WALKER’S PEDIATRIC GASTROINTESTINAL DISEASE

PATHOPHYSIOLOGY • DIAGNOSIS • MANAGEMENT

SIXTH EDITION

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Notice: The authors and publisher have made every effort to ensure that the patient care recommended herein, including choice of drugs and drug dosages, is in accord with the accepted standard and practice at the time of publication. However, since research and regulation constantly change clinical standards, the reader is urged to check the product information sheet included in the package of each drug, which includes recommended doses, warnings, and contraindications. This is particularly important with new or infrequently used drugs. Any treatment regimen, particularly one involving medication, involves inherent risk that must be weighed on a case-by-case basis against the benefits anticipated. The reader is cautioned that the purpose of this book is to inform and enlighten; the information contained herein is not intended as, and should not be employed as, a substitute for individual diagnosis and treatment.
DEDICATIONS

With deepest gratitude to Allan Walker who has mentored and supported me for all of my professional life. And to my family, Martha, Emily, Scott, Ellie, Avery, Adam, Monica, Maya and Jesse for their constant love and support.

—Ronald E. Kleinman, MD

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—Olivier J. Goulet, MD, PhD

To Alex P Mowat, formidable mentor, and to all patients and scientists who have contributed to our research in juvenile autoimmune liver disease.

—Giorgina Meili-Vergani

To Julia and Vita.

—Ian R. Sanderson, MD

This book is dedicated to trainees—past, current, and future—who make the journey through life in academic medicine so interesting, meaningful, and rewarding.

—Philip M. Sherman, MD
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*Hirschsprung Disease (23.2b)*

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*Imaging of Gastrointestinal Tract Disease (49.1)*  
*Cross-Sectional Imaging of Abdominal Masses (49.2)*  
*Interventional Gastrointestinal Radiography (49.3)*

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*Imaging of Gastrointestinal Tract Disease (49.1)*  
*Cross-Sectional Imaging of Abdominal Masses (49.2)*  
*Interventional Gastrointestinal Radiography (49.3)*

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*Prebiotics: Composition and Potential Functions (19.1b)*

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*Upper Gastrointestinal Bleeding (44.2b)*

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*Atypical Colitis and Other Inflammatory Diseases (20.4c)*

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*Other Esophageal Neuromuscular Disorders (4.3)*

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Congenital Enteropathies (15.3c)
Autoimmune Enteropathy and IPEX Syndrome (16.3)
Short Bowel Syndrome (21.1)

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Bilirubin Metabolism (27.2)

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Lysosomal Acid Lipase Deficiencies (34.7)

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Crohn’s Disease (20.4a)

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*Acute Diarrhea (15.2a)*

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*Persistent and Chronic Diarrhea (15.2b)*

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*Peritonitis and Intra-abdominal Abscesses (20.5)*

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*Immune Deficiency and the Liver (30.3)*

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Gastrointestinal Manifestations of Immunodeficiency Disorders (20.2)

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The Statistics and Interpretation of Screening and Diagnostic Tests (54)

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Pancreatic Tumors (41)

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Bile Acid Synthesis and Metabolism (34.11)
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Disorders of Carbohydrate Metabolism (34.2)

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Ch. 19.1: Microbial Interactions with Gut Epithelium (19.1)

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Gastrointestinal Features of Pediatric Illness Falsification (50)

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Systemic Conditions Affecting the Liver (36)

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Intestinal Transplantation (20.4)
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Drug-Induced Bowel Injury (25.1)

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Benign Perianal Lesions (18)

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Appendicitis (17.2)

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Benign Perianal Lesions (18)

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*Intestinal Transplantation (21.3)*

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*Bile Formation and Cholestasis (27.1)*

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*Intestinal Transplantation (21.3)*

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*Parasitic and Fungal Infections (19.2c)*

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Genetic Testing (34.1)

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Congenital Anomalies Including Hernias (13)

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Esophageal and Gastric Polyps and Neoplasms (10)

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Atypical Colitis and Other Inflammatory Diseases (20.4c)

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Liver Biopsy Interpretation (45)

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*Nausea, Vomiting, and Pyloric Stenosis (8)*

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*Surgical Aspects of Inflammatory Bowel Disease in Children (20.4d)*

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*Other Causes of Gastritis (9.3)*

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*Hepatitis C Virus (30.1b)*
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*Nausea, Vomiting, and Pyloric Stenosis* (8)

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*Eosinophilic Gastrointestinal Diseases* (16.2a)

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*Small-Bowel Bacterial Overgrowth* (19.2d)

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*Outcomes Research in Pediatric Gastroenterology* (53)

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*Endoscopic Retrograde Cholangiopancreatography* (44.5)
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*Crohn’s Disease (20.4a)*

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*Pancreatitis Acute and Chronic (42.1)*

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*Appendicitis (17.2)*

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*Probiotics (19.1a)*

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Normal Motility and Development of the Intestinal Neurenteric System (23.1)

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Traumatic and Toxic Injury of the Esophagus (6)

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Intestinal Transplantation (21.3)

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Treatment of End-Stage Liver Disease (38)

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Outcomes Research on Diagnostic and Therapeutic Procedures (53)

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Eosinophilic Esophagitis (16.2a)

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Lower Gastrointestinal Bleeding (44.3b)

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Antimicrobials (19.1c)

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Benign Perianal Lesions (18)
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*Juvenile Tropical Pancreatitis (42.2)*

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*Intestinal Polyps and Polyposis (22.1)*  
*Endoscopic Retrograde Cholangiopancreatography (44.5)*

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*Food Allergic Enteropathy (16.2b)*  
*Upper Gastrointestinal Endoscopy (44.2a)*

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*Amino Acid Metabolism (34.3)*

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*Genetically Determined Disaccharides Deficiency (15.3a)*

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*Fatty Liver Disease in Children (35)*

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*Gastrointestinal Manometry (47)*

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*Normal Motility and Development of the Esophageal Neuroenteric System (4.1)*

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*Toxic and Traumatic Injury of the Esophagus (6)*

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*Intestinal Polyps and Polyposis (22.1)*

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*Other Causes of Gastritis (9.3)*

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*Ethics and Regulatory Issues (55)*

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*Bacterial, Parasitic, and Other Infections (30.2)*

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$\alpha_1$-Antitrypsin Deficiency (34.5)

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Intestinal Failure–Associated Liver Disease (21.2)

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Intestinal Polyps and Polyposis (22.1)

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Intestinal Biopsy (46)

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Tropical Calcific Pancreatitis (42.2)
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*Disorders of the Oral Cavity (2)*

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*Short Bowel Syndrome (21.1)*

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*Functional Constipation (23.2a)*

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*Fibrogenesis and Cirrhosis (27.3)*

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*Prebiotics: Composition and Potential Functions (19.1b)*
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Zellweger Syndrome and Other Disorders of Proximal Metabolism (34.6)

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Esophageal and Gastric Polyps and Neoplasms (10)

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Drug-Induced Hepatotoxicity (32)

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Anatomy and Embryology and Congenital Anomalies (7)

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Eosinophilic Gastrointestinal Diseases (16.2a)

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*Choledocal Cysts and Other Biliary Disorders (29.4)*

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*Peritonitis and Intra-abdominal Abscesses (20.5)*

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*Helicobacter pylori and Peptic Ulcer Disease (9.1)*

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*Gastroesophageal Reflux (4.2)*

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Autoimmune Enteropathy and IPEX Syndrome (16.3)

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*Esophageal pH and Impedance Measurement (48)*

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*Normal Motility and Development of the Gastric Neuroenteric System (11.1)*  
*Motility Disorders (11.2)*

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Bile Acid Synthesis and Metabolism (34.11)

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Adherence to Medical Regimens (52)

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Fibrogenesis and Cirrhosis (27.3)

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Gastrointestinal Manifestations of Immunodeficiency Disorders (20.2)
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*Psychological Aspects of Chronic Disease (51)*

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*Genetic Testing (34.1)*

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*Intestinal Biopsy (46)*

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*Diagnostic Approaches to Common Pediatric Liver Problems (28)*

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*Genetic Testing (34.1)*
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*Normal Motility and Development of the Intestinal Neurenteric System (23.1)*

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*Zellweger Syndrome and Other Disorders of Peroxisomal Metabolism (34.6)*

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*Ethics/Regulatory Issues (55)*

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*Disorders of the Intrahepatic Ducts (29.1)*

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*Wilson Disease (34.8)*
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*Esophageal and Gastric Polyps and Neoplasms (10)*

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*Anatomy, Embryology, and Congenital Anomalies (1)*

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*Esophagitis (5)*
*Ileocolonoscopy and Enteroscopy (44.3a)*
*Interventional Endoscopy: Recent Innovations (44.6)*

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Hemochromatosis (34.9)

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*Acute Diarrhea (15.2a)*

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*Genetically Determined Disaccharides Deficiency (15.3a)*
As I look back on the five previous editions of this textbook, I recognize how much the field has expanded and the importance of our understanding gastrointestinal diseases within the context of ongoing development of infants and children. This edition of the textbook will be published later than previous editions, which have been linked to the Pediatric Gastroenterology World Congresses occurring every four years since 2000. This is due to a change in publishers. People’s Medical Publishing House—USA will now be publishing this textbook as well as its companion text, entitled *Nutrition in Pediatrics* (5th edition). In addition, new sections have been added to reflect the expanding complexity of the field, particularly new techniques now used to accurately establish complex diagnoses.

It is now apparent that pathophysiologic occurrences during infancy, and even during the intrauterine period, may have a profound effect on the expression of disease in later life. Two hypotheses, the Barker hypothesis (fetal programming) and the hygiene hypothesis, which have now been generally accepted, strongly suggest the importance of fetal nutrition and neonatal colonization on the enhanced incidence of metabolic and immunologic diseases increasingly prevalent in developed countries. This is strongly illustrated by the pediatric complications of maternal obesity during pregnancy and the increased incidence of Cesarean section delivery of the newborn for the convenience of the obstetrician and parents at the expense of adequate initial colonization for the newborn infant. Accordingly, this edition of *Pediatric Gastrointestinal Disease* and its companion *Pediatric Nutrition* devote new chapters to the adequate nutrition beginning in *utero* and the colonization of the newborn intestine and its disease consequences.
As with previous editions, the size and content of each section has been modified and new chapters added to reflect an increasing evolution of subspecialty programs within gastroenterology and a better understanding of subspecialty conditions (motility, inflammation, and autoimmune bowel disease) that have emerged in pediatric gastroenterology. As the importance of genetics and molecular biology in the pathophysiology and diagnosis of complex pediatric conditions of the gut, pancreas, and liver have become appreciated, expanded chapters cover their importance in the field. Furthermore, a more comprehensive representation of world leaders in pediatric gastroenterology among the editors of this edition have expanded the authorship to reflect experts in specific diseases within various continents rather than principally in North America. In other words, the edition is dedicated to a comprehensive, worldwide approach to the practice of pediatric gastroenterology.

Finally, as occurs in many rapidly expanding medical fields, difficult decisions are required before treatment of complex gastrointestinal conditions can be recommended that are based on clinical evidence. These therapeutic approaches require large, multi-centered, randomly controlled, single-protocol studies. Accordingly, many pediatric gastroenterologists are now resorting to clinical investigation to answer their therapeutic needs. In this edition, two comprehensive chapters on principles of clinical investigation are provided, and then, in an endeavor to be inclusive, another chapter on ethics and regulatory considerations is included. In addition, psychosocial aspects of gastrointestinal disease are provided in three chapters that consider the physiologic components of intestinal disease.

The editors have provided an excellent background for an approach to evaluating children with gastrointestinal disease in the 21st century. I have been honored to be part of this approach.

—Allan Walker
Mouth and Esophagus
Anatomy, Embryology, Congenital Anomalies of the Mouth and Esophagus

Jonathan E. Teitelbaum, MD

Congenital anomalies of the mouth and esophagus are relatively common. The majority of these anomalies are readily apparent at birth or, in many cases, can be appreciated on prenatal ultrasonography. Our understanding of the embryology of the mouth and esophagus and the associated genes and gene products has increased rapidly over the past decade. With that, there has been a rapid advancement in identifying various genetic mutations that result in abnormalities of development and their phenotypic expression. Whereas some malformations are clinically silent, others can cause difficulties in feeding, articulation, or even life-threatening respiratory difficulties. More complex malformations often require support from multidisciplinary teams, including surgeons (general, otolaryngologic, orthodontic), gastroenterologists, speech pathologists, and geneticists.

FACIAL CLEFTS (CLEFT LIP AND CLEFT PALATE)

Oral clefts are among the most common of all birth defects, second only to clubfoot. Cleft lip with or without cleft palate [CL(P)] occurs with an incidence of 1 in 500 to 1 in 2,500 in different populations based on ethnic group, geographic location, and socioeconomic conditions. The highest incidence is among Native Americans (3.6 in 1,000 live births), whereas
among blacks, it is less (0.3 in 1,000 live births). Whites have an incidence of 1 in 1,000 live births. Defects are unilateral in 80%.2

Isolated cleft palate (CP) occurs in approximately 1 in 2,000 live births, and there is little to no racial preponderance.2 CL(P) is more common in boys, whereas CP is seen more commonly in girls. The cause is likely multifactorial disruption of embryologic morphogenesis.2 Higher birth order may also be a risk factor for CL(P) and CP. However, studies are not conclusive and may be confounded by other factors, such as advanced maternal or paternal age or increased exposure to teratogens, which, in themselves, may be risk factors.3 While nonsyndromic clefts are generally believed to be relatively benign conditions, a study shows that the perinatal mortality rate for babies with isolated facial clefts was significantly higher than the background population (odds ratio 3.3).4

The risk of having subsequent children with clefts is different for those with CL(P) from those with CP. When both parents are unaffected and have an affected child, the risk of recurrence is 4.4% for CL(P) and 2.5% for CP. If one parent is affected, the risk is increased to 15.8% for CL(P) and 14.9% for CP. If two children are affected and the parents are unaffected, the risk for a third child is 9% for CL(P) and 1% for CP.2 Concordance among monozygotic twins ranges between 40% and 60%, whereas it is 5% among dizygotic twins. The lack of 100% concordance rates among monozygotic twins argues against genetic events alone being responsible for the clefting phenotype.5

Cleft lip is a unilateral or bilateral gap in the upper lip and jaw, which form during the third to seventh week of embryologic development.1 The incisive foramen divides the hard palate into a primary and secondary palate. The primary palate lies anterior to the incisive foramen and includes the bony premaxilla, mucoperiosteal covering, and incisor teeth. The secondary palate is posterior to the incisive foramen and is composed of horizontal plates of the maxilla and palatine bone. The remaining dentition arrives from the secondary palate. Primary palate formation begins at four to five weeks gestation with the fusion of the paired median nasal prominences. This marks the separation of the oral and nasal cavities. Ultimately, the median nasal prominences give rise to the dental arch, incisor teeth, and philtrum of the upper lip. Formation of the secondary palate (hard and soft) begins at approximately the seventh week of gestation. The posterior maxillary prominences form palatal shelves, which rotate inferiorly and medially to fuse with the vomer in the midline. Anterior to posterior palatal closure occurs in a zipper-like fashion. At nine
weeks gestation, the hard palate fuses with the septum to complete the separation of the oral and nasal cavities. The soft palate is composed of five paired muscles: tensor veli palatini, levator veli palatini, palatoglossus, palatopharyngeus, and musculus uvulae. Midline approximation of the soft palatal musculature marks the completion of palatogenesis at approximately 12 weeks gestation.²

The multifactorial inheritance model is currently the most widely accepted theory of nonsyndromic clefts. In this model, the risk of developing a given anomaly is determined by the presence of either genetic or environmental liabilities. Each liability occurs in a normal distribution within the population. The accumulation of multiple small liabilities eventually reaches a threshold, beyond which a defect occurs. Variable penetrance of the phenotype for many genes results in non-Mendelian inheritance patterns. Ongoing research is investigating the role that associated features play in the familial transmission patterns of nonsyndromic clefts. Associated features include fluctuating and directional asymmetry, left handedness, dermatoglyphic patterns, craniofacial morphology, orbicularis oris muscle defects, structural brain and vertebral anomalies, minor physical anomalies, and velopharyngeal incompetence.⁶

An estimated 300 syndromes include CL(P) in their phenotype; however, syndromic clefts account for only 30% of CL(P).¹ The proportion of patients with CP who are syndromic versus nonsyndromic remains unresolved, with estimates varying widely, between 15% and 80%.¹ Approximately 25% of syndromic clefts are associated with Stickler syndrome, whereas another 15% are associated with velocardiofacial syndrome.² The most common malformations in association with clefts are found in the central nervous system and the skeletal system, followed by the urogenital and cardiovascular systems.⁷ Various syndromes associated with CP (Table 1-1) and CL(P) (Table 1-2) have been described.

Defects in the PVRL1 gene (chromosome 11q23) result in abnormal formation of nectin 1, a cell–cell adhesion molecule expressed in the developing face and palate that is essential for fusion of the medial edge epithelia. A 50% reduction in the amount of nectin 1 appears to be a risk factor for nonsyndromic CL(P) in patients in Margarita Island and Venezuela.¹ A similar gene, OFC3 (19q13, MIM#600757), has also been implicated in nonsyndromic CL(P) based on genetic linkage studies. Other candidate genes include OFC1 (6p24.3, MIM #119530), OFC2 (2p13, MIM #602966), OFC4 (4q, MIM#608371), OFC5 (MSX1, 4p16.1, MIM
#608874, OFC6 (MIM#608864), TP63 (3q27), TGFA (2p13), TBX22,1
PGD1 (1p36), 6 methylenetetrahydrofolate reductase (1q36),\(^8\,9\) transcobalamin 2,\(^10\) and TGFalpha (2p13).\(^8\) A defect in the CDH1/E-cadherin gene (MIM#192090) has been associated with CL(P) and hereditary diffuse gastric cancer.\(^11\)

The causative role of teratogens in the formation of clefts has been supported by studies of maternal exposures to corticosteroids, phenytoin, valproic acid,\(^5\) thalidomide,\(^5\) alcohol,\(^5\) cigarettes,\(^5\) dioxin,\(^5\) or retinoic acid. In addition, maternal diabetes mellitus, hormone imbalance, and various vitamin and trace mineral deficiencies have been associated with clefts in the offspring.\(^12\) Although there is no consensus that any particular teratogen or environmental factor is implicated in most clefts,\(^1\) some studies suggest that the risk may be increased with exposure to oxygenated (odds ratio 1.8), chlorinated (odds ratio 9.4), and petroleum (odds ratio 3.6) solvents.\(^13\) Folic acid may have a protective effect to reduce the risk of clefting, although this is controversial.\(^8,\,14\) Studies suggest that maternal zinc deficiency may also be associated with nonsyndromic clefting.\(^15,\,16\)

Prenatal diagnosis allows for early parental counseling. Current technology can detect CL(P) at 15 weeks gestation because the soft tissues of the fetal face become distinct to transabdominal ultrasonography.\(^7\) During the second trimester, ultrasonography detects less than 20% of cases of isolated CL(P) and far fewer cases of isolated CP.\(^7\) However, syndromic CL(P) is detected in more than 30%, perhaps because a more detailed scan is undertaken given the associated anomalies, or because these clefts are larger and more readily visualized. Optimum timing for diagnosis is between 20 and 22 weeks gestation. The ability to see the defect is influenced by the position of the fetus, position of an overlying hand or umbilical cord, maternal obesity, multiple pregnancies, oligohydramnios, and the experience of the technician. The use of transvaginal ultrasonography and three-dimensional ultrasonography also increases the sensitivity and specificity of the test.\(^2\) Real-time magnetic resonance imaging (MRI) has also been proven useful in prenatal diagnosis of CP.\(^17\) A delay of greater than 24 hours in diagnosis of nonsyndromic CP without cleft lip in the newborn can occur in as much as 37%.\(^18\) Those with a delay in diagnosis often had feeding problems or nasal regurgitation. The authors suggest that all newborns should undergo visual inspection of the palate as palpation alone is inadequate.
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>OMIM Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catel-Manzke</td>
<td>302380</td>
</tr>
<tr>
<td>Cerebrocostomandibular</td>
<td>117650</td>
</tr>
<tr>
<td>Deletion 4q</td>
<td></td>
</tr>
<tr>
<td>Dubowitz</td>
<td>223370</td>
</tr>
<tr>
<td>Duplication 3q</td>
<td></td>
</tr>
<tr>
<td>Duplication 10q</td>
<td></td>
</tr>
<tr>
<td>Escobar</td>
<td>265000</td>
</tr>
<tr>
<td>Femoral hypoplasia–unusual facies</td>
<td>134780</td>
</tr>
<tr>
<td>Fibrochondrogenesis</td>
<td>228520</td>
</tr>
<tr>
<td>Hay-Wells syndrome of ectodermal dysplasia</td>
<td>106260</td>
</tr>
<tr>
<td>Hydrolethalus</td>
<td>236680</td>
</tr>
<tr>
<td>Kabuki make-up</td>
<td>147920</td>
</tr>
<tr>
<td>Kniest dysplasia</td>
<td>156550</td>
</tr>
<tr>
<td>Marden–Walker</td>
<td>248700</td>
</tr>
<tr>
<td>Meckel–Gruber</td>
<td>249000</td>
</tr>
<tr>
<td>Nager</td>
<td>154400</td>
</tr>
<tr>
<td>Orofaciodigital</td>
<td>311200</td>
</tr>
<tr>
<td>Otopalatodigital, type I</td>
<td>311300</td>
</tr>
<tr>
<td>Otopalatodigital, type II</td>
<td>304120</td>
</tr>
<tr>
<td>Syndrome</td>
<td>OMIM Number</td>
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<tr>
<td>---------------------------------------------------------------</td>
<td>-------------</td>
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<tr>
<td>Popliteal pterygium</td>
<td>119500</td>
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<tr>
<td>Retinoic acid embryopathy</td>
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<td>Short-rib polydactyly, type II</td>
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<td>Velocardofoacial</td>
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<td>Spondyloepiphyseal dysplasia congenita</td>
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<td>Stickler 1</td>
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<td>Treacher Collins</td>
<td>154500</td>
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<tr>
<td>Van der Woude</td>
<td>119300</td>
</tr>
</tbody>
</table>


Source: Adapted from Jones.120

**TABLE 1-2** Syndromes With Cleft Lip With or Without Cleft Palate

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>OMIM Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deletion 4p</td>
<td></td>
</tr>
<tr>
<td>Ectrodactyly–ectodermal dysplasia–clefing</td>
<td>604292</td>
</tr>
<tr>
<td>Fryns</td>
<td>229850</td>
</tr>
<tr>
<td>Hay-Wells syndrome of ectodermal dysplasia</td>
<td>106260</td>
</tr>
<tr>
<td>Holoprosencephaly sequence</td>
<td>157170</td>
</tr>
<tr>
<td>Miller</td>
<td>247200</td>
</tr>
<tr>
<td>Mohr</td>
<td>252100</td>
</tr>
<tr>
<td>Orofaciodigital</td>
<td>311200</td>
</tr>
</tbody>
</table>
Initial evaluation of a patient with CP should include prenatal care, birth history, teratogen exposure, and a family history of clefting or syndromes. A multidisciplinary team is often helpful in assessing the family’s medical and psychosocial needs. The cleft team should consist of a maxillofacial or plastic surgeon, otolaryngologist, audiologist, dentist (orthodontist or oral surgeon), social worker, geneticist, pediatrician, nutritionist, and speech pathologist. Breastfeeding is possible in some patients with a short or narrow cleft. Infants with larger clefts can rarely generate adequate suction for traditional breastfeeding or bottle feeding. Various specialized nipples have been created to facilitate feeding. Feeding typically takes longer, and frequent burping may be required in these infants because they often swallow large amounts of air. Infants should be weighed on a weekly basis initially to ensure adequate intake.

Evidence suggests that children with CL have a lesser degree of weight and length impairment in the first few years of life compared to those children with cleft lip and palate or CP.

Palatal clefting disrupts all layers of the normal palate architecture, including mucosa, muscle, and bone. The muscles of the soft palate must wrap anteriorly and insert on the cleft margin or the posterior palate. Aberrant tensor veli palatini insertion results in eustachian tube dysfunction, so nearly all CP patients will have chronic otitis media requiring myringotomy tube placement. Abnormal insertion of the levator veli palatini results in loss of normal velopharyngeal competence.
CP may be classified as primary or secondary, complete or incomplete, unilateral or bilateral, or submucous. Primary CP results in incomplete closure of the hard palate anterior to the incisive foramen, whereas secondary CP results in a midline defect posterior to the incisive foramen. Secondary clefts appear to be distinct genetic entities, unrelated to cleft lip but often associated with Pierre Robin sequence (PRS). Complete CP involves the primary secondary and soft palate and is usually associated with cleft lip. Submucous CP results from inadequate development of the muscles of the soft palate without disruption of the mucosa. They can characteristically include a bifid uvula, dehiscence of the central palatal musculature (may be palpable or result in bluish discoloration in the midline, termed a zona pellucida), and loss of the posterior nasal spine.

Presurgical orthopedic techniques are used to modify the shape of the cleft deformity before definitive cleft repair. These increase the ease of the primary repair, normalize facial growth, and prevent alveolar collapse. Active techniques include finger massage, lip taping and strapping, and oral prosthetics. Passive techniques are aimed at inhibiting tongue protrusion between the palatal shelves by using oral obturators. Although these techniques have been shown to effectively narrow the distance between alveolar segments, no differences in esthetic outcome, need for revision surgery, or improvement in feeding have been prospectively demonstrated.

Palatoplasty aims to separate the oral and nasal cavities and restore velopharyngeal competence. An aggressive approach must be balanced with the risk of maxillary growth disturbance.

Although 90% of patients with a cleft lip have repair between 3 and 6 months of age, the timing of CP repair is controversial. Proponents of early CP repair (3–6 months) believe that early velopharyngeal competence is critical to normal speech development. Proponents of late palatal repair (2–15 years) believe that the risk of iatrogenic disruption of palatal growth and midfacial hypoplasia outweighs the risk of speech abnormalities. Clefts delayed for more than two years generally require obturation to overcome velopharyngeal incompetence and allow normal speech development. Oral obturators placed prior to two years are often poorly tolerated. The lack of clear evidence supporting early versus late repair has led to a compromise in which most surgeons perform repair from 12 to 24 months. Experience with neonatal cleft lip and palate repair has been described as safe, although long-term follow-up is not yet available. Fetal surgery for CL(P) has also been described. The risks