this exposes the medicine to degradation high in the GI tract not affected in UC.

Balsalazide (Colazal) is another form of 5-ASA that is active in only the colon.

Corticosteroids

Corticosteroids (eg, prednisone) are effective in controlling acute flares of disease but less effective at maintaining long-term remission, and numerous adverse effects make their long-term use undesirable.

Corticosteroids are known to cause linear growth failure, which can be a clinically significant problem in the patient with IBD. Corticosteroids cause osteoporosis, which can also be a problem, which leads to compression fractures of the spine.

The many undesirable cosmetic effects of corticosteroids include weight gain, acne, and cushingoid appearance.

Steroids may cause agitation and restlessness, as well as personality changes, such as irritability or emotional lability.

Despite the undesirable adverse effects, some patients depend on steroids to keep their disease under control. In other patients, the disease does not respond well to steroids. When a patient with UC demonstrates signs of steroid dependence, other treatments should be used to limit the patient's steroid exposure.

Immunomodulatory agents

Immunomodulatory agents are purine analogs that inhibit purine ribonucleotide synthesis and cell proliferation. Immunosuppressive agents also inhibit the immune response of natural killer cells and cytotoxic T cells.

Use immunomodulatory agents, such as 6-mercaptopurine (Purinethol) and azathioprine (Imuran), in patients with IBD who are steroid dependent or whose disease is refractory to steroid treatment. These medications take approximately 3 months to have effect and, therefore, are not useful in acute exacerbations of disease.

Although immunomodulatory agents are usually well tolerated, they do have the potential adverse effects of pancreatitis, hepatitis, and bone-marrow suppression. The pancreatitis is usually an idiosyncratic reaction that is not dose related and that resolves on removal of the drug. The hepatitis appears to be related to the buildup of a metabolite of the medication and may resolve when the dose is adjusted. Bone-marrow suppression is dose related and may have delayed onset.

Monitor patients for leukopenia on a frequent basis early in the course of therapy and then less so later on.

Intravenous corticosteroids

Intravenous corticosteroids (eg, methylprednisolone) may be effective in inducing remission when oral steroids are ineffective.

Significantly increased efficacy does not appear to occur with doses above 2 mg/kg/d (not to exceed 48 mg/d).

High-dose intravenous steroids have the adverse effects of oral steroids and increase the likelihood of hyperglycemia and hypertension.
Cyclosporine

Cyclosporine (cyclosporin A) is a potent inhibitor of the inflammatory cascade that primarily acts by inhibiting interleukin (IL)-2 production, though it also decreases the recruitment of cytotoxic T cells and blocks other inflammatory cytokines.

In refractory fulminant UC, cyclosporine has effectively induced remission, obviating immediate surgery. Because cyclosporine is such a potent immunosuppressive agent, the physician must be absolutely certain that an infection is not contributing to the colitis. The patient must also be considered susceptible to opportunistic infections, such as those due to cytomegalovirus (CMV) and Pneumocystis carinii.

Cyclosporine is nephrotoxic and may cause irreversible renal insufficiency. In addition, cyclosporine is epileptogenic and may precipitate seizures in patients, especially those with low cholesterol or magnesium levels.

Because of its many potential toxicities, only physicians who are experienced in its administration should use cyclosporine. In addition, for patients with UC, strongly consider surgical colectomy to treat fulminant disease because of the long-term risk of cancer and the curative nature of the surgery.

Infliximab

Infliximab is a monoclonal antibody against tumor necrosis factor (TNF)-alpha, a proinflammatory cytokine that occurs early in the inflammatory cascade.

Infliximab is effective in treating Crohn disease (CD) and has recently received attention and indications for use in UC.3

The drug is given as an intravenous infusion, typically in an induction regimen of 2 infusions over 2 weeks. In several reports, refractory UC responded to infliximab, and emergency colectomy was avoided.

In a retrospective series of pediatric patients with UC, 100% of patients were short-term responders, with 75% showing complete resolution of symptoms and the remaining 25% showing partial improvement after a median of 6 infusions; 67% were long-term responders after a median of 10.4 months.4 A better response was noted in patients who were considered steroid-dependent rather than steroid-refractory. A better response to infliximab infusions was also observed among patients concurrently taking 6-mercaptopurine; however, the concurrent use of 6-mercaptopurine and infliximab has become more controversial following reports of hepatosplenic T-cell lymphoma in patients with IBD receiving both medications.

Surgical Care

If colectomy is not performed to control symptoms, the risk of death from colon cancer is about 8% 10-25 years after colitis is diagnosed. Therefore, surgical removal of the colon is a virtual necessity for most patients with UC. Because UC is limited to the colon, colectomy is considered a curative procedure.5

Approximately 5-10% of patients with UC require acute surgical intervention because of fulminant colitis refractory to medical therapy.

In children, elective colectomy is indicated when refractory disease significantly interferes with their growth and nutrition or with their ability to maintain a normal lifestyle (ie, attend school) or when dysplasia or malignancy is detected.

The most common procedure is the ileo-pouch anal anastomosis, in which an ileal pouch is connected to the anus to maintain continence.

Complications

Toxic megacolon is the most serious acute complication of ulcerative colitis (UC) and is reported to occur in up to 5% of patients; it is rare in young patients.

Consider toxic megacolon a medical and surgical emergency.

The pathogenesis of toxic megacolon is related to severe inflammation resulting in disordered intestinal motility. Disrupted mucosal integrity then may allow bacteria to enter the submucosal tissues, leading to necrosis and peritonitis. Absorptive function is also impaired, resulting in increased luminal fluid volume and electrolyte losses. Toxic megacolon usually occurs in the presence of severe pancolitis. Use of antidiarrheal agents or recent barium enema study or colonoscopy has been implicated as causes of this condition. In addition, metabolic abnormalities (eg, hypokalemia, hypomagnesemia, hypoproteinemia), impaired epithelial integrity of the colon, and altered motor function and are frequently found in patients with toxic megacolon.

Toxic megacolon is associated with fever, abdominal distention, and tenderness. Abdominal obstruction series reveals dilatation of the colon with loss of normal haustral markings and signs of edema. Toxic megacolon places the patient at risk for colonic perforation, gram-negative sepsis, and massive hemorrhage.

Colonic malignancy is a clinically significant complication in patients with UC.

The duration of disease and pancolitis are well-recognized risk factors for malignancy, with the risk of cancer increasing over that of the general population after 10 years. Other less-characterized risk factors include sclerosing cholangitis, a bypassed and defunctionalized segment of bowel, and a low folate level.

Children who develop UC before age 14 years have a cumulative colorectal-cancer incidence of 5% at
age 20 years and 40% at age 35 years. Patients aged 15-39 years who develop UC have a cumulative incidence of 5% at age 20 years and 30% at age 35 years. The risk for children with onset of disease in the first decade of life is unknown, but these children should undergo colonoscopic screening for dysplasia beginning in adolescence.

Epithelial dysplasia generally precedes carcinoma; therefore, perform yearly screening with surveillance colonoscopy and biopsy. Dysplasia can be missed on surveillance biopsy; therefore, consider prophylactic colectomy in adults who developed UC during childhood. With this in mind, psychologically prepare adolescents and young adults by discussing surgical options before the need for surgery arises.

Extraintestinal manifestations are common in UC. Approximately 25-35% of patients with inflammatory bowel disease (IBD) have at least one extraintestinal manifestation. Extraintestinal disease may be prognostically important because the rate of pouchitis increases after colectomy in patients with UC and extraintestinal manifestations.

Pyoderma gangrenosum occurs in 1% of patients with UC. An indolent chronic ulcer may occur even when disease is in remission. Intralesional therapy with steroids is useful, and colectomy results in healing in approximately one half of patients.

Ophthalmologic manifestations most frequently occur when the disease is active. The incidence in adults is 4% but is less in children. The most common findings are episcleritis and anterior uveitis. Uveitis is usually symptomatic, causing pain or decreased vision. Patients with IBD should likely undergo routine ophthalmologic examination.

Arthritis is the most common extraintestinal manifestation of IBD, occurring in 10-25% of adolescents. The arthritis is usually a transient, nondeforming synovitis that involves the large joints in an asymmetric distribution. In children, arthritis may precede GI symptoms by years.

Hepatobiliary disease is another common extraintestinal manifestation of UC in children. Hepatobiliary complications may precede the onset of GI symptoms, they may accompany active disease, or they may develop after surgical resection. Chronic active hepatitis, granulomatous hepatitis, amyloidosis, fatty liver, and pericholangitis are some of the intrahepatic manifestations of IBD. Extrahepatic manifestations include cholelithiasis and primary sclerosing cholangitis.

Thromboembolic disease is considered to be the result of a hypercoagulable state that parallels disease activity and is manifested by thrombocytosis; elevated plasma fibrinogen, factor V, and factor VIII; and decreased plasma antithrombin III. The hypercoagulable state may lead to deep venous thrombosis, pulmonary emboli, and neurovascular disease.

Cholecystitis and Cholelithiasis.

Acute cholecystitis occurs in childhood very rare. Chronic cholecystitis is caused by dyscholia, dyskinesia and congenital anomalies of bile ducts.

Acute acalculous cholecystitis is uncommon in children and is usually caused by infection. Pathogens include streptococci (groups A and B), gram-negative organisms, particularly Salmonella, and Leptospira interrogans. Parasitic infestation with ascaris or Giardia lamblia may be found. Acalculous cholecystitis may rarely follow abdominal trauma or burn injury or may be associated with a systemic vasculitis, such as periarteritis nodosa.

Clinical features include right upper quadrant or epigastric pain, nausea, vomiting, fever, and jaundice. Right upper quadrant guarding and tenderness are present. Ultrasonography discloses an enlarged, thick-walled gallbladder, without calculi. Serum alkaline phosphatase activity and direct-reacting bilirubin levels are elevated. Leukocytosis is usual.

Criteria of diagnosis

1. Clinical
   - presence of relapses with marked intoxication;
   - subfebrile condition;
   - intensive pain in the right hypochondrium;
   - nausea, vomiting;
   - constipation;
   - yellowish fur; the enlarged liver (the lower margin is not lower than 1-2 cm below the costal arch);
positive bladder signs (Örntner, Merfi, frenicus, Boas, Ker).

II. Laboratory:
indicators of active inflammatory process (WBC - leucocytosis, sometimes leukopenia, ESR is increased; proteinogram reveals increased level of gamma-globulin);
the signs of dyscholia (decreased level of bilirubin in bile);
shift of bile pH to acidity.

III. Instrumental:
USE plays a decisive role (the gall-bladder wall is thickened by more than 1.5 mm).
Relative meaning has:
- increased amount of leukocytes and epithelium cells (more than 10) in B portion of duodenal contents according to the results of duodenal tubing;
- revealing microbes or lamblias (giardias) in duodenal content.
The diagnosis is confirmed at laparotomy. Cholecystectomy and treatment of the systemic infection are required.

**Cholelithiasis** is relatively rare in otherwise healthy children, occurring more commonly in patients with various predisposing disorders.

**Conditions Associated with Cholelithiasis**
- Chronic hemolytic disease (sickle cell anemia, spherocytosis)
- Obesity
- Ileal resection or disease
- Cystic fibrosis
- Chronic liver disease
- Crohn disease
- Prolonged parenteral nutrition
- Prematurity with complicated medical or surgical course
- Prolonged fasting or rapid weight reduction
- Treatment of childhood cancer
- Abdominal surgery

Gallstones, composed of a mixture of cholesterol, bile pigment, calcium, and inorganic matrix, are common. In children, more than 70% of gallstones are the pigment type, 15–20% are cholesterol stones, and the remainder is of unknown composition. Stones of pure cholesterol or bile pigment may also occur. Biliary dyskinesia, a disorder of impaired gallbladder contractility, is an abnormality predisposing to gallstones in late childhood and teenage years.

Acute or chronic cholecystitis is often associated with gallstones. The acute form may be precipitated by impaction of a stone in the cystic duct. Proliferation of bacteria within the obstructed gallbladder lumen can contribute to the process and lead to biliary sepsis. Chronic calculous cholecystitis is more common. It may develop insidiously or follow several attacks of acute cholecystitis. The gallbladder epithelium commonly becomes ulcerated and scarred.

The most important clinical feature of cholelithiasis is recurrent abdominal pain, which is often colicky and localized to the right upper quadrant. An older child may have intolerance for fatty foods. Acute cholecystitis may be the first manifestation, with fever, pain in the right upper quadrant, and often a palpable mass. Pain may radiate to an area just below the right scapula. A plain roentgenogram of the abdomen may reveal opaque calculi, but radiolucent (cholesterol) stones are not visualized. Accordingly, ultrasonography is the method of choice for gallstone detection. Hepatobiliary scintigraphy is a valuable adjunct in that failure to visualize the gallbladder provides evidence of cholecystitis.

Cholecystectomy is usually curative; operative cholangiography should be done at the time of surgery to preclude common duct calculi. Dissolution of cholesterol gallstones with oral ursodeoxycholic acid is ineffective in the treatment of gallstones in children, except in terms of relieving symptoms while on treatment.

Laparoscopic cholecystectomy is commonly performed in symptomatic infants and children with cholelithiasis. Common bile duct stones are unusual in children, occurring in 2–6% of cases with cholelithiasis, often in association with obstructive jaundice and pancreatitis. Endoscopic retrograde cholangiography with stone extraction performed before or after laparoscopic cholecystectomy is the procedure of choice in this setting.

Patients with hemolytic disease (including sickle cell anemia, the thalassemias, and red blood cell enzymopathies) and Wilson disease are at increased risk for black pigment cholelithiasis. In sickle cell disease, pigment gallstones may develop before age 4 yr and have been reported in 17% to 33% of patients aged 2 to 18 yr.

Cirrhosis and chronic cholestasis also increase the risk for pigment gallstones. Increasing numbers of sick premature infants are being found to have gallstones; their treatment is often complicated by such factors as bowel resection, necrotizing enterocolitis, prolonged parenteral nutrition without enteral feeding, cholestasis, frequent blood transfusions, and use of diuretics. Cholelithiasis in premature infants is often asymptomatic and may resolve spontaneously. Brown pigment stones have been found in patients with obstructive jaundice and infected intra- and extrahepatic bile ducts. These stones are
usually radiolucent, owing to a lower content of calcium phosphate and carbonate and a higher amount of cholesterol than in black pigment stones.

Cholesterol cholelithiasis in children most frequently affects obese adolescent girls. Cholesterol gallstones are found also in children with disturbances of the enterohepatic circulation of bile acids, including patients with ileal disease and bile acid malabsorption, such as those with ileal resection, ileal Crohn disease, and cystic fibrosis. Pigment stones may also occur in these patients.

Cholesterol gallstone formation seems to result from an excess of cholesterol in relation to the cholesterol-carrying capacity of micelles in bile. Supersaturation of bile with cholesterol leading to crystal and stone formation could result from decreased bile acid or from an increased cholesterol concentration in bile. Other initiating factors that may be important in stone formation include gallbladder stasis or the presence in bile of abnormal mucoproteins or bile pigments that may serve as a nidus for cholesterol crystallization.