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Introduction

The editors are pleased to present a compilation of articles of interest to primary care physicians and subspecialists. We honor the late Dr. Joseph St. Geme, Jr., with a tribute written by his son, Joseph St. Geme III, in our “Foundations of Pediatrics” section.

Our series on genomics/proteomics continues with an article by Hunsaker and Accurso, and our biennial review of advances in pharmacology submitted by Ian Paul.

Advances in the field of pediatric surgery are presented by Gerard Glancy (scoliosis) and Francois Lecour-Gayet and colleagues (congenital cardiac surgery). Approaches to the diagnosis and treatment of metabolic disorders of bone are given in the articles by Steelman and Simmons (osteoporosis/osteogenesis imperfecta) and Iyer and Diamond (rickets—a sometimes forgotten but still prevalent condition).

A new feature in this volume is the excellent and comprehensive update on vaccines by Mirza and Rathore, and we hope to publish ongoing updates in this area in future volumes.

Two articles of special interest in the field of “social pediatrics” were contributed by the staff of the Children’s Health Fund: an update on homelessness by Grant and colleagues and lessons learned about the vulnerability of children during megadisasters (eg, Hurricane Katrina) by Garrett and colleagues.

Finally, advances in our understanding of childhood oral health problems (Krol), atopic dermatitis (Leung and colleagues), and an update on the benefits and risks of breastfeeding (Goldman and colleagues) are presented.

As in the past, the editors welcome suggestions for topics in future volumes of the Advances in Pediatrics as well as an evaluation of the breadth and quality of articles published in this volume. Comments can be directed to Michael S. Kappy at kappy.michael@tchden.org.

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He was a star in the sky. He showed us the way. We followed him.
And then he went.

George Emmanouelides, MD

As a young child I would join my dad periodically on his trips into the laboratory over the weekend. I recall peering through the microscope and hearing him tell me about cells, and tissues, and viruses. Roughly a decade later, when I was home from college on breaks, I would shadow him when he made rounds on the pediatric ward and in the neonatal ICU. I remember observing him interact with residents and nurses, and I remember having the opportunity myself to listen to the heart of a child with a murmur and to examine the lungs of a premature infant who had respiratory distress syndrome under his watchful eye. My dad loved the process of scientific inquiry, the challenge of helping sick children get better, and the opportunity to teach colleagues at all levels of training. He was always positive, and he had a remarkable capacity to share enthusiasm, to inspire confidence, and to motivate. He was an amazing role model for me.

Throughout my time as an undergraduate, as a medical student, and as a resident in pediatrics, I consulted with my dad about life in general and about medicine in particular. Over this period, I gained a growing understanding of his professional responsibilities and a deepening respect for him as an academic pediatrician.

Joseph William St. Geme, Jr. was born to Malvina Pozzo St. Geme and Joseph William St. Geme, Sr. on April 10, 1931, in Los Angeles, California. He was the older of two boys and grew up in Los Angeles, where his father was a pediatrician in private practice and a member of the California Medical Group. Early on he developed an interest in science and athletics, and as
a student at Loyola High School he excelled in the classroom and also demonstrated prowess as a quarterback on the football team and as a quarter miler on the track team. Following his successes in high school, he matriculated at Stanford University, where he majored in basic medical sciences in preparation for medical school and continued his exploits in football and track. As a freshman, he ran the quarter mile in a personal record time of 49.0 seconds before hanging up his spikes to focus on football and his studies. On the football field, he moved from quarterback to defensive back and eventually earned All Pacific Coast Honorable Mention in 1950 and 1952 and All America Honorable Mention in 1952. He was a member of the “How Boys” and played in the Rose Bowl against the University of Illinois on January 1, 1952, under the guidance of Head Coach Chuck Taylor. Most important among his accomplishments as an undergraduate, he met his bride, Monica Verdurmen, a Stanford coed who first spotted him on the football field because of his conspicuous low-cut cleats (a rarity in those days).

Following completion of his undergraduate studies, he began medical school at Stanford, at the time a split campus between Stanford for the first year of the curriculum and San Francisco for the second, third, and fourth years. Less than two years later, on June 12, 1954, he and Monica were married at St. Ann’s Chapel in Palo Alto, the Stanford Newman Club chapel. While he pursued his medical studies, Monica practiced as a medical social worker at Stanford Hospital in San Francisco and supported the couple. During medical school, he began to cultivate his interest in laboratory research, studying the relationship between melanin and melanomas. Ultimately this work earned the Borden Undergraduate Research Award (for Stanford medical students) and was published in *Lancet* [1].

In 1956, he moved to the University of Minnesota for postgraduate medical education, where he completed a rotating internship, a 1-year residency in pediatrics, a chief residency in pediatrics, and then a 1-year fellowship in neurology, metabolism, and endocrinology. This was a banner era in pediatrics at Minnesota, with Dr. John Anderson as Chairman and with notable faculty including Lewis Thomas, Lewis Wanamaker, Robert Good, Paul Quie, Elia Ayoub, and Bascom Anthony, among many others. There were impressive colleagues in other departments as well, including Owen Wangensteen, C. Walton Lillihei, Norman Shumway, and Richard Varco in surgery, Cecil Watson and Wesley Spink in internal medicine, and John McKelvey in obstetrics and gynecology. At the urging of John Anderson, following his fellowship, he spent 2 years as an instructor in the Department of Bacteriology, protected from clinical responsibilities and able to focus on research and teaching. Over this period, he began studies of viral cytopathology and pathogenesis, examining enteroviruses, vaccinia virus, measles virus, mumps virus, and herpes viruses and laying the foundation for his investigative career as a virologist. In 1962, he was promoted to assistant professor in the Departments of Pediatrics, Microbiology, and Laboratory Medicine at the University of Minnesota and was appointed medical director of the University of Minnesota Medical Center Diagnostic Microbiology Laboratory.
In 1965, at the age of 34, he accepted a position as associate professor of pediatrics at the University of California Los Angeles (UCLA) School of Medicine and chief of pediatrics at Harbor-UCLA Hospital. A year later, he was promoted to professor of pediatrics and Chairman of the Department of Pediatrics at Harbor-UCLA and began steps toward assembling a top-flight academic program. Over his 19 years in a leadership role at Harbor-UCLA between 1965 and 1984, the faculty in pediatrics grew from 3 to 50, and the Department of Pediatrics emerged as a national leader in clinical care, postgraduate education, and research. Among the faculty he recruited to Harbor-UCLA, at least seven moved on to positions as chair of pediatrics, including Michael (Spike) Miller (UC Davis), Michael Kaback (UC San Diego), Larry Shapiro (UC San Francisco), David Rimoin (Cedars Sinai-UCLA), Delbert Fisher (Harbor-UCLA), Rosemary Leak (Harbor-UCLA), and Mark Sperling (University of Pittsburgh).

His visibility in the UCLA community grew over time, and in 1977 he was named the executive chairman of pediatrics at UCLA. In this role, he combined his responsibilities as chairman of pediatrics at Harbor-UCLA with oversight of the pediatric programs at four additional UCLA sites, including UCLA Hospital, Cedars-Sinai Hospital, Charles Drew Medical Center, and Olive View Medical Center.

In January 1985, he moved to the University of Colorado Health Sciences Center and assumed responsibilities as dean of the School of Medicine. Over the next 16 months, he used his remarkable recruiting skills to attract five new department chairs to the University of Colorado, including Donald Gilden in neurology, James Shore in psychiatry, Charles Gibbs in anesthesiology, Robert Meier in rehabilitative medicine, and Karl Pfenninger in cell biology. Over the same period, he recruited three additional chairs from existing University of Colorado faculty, namely Larry Green in family medicine, Jerry Weidel in orthopedics, and Laz Gershenson in pathology, increasing the tally of new department leaders to eight.

In the winter months of 1986, he developed symptoms of congestive heart failure, and in August 1986, he was diagnosed with an idiopathic dilated cardiomyopathy and began a period of medical leave. Two months later, on Oct. 11, 1986, he suffered a cardiac arrest while watching his beloved Stanford football team on television. He was rushed to the emergency room at the University of Colorado Hospital, where resuscitation attempts were unsuccessful, and he died. He was attended in the emergency room by Dr. Martin Smilkstein, a former resident of his at Harbor-UCLA Hospital, who was an instructor in emergency medicine at the time and who ultimately wrote a eulogy entitled “The Saint” that was published in Pediatrics [2].

During the course of his career, he served in a leadership role with virtually every major organization in academic pediatrics. In particular, he was president of the Association of Medical School Pediatric Department Chairs, president of the American Board of Pediatrics, president of the Western Society for Pediatric Research, and vice-president of the Society for Pediatric Research. In

OPTIMIST, SCHOLAR, VISIONARY, AND ROLE MODEL
addition, he was a member of the American Board of Medical Specialties, the Residency Review Committee for Pediatrics, the National Board of Medical Examiners, the Committee on Government Affairs of the American Academy of Pediatrics, and the Clinical Evaluation Program of the Association of American Medical Colleges. He was also an original member of the Association of Pediatric Program Directors Steering Committee. At the time of his death, he was president-elect of the American Pediatric Society.

The myriad of influential roles that he assumed reflected his profound leadership abilities and his impressive talents as a consummate academician. As a leader, he stressed that general pediatricians are pediatric specialists and should take pride in their unique clinical skills, that pediatric subspecialty training should include an emphasis on rigorous investigation, that the National Institutes of Health should allocate appropriate funds to support pediatric investigators and pediatric research, that nurse practitioners represent an important resource in facilitating pediatric care, and that prehospital emergency medical systems addressing the specific needs of pediatric patients are essential for high-quality care for children. As an academician, he received teaching awards from the medical students at UCLA, the interns and residents at Harbor-UCLA Hospital, and the Western Society for Pediatric Research. He was among the first to hypothesize that mumps virus caused endocardial fibroelastosis (a hypothesis ultimately confirmed by Ni and colleagues [3]), and he performed fundamental studies characterizing intrauterine mumps infection, the effect of mumps infection on delayed type hypersensitivity, and the determinants of mumps immunity. In addition, he developed effective cultivation techniques for enteroviruses and various herpes viruses, allowing recognition of the specific clinical manifestations of infection with these agents. Later in his career, he led a landmark study that defined risk factors for neonatal bacterial infection following prolonged rupture of membranes [4]. In recognition of his accomplishments, he was elected to the Institute of Medicine in 1985.

Beyond his commitment and his contributions to pediatrics and academic medicine, he felt a sincere responsibility to the community. Along these lines, he was a member of the board of directors of the Charles R. Drew Postgraduate Medical School for 15 years and the board of directors of Little Company of Mary Hospital (a community hospital in Torrance, California) for 6 years. In addition, he served as chairman of the Area Health Education Consortium (AHEC) for the Inglewood-Centinela/South Bay Area for 2 years. Closer to home, he was a trustee of the local homeowners association for 3 years and was president of the Silver Spur Little League baseball program for 2 years and the Rolling Hills Junior Football League for 3 years. All along, his family remained his top priority. At the time of his death, he had shared 32 years of marriage with Monica, raised six children, and greeted four grandchildren (there are now a total of 23). He made every member of the family feel special, and he had a remarkable ability to sense the need for a warm smile, a big bear hug, and words of advice and encouragement, gifts that we all miss today. Following his untimely death, numerous awards were established in his name, highlighting the scope of his efforts and the magnitude of his influence.
Fig. 1. Joseph W. St. Geme, Jr. in his office at Harbor-UCLA Hospital.

Fig. 2. Joseph W. St. Geme, Jr. with Mickey Mouse at Disneyworld in 1984 during an American Board of Pediatrics meeting.
The Joseph W. St. Geme, Jr. Leadership Award was established by the Federation of Pediatric Societies (the Ambulatory Pediatric Association, the American Academy of Pediatrics, the American Board of Pediatrics, the American Pediatric Society, the Association of Medical School Pediatric Department Chairs, the Association of Pediatric Program Directors, and the Society for Pediatric Research) and honors individuals whose contributions to pediatrics are significant and broad enough to be considered as “creating the future” of the discipline.

The Joseph W. St. Geme, Jr. Education Award was established by the Western Society for Pediatric Research and is conferred biannually in recognition of outstanding achievement in pediatric education.

The Joseph W. St. Geme, Jr. Award for Outstanding Research by a Resident was established by the Department of Pediatrics at the University of Colorado School of Medicine.

The Joseph W. St. Geme, Jr. Pediatric Resident Research Award was established by the Department of Pediatrics at the UCLA School of Medicine.

The Joseph W. St. Geme, Jr. Professorial Chair in Pediatrics was established by the UCLA School of Medicine.

The Joseph W. St. Geme, Jr. Research Fund for medical students was established by the UCLA School of Medicine and the University of Colorado School of Medicine.

Joseph W. St. Geme, Jr., MD, saw the best in people and had an uncanny ability to elevate the performance of everyone around him, always with an eye toward excellence. He taught me the principles of respect for others, teamwork, optimism, integrity, planning, humility, and passion. I feel lucky to say that he was my dad, and I only wish that I still had him with me today.

References
Proteomics offers insight into studies of human disease including the opportunity to: define underlying mechanisms of disease; determine disease susceptibility; stage disease and monitor its progression; assess susceptibility to, or identify exacerbation; select treatment and monitor response to it; and to assist in the performance of clinical trials. Although the common perception is that proteomics is primarily a tool for identifying biomarkers, this view sells the significant potential of this evolving technology short of its full potential.

Proteomics, by definition, is the comprehensive depiction of the proteins in a biological tissue or fluid, and optimally, studies should provide both qualitative and quantitative information. These data can provide unprecedented insight into the function (and dysfunction) of complex biological systems, because proteins are key structural, communication, enzymatic, and other functional components of biological systems. Given the central role of proteins in human biology, understanding their complex interplay offers the opportunity to define, at the molecular level, key events in growth, development, aging, and disease onset. This information can enhance one’s understanding of physiology and biochemistry, improve one’s ability to diagnosis disease and to predict outcomes, and provide insights into the action of drugs, the design of new drugs, and the assessment of the relationship between therapy and response.

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This article summarizes existing proteomic methods—their principles, potential and limitations—and the authors focus on reviewing what has been done and what is feasible given the existing tools. Wherever possible the article draws on studies from pediatric diseases and childhood development to illustrate principles, but at times the authors resort to other examples that they believe are more illuminating. The article illustrates that the adroit application of the tools already at hand, despite their limitations, offers enormous promise. All too often failure to realize the full potential of proteomics has more to do with inadequacies in study design, rather than fundamental technological limitations. Nevertheless, proteomics is a rapidly evolving area, and advances on any one of several fronts could shift the field profoundly and change what practitioners do and how they do it. The authors comment on the areas where they anticipate the most significant advancements.

**THE PROTEOME AND PROTEOMICS**

Assessment of the qualitative and quantitative changes in global protein expression can provide indispensable insights into health and disease, because proteins are essential to all living organisms. Among other things, they serve as catalysts, intracellular and extracellular structural elements, signaling molecules, receptors, mediators of cellular activity, and regulators of gene expression. Many diseases are caused by defects in protein synthesis, regulation, transportation, and modification; therefore proteins and peptides increasingly are becoming targets for therapy, monitoring, and prevention of disease.

The term proteome, first introduced by Wasinger and colleagues [1] in 1995, is defined as the expressed protein complement of a cell, organ, or organism, and it includes all isoforms and post-translational variants. Proteomics is the process of identifying the proteome, ideally with both temporal and regional specificity. Defining the differences in protein expression or abundance between two states (eg, normal versus disease, young versus old or pre- versus post-treatment)—often referred to as comparative proteomics—is one of the most informative exercises in clinically relevant research.

**WHAT CAN PROTEOMICS OFFER CLINICAL MEDICINE?**

There is an urgent need for additional biomarkers in various clinical settings and across disease states (Box 1). Biomarkers are characteristics that can be measured reproducibly and that provide information regarding health or disease in an individual or in populations. Protein biomarkers are commonly used in general medicine, including pediatrics (eg, the measurement of serum levels of circulating hepatic enzymes to follow patients with hepatitis, alpha-1-antitrypsin to help diagnose liver cirrhosis in children, amylase and lipase to help diagnose pancreatic disease, transthyretin [prealbumin] as a measure of visceral protein status and immunoreactive trypsinogen as part of newborn screening for cystic fibrosis). Proteomics offers the promise of greatly expanding the armamentarium of protein biomarkers in pediatrics, and activities...
generally are divided into two phases: A discovery phase to identify potential biomarkers, and a validation phase to bring useful biomarkers into clinical practice. After exploratory experiments in a given condition have identified a manageable number of biomarkers, say 5 to 20, the subsequent approach to clinical proteomics can be thought of in three phases (Fig. 1). In the first phase, laboratory assays for biomarkers are developed and validated with careful attention to specimen acquisition, processing, precision, accuracy, reproducibility, storage requirements, high throughput, and other aspects of analytical validation. In the second phase, assays are applied prospectively to collect data from large populations. Prospective validation is a key step to establishing biomarker utility, because retrospective analyses often have high false-positive rates. In the last phase, there is large-scale application that involves commercialization of assays. The goal of pediatric clinical proteomics is to introduce novel biomarkers, either individual proteins or panels of proteins, that are noninvasively and easily obtained and that can be applied rapidly to improve health of

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<th>Box 1: Potential applications of protein biomarkers determined through proteomics</th>
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<tr>
<td>Population screening</td>
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<td>Disease susceptibility</td>
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<td>Progression of disease</td>
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<td>Disease staging</td>
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<td>Susceptibility to exacerbation</td>
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<td>Identification of exacerbation</td>
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<td>Toxicity with treatment</td>
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<td>Stratification for clinical trials</td>
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**Fig. 1.** The three-phase approach to clinical proteomics, which follows from discovery proteomic experiments.
children [2]. The various aspects of discovery and validation approaches are discussed in more detail in the sections that follow.

**PROTEOMIC METHODS**

This article does not provide a comprehensive review of the methods of proteomics; instead, it summarizes the basic principles and where appropriate, refers the reader to specialized reviews. Discovery, validation, and routine testing platforms are generally distinct. This section introduces the most commonly adopted analytical strategies and discusses where they fit in.

It is important to stress that there is a plethora of proteomic paradigms that incorporate, to varying degrees, multiple analytical strategies such as mass spectrometry (MS), two-dimensional gel electrophoresis, liquid chromatography–tandem mass spectrometry (LC-MS/MS) and antibody–antigen-based protein microarrays. There are, however, four commonly adopted paradigms that fall into two subcategories: untargeted and targeted strategies.

Untargeted strategies, such as two-dimensional gels and LC-MS/MS, are appropriate for first-pass semiquantitative comparisons between large numbers of proteins in relatively small sample populations. Sample numbers need to be kept small because these procedures are complex, costly, relatively imprecise, and time-consuming. These approaches aid in discovering the relatively small subset of proteins that exhibit the greatest difference in abundance between two biological states (eg, healthy versus disease or wild-type versus mutant). Discovery studies generally have very broad hypotheses: Differences in the relative abundances of some circulating proteins make it possible to distinguish between healthy and diseased states. Findings from these first-pass untargeted strategies lead to dozens of new, more focused hypotheses that could not have been deduced a priori. These new hypotheses then can be explored in a more conventional, hypothesis-driven manner by adopting targeted strategies.

Targeted platforms, such as protein microarrays and other immunoaffinity-based methods, are suited best for determining quantitative differences between known protein families and pathways. Targeted platforms offer enhanced reproducibility, scalability, and quantitative precision, with the additional advantage of moderate-to-high-throughput. The value and scale of these approaches, however, are limited by the availability of high-quality antibodies. These platforms can be used to validate findings from untargeted strategies, but they also can be employed in a discovery mode to interrogate hundreds of proteins simultaneously. Targeted approaches address multiple well-defined hypotheses: Is molecule X associated with disease Y?

The four commonly adopted paradigms in proteomics are discussed in brief in the following sections:

- Protein profiling strategies (mass spectrometry is common to these strategies) —MALDI-TOF MS and similar approaches
- Protein-centric (top-down) strategies, notably two-dimensional gel based approaches
Protein profiling strategies—discovery, validation, and routine testing all in one

The key analytical platform for protein profiling strategies is matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS). With this approach, a small volume of a biological fluid, typically 1 μL or less, is placed on a metal plate (target), mixed with matrix solution and allowed to dry into a crystalline form. When the laser irradiates a discrete region of the crystalline sample, the matrix efficiently absorbs light at the emission wavelength of the laser, and the analyte is vaporized. Typically the matrix is a weak acid that can protonate the analyte to yield, predominately, singly charged ions for each component of the sample. Ions then are separated based on their mass-to-charge ratio \((m/z)\) in the TOF chamber and detected. (Lower mass ions fly faster and reach the detector first.) A full-mass spectrum is collected on the millisecond time scale, but in practice, multiple spectra usually are acquired and averaged to increase the signal-to-noise ratio for the observed peptide and protein signals. Typically a MALDI mass spectrum of a complex mixture such as serum or plasma contains 100 to 200 peaks at most, each one representing a distinct entity in the biological sample. It should be noted that detection of such low numbers of peptides and proteins represents poor coverage of the proteome, particularly when compared with other common paradigms. Peak position \((x\text{-axis})\) defines \(m/z\); peak height \((y\text{-axis})\) is a crude measure of relative abundance. In a typical clinical study, spectra are acquired on multiple samples collected from subjects representative of a test population. These are averaged to yield a typical mass spectrum, or signature, that then can be compared with spectra representative of other populations.

Surface-enhanced laser desorption ionization TOF mass spectrometry (SELDI-TOF MS) is a commercial variant of MALDI-TOF MS that incorporates some proprietary sample prefractionation. The sample is applied to one or more of a series of patented ProteinChip (Bio-Rad, Hercules, California) surfaces that provide various different physical and/or chemical properties: for example hydrophobic, hydrophilic, anion exchange, cation exchange and immobilized-metal affinity surfaces. Each chip retains a different subset of proteins, and the unbound proteins are washed away. A matrix is added to the ProteinChip to facilitate desorption and ionization of the retained proteins so that their mass-to-charge ratio can be measured in the mass spectrometer. In a manner exactly analogous to that described previously, a protein profile is generated. Many reports describe clinical application of SELDI-TOF MS based on the analysis of body fluids such as serum or plasma. (Over 500 papers have been published on the application of SELDI, and only a subset of representative, more recent work is cited herein.)

To obtain clinically meaningful results from a protein profiling strategy, careful thought must be given to experimental design, sample handling, and sample
storage. Many early profiling studies proved irreproducible, because they were marred by poor sample handling and/or collection strategies [3–6]. As in all other areas of chemical analysis, these experiments must incorporate the analysis of samples that provide data on reproducibility (ie, intra- and intersample variability, instrument reproducibility, day-to-day variation). Sample collection and storage protocols should be standardized and strictly enforced, and issues such as the impact of freeze-thaw cycling, time from collection to storage, and time from storage to processing also should be addressed.

Besides the poor coverage of the proteome, there are several other important limitations of profiling strategies that are worthy of note. The profiling strategy is potentially a one-stop biomarker discovery, validation, and routine-testing tool, but because the diagnostic peaks are neither identified nor quantified in absolute terms, the approach is locked into the platform. Most investigators would prefer to see routine analysis move to an alternative approach (eg, ELISA) that offers precise and accurate absolute quantification of well-defined chemical entities, but the unambiguous identification of the peptides and proteins observed in a profiling experiment is far from trivial. Consequently, most diagnostic peaks reported in the literature have not been identified. Additionally, profiling strategies are particularly biased toward seeing (ie, ionizing and detecting) molecules of less than about 20 kDa [7]. A few peaks from serum protein profiles in this mass range tentatively have been identified as truncated forms of high-abundance, ubiquitous proteins. These are unlikely to serve as disease-specific biomarkers, but instead are secondary products of more general processes like inflammation. Nevertheless, when measured together with other parameters (eg, additional biomarkers and/or clinical parameters), these indirect measures may offer clinical utility [8].

In summary, a major strength of the protein-profiling approach is the speed with which these analyses can be performed. Under optimal conditions, results can be generated within a few minutes. The technique is simple to perform, relatively inexpensive, and amenable to automation and high-throughput. Published studies indicate that multiple individual protein peaks can be linked to clinical parameters through the thoughtful selection of clinical samples (populations) and the use of reliable software for pattern recognition and comparison. Unfortunately, because diagnostic peaks rarely are identified, the investigator is robbed of valuable information that can provide valuable insights into the underlying biochemical events.

Several recent reviews provide a detailed discussion of protein profiling [3–7,9–12]. In addition, some reports demonstrate the application of these techniques to pediatric diseases including various childhood cancers [13–17], sleep disorders [18], and arthritis [19].

Two-dimensional gel based approaches—discovery alone
In two-dimensional gel electrophoresis, after the proteins have been isolated from their biological matrix, they are separated in the first dimension based on isoelectric point and in the second dimension based on molecular size.
Following separation, the proteins can be visualized using one of various staining or labeling techniques [20]. The resulting image generally reveals thousands of spots, and the proteins then can be identified by excision, enzymatic digestion, and mass spectrometry [21–25]. Two-dimensional gel electrophoresis offers special insights into the proteome and its intricacies, because the resolving power of this technique at the protein level surpasses any other analytical technique, including liquid chromatography.

Two-dimensional gel electrophoresis, first reported in the 1970s, is amenable to protein isolates from various sources including tissues, biological fluids, cell cultures, bacteria and plants. Until recently, however, wide-spread application of two-dimensional gels was limited for two reasons. First, there was no method available to identify the protein spots, and second, there is considerable inherent intergel variability. This second issue stymies attempts to obtain statistically meaningful comparisons when traditional staining techniques (eg, Coomassie, silver and noncovalent fluorescent dyes) are employed. It is difficult to compare protein levels from different samples because of the additive impact of intergel and biological variability.

The development of difference gel electrophoresis (DIGE) has changed the face of two-dimensional gel electrophoresis, because it allows multiple samples to be analyzed on a single gel. In DIGE, two protein samples (eg, normal versus disease or treated versus untreated) are labeled differentially with two cyanine dyes, mixed together and then separated by two-dimensional gel electrophoresis [26–28]. Distinct fluorescence signals—one for each sample/dye combination—are measured by laser scanning of the gel and the images overlaid. Relative protein abundance is measured by comparing the spot volume in one channel (sample) to the spot volume in the other channel (sample) on a protein-by-protein basis. The capability to run two samples on the same DIGE gel, along with an internal standard, reduces the intergel variability dramatically, and DIGE represents a substantial improvement in gel-based comparative proteomics.

There are notable limitations of the two-dimensional gel approach. This technique is time-consuming, expensive, and requires a good deal of technical expertise. As with other strategies, the subset of proteins visualized has constraints, and the entire proteome is not amenable to analysis. The advantage of the two-dimensional gel strategy lies in the possibility to resolve and visualize thousands of proteins, including post-translationally modified isoforms, and begin to appreciate the diversity of the proteome at the protein level. Furthermore, when combined with approaches such as DIGE, relative protein abundances can be measured with an acceptable degree of quantitative precision.

Several recent reviews provide a more detailed discussion of two-dimensional gels and their refinements [27,29–31]. Of special significance, several reports have applied two-dimensional gels to studies of pediatric health problems such as sickle cell disease [32], leukemia [33], blood disorders [34], allergen exposure [35], and cystic fibrosis [36,37].
Liquid chromatography–tandem mass spectrometry approaches—discovery alone

Shotgun LC-MS/MS strategies begin by first enzymatically digesting proteins to yield a more complex mixture of peptides that then can be separated and detected. This approach is forced on the analyst, because proteins denature under reversed-phase conditions (i.e., at low pH and high organic solvent concentrations), making their quantitative recovery problematic, and because the molecular weight alone of a protein is insufficient for unambiguous identification. The complex mixture of peptides is separated by liquid chromatography, and the column eluate is passed directly into a tandem mass spectrometer by means of electrospray ionization. A product ion spectrum is generated for each peptide, or at least as many as can be determined practically. The MS/MS spectra of most peptides (at least those of unmodified peptides less than about 20 amino acid residues) provide an unambiguous amino acid sequence when they are searched against an appropriate database with commercial software packages (e.g., Mascot or SEQUEST). The sequence of one or more peptides then can be assigned to a gene product.

An estimation of relative protein abundance in a sample is possible based on the number of peptide spectra that match a given protein in the sample [38]. Precise quantitative comparison between different samples is problematic, however, unless labeling strategies are adopted. Numerous isotopic labeling strategies have been developed, and some of these have been commercialized. The most common strategies are the isotope-coded affinity tag (ICAT) [39–42], amine-reactive isobaric tagging reagents (iTRAQ) [43,44], and stable isotope labeling by amino acids in cell culture (SILAC) [45].

The complexity and ambiguities inherent in this approach must be appreciated so that the data generated can be put into perspective. Typically, a single protein with a molecular weight of 50,000 yields about 50 peptides when treated with trypsin. Consequently, a complex protein mixture of several thousand proteins will yield tens of thousands of peptides that must be separated and analyzed by tandem mass spectrometry. This is a substantial analytical challenge that pushes existing instruments to the limits of their performance, both in terms of the resolution of the chromatographic system (multidimensional chromatography often is adopted) and the scan rate, resolution, and sensitivity of the mass spectrometer. Consequently, only a fraction of the peptides are recovered, and as anticipated, peptides derived from the more abundant proteins are represented well; peptides derived from the low-abundance proteins may be sparse or completely absent. Further, repeat analysis of the same sample routinely returns a different set of peptides because of complexity of the chromatogram and the finite scan rate of the mass spectrometer. Each sample therefore should be run multiple times to gain maximum coverage [38].

Perhaps the most serious limitation of this strategy relates to the ambiguities inherent in reassembling the peptide data into meaningful protein information [46]. Although it is not highlighted in many discussions of proteomic data, it is not uncommon to report 10% sequence coverage as sufficient to identify
a protein. Clearly, in these instances, changes elsewhere in the sequence are missed completely. To illustrate this point, consider the scenario depicted in Fig. 2. Here, four isoforms of a protein are shown, where the primary structure is unchanged, but specific amino acids have been post-translationally modified or cleaved from the parent protein. To identify proteins in a typical shotgun experiment, they are enzymatically cleaved, usually by trypsin, to produce a series of predictable peptides that can be detected by mass spectrometry. Unless 100% of the sequence is detected, including all modifications, a problem arises. In this example, whether a peptide is detected as modified or unmodified (ie, phosphorylated or oxidized), it is impossible to unambiguously assign that peptide to one or more of the four different isoforms. Furthermore, many modifications go completely undetected (eg, glycosylation), and truncated forms are nearly impossible to detect with this approach. This example highlights the primary limitation of LC-MS/MS-based strategies, especially when attempting to obtain quantitative information. Using a peptide-centric approach, the quantitative information is confounded by the presence of multiple isoforms, and most of these go undetected. The protein-centric approaches, such as two-dimensional gels, allow for quantification of intact proteins, and therefore isoform information is retained. Most modifications change either the molecular weight, the isoelectric point, or both, which means they will migrate to different positions on a two-dimensional gel and can be quantified independently. Although it is not common to completely characterize the modifications that characterize the various isoforms that are evident on a two-dimensional gel, at least one has a sense of the diversity and complexity of the sample.

Fig. 2. This example illustrates the difficulty inherent in reassembling peptide-centric shotgun data into meaningful protein information. The gray lines represent different post-translationally modified isoforms of the same polypeptide sequence.
Several recent reviews provide a detailed discussion of LC-MS/MS approaches [40,47–53].

Arrays—some discovery, some validation, some routine testing
Proteome analysis based on either two-dimensional gel electrophoresis or LC-MS/MS may miss many proteins of interest when they are expressed at low levels, and/or when quantitative changes are subtle. Alternative strategies for protein detection, quantification, and differential expression analysis are therefore of considerable interest.

Because there now is access to thousands of recombinant proteins, these can be arrayed to generate protein chip arrays. Alternatively, these proteins can be used to generate specific antibodies, which themselves can be arrayed to produce antibody chips. In fact, arrays of this type offer remarkable versatility, because it is possible to capture and quantify specific antibodies or proteins from complex mixtures. Further, protein–drug and enzyme–substrate interactions also can be studied. The key feature of these approaches is that they allow parallel (or multiplexed) analysis of a few to thousands of discrete interactions simultaneously; therefore they can be used in mechanistic research (eg, protein–protein interaction studies), biomarker discovery studies (ie, involving preselected proteins of known identity), biomarker validation studies and routine analysis in clinical laboratories. In theory, a systematic survey of a complex biological system is therefore possible, and in contrast to other methods, arrays can offer a selective, sensitive, precise and fully-automated, high throughput approach that is time-, cost- and sample-efficient. Some specific examples of how arrays can and have been employed are illustrated.

Antibody arrays in basic research
High-density, comprehensive antibody arrays can be employed to discover new biomarkers and to better understand the involvement of specific pathways in the pathophysiology of disease. Two complementary types of antibody arrays commonly are used: direct labeling and sandwich assays. In the label-based assay, the targeted proteins are labeled with a fluorescent tag, such as Cy3 or Cy5, that allows their detection following capture by an immobilized antibody. In a sandwich assay, immobilized antibodies capture unlabeled proteins, and the captured proteins are detected by a second labeled antibody. Label-based assays allow the coinubcation of two different samples, each labeled with a different tag, and because the assay is competitive, the analytes in the test and reference solutions compete for binding at the antibodies. With label-based detection, however, there is the potential for the labeling process itself to compromise antibody–antigen interaction, and sometimes specificity and sensitivity are suboptimal. Sandwich assays often have higher specificity, because two antibodies target each analyte, and the practical limit of quantification can be improved, because the background is reduced. Sandwich assays by nature are noncompetitive, as only one sample can be incubated on each array. There is always the possibility of cross-reactivity between
detection antibodies when multiple analytes are incorporated, and so to retain specificity, multiplexed sandwich assays usually are restricted to 30 to 50 distinct targets. This is in contrast to arrays based on label-based detection, which generally are limited only by the availability of antibodies and the density with which these can be applied to the substrate practically.

As with any technique of this complexity, there are major technical challenges with antibody arrays [54]. The primary limitation to the development of protein arrays is the availability of antibodies with high specificity and sensitivity for each analyte. Antibodies can be custom-made, which is a laborious and costly procedure, or purchased from commercial sources, but in either case, the sensitivity and specificity must be defined.

Antibodies also must be bound uniformly to the substrate and remain properly folded so that antigen–antibody binding is uncompromised, and there is no universally applicable set of conditions for doing this optimally (ie, proteins denature under different conditions). Thereafter, it is necessary to block nonspecific protein-binding sites on the microarray, and again, optimal conditions may vary markedly for each constituent antibody. Further, each antibody needs to be present at levels sufficient to bind to the antigen in the sample and induce a detectable signal. Across a range of antibodies, these are demanding and time-consuming requirements. For all these reasons, these assays typically offer lower accuracy and reproducibility than single-component immunoassays employed in routine clinical settings. Additionally, extensive coverage of the proteome by antibody arrays is not practical currently, and arrays more likely will be developed for specific subproteomes.

**Antibody arrays in clinical research**

Multiplexed sandwich assays in microarray format now are transitioning into routine diagnostic testing. For example, multiplexed analysis based on planar microarrays or microbeads are applied to the simultaneous assay of antibodies, cytokines, allergens, drugs, and hormones [54]. Typically these arrays are low-density (3 to 100 elements/array) and employ known antibodies to capture specific antigens from the clinical samples. A second antibody is used to create a sandwich assay [55]. Multiplexed arrays of this type will continue to make inroads into routine clinical testing, but quality assurance/quality control (QA/QC) issues will provide some challenges, at least in the short term [56,57].

**Arrays in the biomarker validation process**

Proteomics discovery studies routinely identify a manageable short-list of 5 to 50 candidate biomarkers for further validation. As discussed earlier, this process can be thought of to consist of at least four phases (see Fig. 1). In the first validation phase, laboratory assays of biomarkers are developed and validated, with careful attention to specimen acquisition, processing, precision, accuracy, reproducibility, storage requirements, high throughput, and other aspects of analytical validation. These assays should be validated in the biological matrix being proposed for routine testing (eg, blood, urine, cerebrospinal fluid, breath
condensate, sputum, bronchoalveolar lavage, and various tissue samples). Multiplexed antibody arrays provide a perfect format for review of candidate biomarkers, because they minimize the time, effort, and precious sample involved in validation.

In summary, antibody arrays can be employed in many settings and hold considerable promise. Several recent review articles provide a more detailed discussion of protein microarrays and illustrate applications of this approach [58–61]. Specifically, several research studies have reported using microarrays for studying autoimmunity [62], signaling transduction pathways [63], lupus [64], protein–protein interactions [65], and cystic fibrosis [66].

LIMITATIONS OF EXISTING PROTEOMIC METHODS: SOME ADDITIONAL CONSIDERATIONS

Proteomic methods hold great promise, but it is important to be pragmatic and objective about what existing tools and strategies offer. Commonly adopted approaches do not determine the primary sequence of proteins de novo, but rather infer a sequence from mass spectrometric data by means of database searching. In other words, the speed with which proteins can be identified is impressive, but many corners are cut in the process. To identify a protein, its primary amino acid sequence must be represented in a database. Additionally, experimental strategies determine one or several small segments of amino acid sequence (5 to 25 amino acids) and use these data to infer the complete protein structure. Typically much less than 50% of the sequence is detected, and the remainder is assumed without being expressly determined. Consequently, it should not be surprising to find that, in a rush to ascribe a name to proteins based on minimal data, amino acid substitutions and post-translational modifications are frequently missed completely. Errors and inconsistencies in the rapidly expanding literature are therefore likely to be common.

The complexity of the proteomics exercise should not be understated, and significant analytical challenges arise because of the enormous dynamic range representative of protein abundances in biological samples [67–69]. This problem is pronounced particularly in circulating fluids. The challenge is to detect the low abundance proteins in samples when they are dispersed in an ocean of high abundant proteins. Most current solutions rely on immunoaffinity fractionations that aim to selectively retain the high abundance proteins and leave the low abundance proteins in the flow-through. This approach allows the experimentalist to cut deeper into the proteome, but it is dependent on the affinity and selectivity of the antibodies that are employed. The process is costly, time-consuming, and unless rigorously controlled, it can be irreproducible. Additionally, there is the risk that low abundance proteins may bind to more abundant proteins under nondenaturing conditions and themselves be removed from the sample.

At this stage there is no standardized, well-established technology platform in proteomics. In fact, different laboratories approach proteomics in very different ways. Experimental outcomes can vary markedly, even when the same samples
and study design are employed. One should remember that in human studies researchers are, at best, only shaving the surface with existing methods and recovering information on only a few percent of the proteins present. Small changes in the experimental conditions (pH, solvent composition, method of protein isolation, and ionic strength) markedly influence what is recovered from a given experiment, and while this is unsettling to many scientists, it is the reality. What appears to be the same experiment can give markedly different results, but this outcome should not come as a surprise given the complexity of the analytical approach (including study design and sampling), the organism and its proteome (the chemical and physical diversity of the proteins present), and the (incomplete) data generated and surveyed.

**THE NEXT FRONTIER: FOCUSED ATTENTION TO CO- AND POST-TRANSLATIONAL EVENTS AND THE COMPLEXITY OF THE PROTEOME**

Determining the proteome is an especially valuable exercise. It offers insights over and above those accessible through genomics, because the complexity of the human proteome far exceeds that of the genome. When variables such as alternative gene splicing and post-translational modifications are taken into account, the number of different protein species in humans is likely to be at least an order of magnitude greater than the number of genes (ie, about 500,000 proteins). Most if not all human proteins undergo post-transcriptional and/or post-translational refinements, and these markedly augment the structural and functional repertoire of the genome [70]. These changes add functional groups that modulate the activity of most proteins by altering physical and chemical properties including conformation, stability, and activity. The list of known modifications is extensive and includes phosphorylation (eg, signal transduction); ubiquitination (involved in proteolysis); covalent attachment of fatty acids (for membrane anchoring); oxidation; methylation, and glycosylation. In addition to the vast array of covalent modifications to specific amino acids, there is also N-terminal acetylation, C-terminal deamidation, truncation, and alternative splicing. These events transform the 30,000 human genes into over half a million proteins [68,69,71].

Protein modifications have important implications for the proteomics practitioner, because characterizing them presents a formidable challenge. Without this information, however, indispensable insights into biological function are lost completely. The most important of all advances in this evolving area is to increase the ability to identify, characterize and quantify these changes. The following sections discuss some key events in protein synthesis and modification and highlight their essential role in normal biological processes.

**One-gene yields many products: site-specific enzymatic cleavage of a single gene product**

Secreted proteins are often translated within the cell as preproproteins that contain short amino acid sequences, usually at the N-terminus, which make
them nonfunctional until proteolytically cleaved (ie, activated) during trafficking or when they reach their final destination. Furthermore, some genes encode for a single polypeptide that is enzymatically cleaved in a cell-specific manner to produce multiple functional peptides. Proopiomelanocortin (POMC) is a good example of a polypeptide chain translated from a single gene that incorporates about a dozen important peptide hormones, each with distinct biological functions [72].

Cleavage of POMC to various peptides is cell-specific and is accomplished by two enzymes, prohormone convertases PC1 and PC2, acting at a combination of eight cleavage sites (Fig. 3). In corticotroph cells of the anterior pituitary, six peptides are generated by PC1 acting at four cleavage sites: (1) the N-terminal peptide (NT); (2) the joining peptide (JP); (3) adrenocorticotropic hormone (ACTH); (4) beta-lipotrophin (βLPH), gamma-lipotrophin (γLPH), and beta-endorphin (βend). In melanotrophs of the hypothalamus, PC1 and PC2 act together to cleave POMC at all eight cleavage sites and produce the smaller peptide hormones γ-melanocyte-stimulating hormone (γMSH), α-melanocyte-stimulating hormone (αMSH), corticotrophin-like intermediate peptide (CLIP), β-melanocyte-stimulating hormone (βMSH), and two forms of βend (βend1-27 and βend1-31). The biological effects of these hormones are observed in adrenal function (ACTH), melanocyte stimulation (ACTH, LPH and MSH), immune modulation (αMSH), the central nervous system (MSHs), response to pain (βend) and during pregnancy. It is clear from this example that,

Fig. 3. Proopiomelanocortin is translated from a single gene, but is cleaved post-translationally to yield numerous functionally distinct peptide hormones. This example illustrates the complexity of the proteome relative to genomic information. (Data from Raffin-Sanson ML, de Keyzer Y, Bertagna X. Proopiomelanocortin, a polypeptide precursor with multiple functions: from physiology to pathological conditions. Eur J Endocrinol 2003;149:79–90.)
after proteolysis, one or two peptides alone cannot unambiguously identify the in vivo form(s) of one or more products of this gene.

**Alternative splicing of a gene product**

Alternative splicing can lead to multiple isoforms of a protein from a single gene. It is estimated that 35% to 75% of all human genes are alternatively spliced [73], and while some of these events may not have functional significance, there are many examples to the contrary [74]. There are numerous reports of where alternative splicing affects protein binding properties, intracellular location, enzymatic and signaling activity, stability, post-translational modification and ion-channel properties [73].

**Some common modifications to amino acids**

*Glycosylation*

Glycosylation is likely the most common of all post-translational modifications as it occurs in most human proteins [75,76], and its functional significance is being recognized increasingly. In particular, missing, aberrant, or additional glycosylations are known to be linked to certain diseases and may be used as markers for diagnosis and/or therapeutic monitoring. Glycosylation plays an essential role in protein folding, therapeutic efficacy, activity and half-life of circulating proteins, as well as key biological processes such as immune response [77,78], regulation of signaling pathways [79,80], and development [81,82]. The importance of glycosylation for proper protein function is well-illustrated by studies of therapeutic efficacy of peptides and proteins [76,83]. Glycosylation frequently is missed completely in proteomic studies, and approaches to reliably identify and characterize this important modification need further development [84,85].

*Phosphorylation*

It is established that reversible phosphorylation plays an essential role in regulation of protein activity, ligand binding, protein–protein interaction, post-translational modification, and coordination of multiple biological pathways. About 30% of mammalian proteins are believed to be phosphorylated [86]. Because of their important role in biological pathways, the proteins responsible for reversible phosphorylation, phosphatases, and kinases often are the target of therapeutic intervention. For example, the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors gefitinib and erlotinib have shown some success in the treatment of non–small cell lung cancer [87,88]. Although considerable attention has been directed toward identifying and characterizing phosphorylation sites by mass spectrometry, this modification is also often missed. The dynamic nature of the phosphorylation process and the requirement to determine relative quantification of the extent of phosphorylation make this area of investigation especially challenging [89,90].

**Protein modifications and disease**

Protein modifications are not only critical in the normal function of an organism, but aberrant post-translational modifications can lead to disease
Aberrant glycosylation of proteins causes a range of diseases classified as congenital disorders of glycosylation (CDG) [92]. Advanced glycation end products contribute to the complications of type I diabetes, neurodegeneration and aging [93,94]. Alternative splicing plays a role in several types of cancer, cystic fibrosis, amyotrophic lateral sclerosis, myotonic dystrophy and spinal muscular atrophy [95–97]. Phosphorylation of Bcl2 plays an important role in functional regulation and therefore disease outcome in leukemia [98].

The examples cited herein illustrate the remarkable functionality incorporated postgenomically and highlight the need to define and quantify these changes. Although proteins better reflect phenotype than the genome, one should acknowledge that this additional complexity is generally not realized in current applications of the existing tools of proteomics. Ongoing methodological developments and an increasing focus on the details of protein structure are essential if the full potential of proteomics is to be realized.

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In September 2005, the American Academy of Pediatrics (AAP) celebrated its 75th anniversary. As part of the celebration of this milestone, the AAP recognized the 10 greatest advancements in child health over that time, to which the group contributed [1]. One of these was the advocacy that led to the 1998 Final Rule, which required that new drugs be studied in children if they provided a significant therapeutic benefit over existing therapies, if the absence of pediatric labeling posed a risk to children, or if the new therapy provided a treatment where no others existed [2]. This advocacy also led to the Pediatric Research Equity Act (PREA) of 2003 and The Best Pharmaceuticals for Children Act (BPCA) that was passed by the US Congress in 2002 [3], a law that provides incentives for industry to conduct trials with children for drugs already approved for adults or those in development.

Before the passage of these laws, it was reported that over 75% of the drugs used by children did not have pediatric labeling information [4]. Although an ongoing effort is needed, there have been significant changes over the past decade in the way medications are studied in children largely because of the Final Rule and BPCA that have resulted in improved knowledge about the safety, efficacy, and dosing of medications for children. Demonstrating this, as of Dec. 4, 2006, 129 drugs have been granted exclusivity under Section 505A of the Federal Food, Drug, and Cosmetic Act, which indicates that sufficient testing of these drugs has been performed on children [5]. Among these are commonly used medications such as ibuprofen and loratadine, as well as medications for more rare conditions. Examples of the latter include oxcarbazepine, a drug used to treat seizures, which became the 100th drug to receive special pediatric labeling.

Another major advancement in patient safety, therapeutics, and information regarding therapeutic agents, came when leading medical journals announced a new policy regarding the registration of clinical trials [6]. In short, for a study to be published in these leading journals, the trial must be registered before their onset and include information such as a statement of the intervention
(or interventions) and comparison (or comparisons) studied, a statement of the study hypothesis, definitions of the primary and secondary outcome measures, and eligibility criteria. This policy was announced to combat selective reporting of results favorable to the investigators conducting a trial and allow for a more transparent process in determining the true sum of the evidence for a given subject. In the United States, the registry most commonly used is available on the Internet at www.clinicaltrials.gov, a site sponsored by the US National Library of Medicine.

The remainder of this article will focus on the advances in pediatric therapeutics that occurred between July 2004 and June 2006. It will also discuss some notable controversies including the US Food and Drug Administration’s (FDA) decision regarding emergency contraception, the reported risk of sudden death with long acting β-agonists, and possible adverse cardiac effects with stimulant medications.

**SYMPTOMATIC CARE**

Over the past 2 years, many important studies have been published that relate to common pediatric symptoms. These symptoms, such as fever, cough, or nausea, result in most pediatric acute care visits each year, and often medications are used as an attempt to remedy these symptoms. Some of these medications are used despite a lack of evidence supporting their use, and one recent publication suggested that parents give these drugs as a social medication to control behaviors in their children that they perceive as irritating [7].

**Fever**

The fear of fever, or fever phobia, causes many parents to treat fever aggressively with antipyretics such as ibuprofen and acetaminophen, often in combination or using alternating doses within a given 6-hour time period. This practice is thought to be quite common despite the lack of proven efficacy of coadministration compared with the use of a single agent. Two recent studies examined this issue. The first study, from Israel, compared monotherapy with either acetaminophen or ibuprofen with an alternating regimen using both drugs [8]. The study followed the young children who participated for several days and found that the alternating regimen had a greater antipyretic effect, but the conclusions drawn from the study were severely limited by the nontraditional dosing scheme that included a loading dose of 25 mg/kg of acetaminophen for some participants, questionable choices for subsequent individual drug doses of acetaminophen and ibuprofen, and several other design issues.

In the second study, British investigators sought to add to the limited available evidence by comparing a single combined dose of paracetamol (acetaminophen) 15 mg/kg/dose plus ibuprofen 5 mg/kg with single doses of the individual compounds in febrile children [9]. One hour after medication administration, the combined treatment group’s mean temperature fell by a mean 1.22°C at 1 hour compared with 0.95°C and 0.92°C for the paracetamol and ibuprofen groups, respectively. The authors concluded that while the
combination regimen did appear to be somewhat more effective at reducing temperatures 1 hour after administration, the difference between treatment groups was not clinically significant. When evaluating these findings, clinicians should note the recommendations of the AAP Committee on Drugs, which stated in 2001 that clinicians and parents should exercise discretion when considering alternating doses of antipyretics and that the goal of antipyretic therapy should be comfort, not the complete normalization of temperature [10].

Because hospitalized patients cannot always tolerate oral antipyretic medications, the antipyretic efficacy of the intravenous medication propacetamol was compared with placebo for febrile children [11]. Propacetamol is a prodrug that is hydrolyzed into acetaminophen and a second compound that is pharmacologically inactive. The results showed that propacetamol was a significantly better antipyretic than placebo at each hourly measurement for 6 hours, and the drug was tolerated equally well as the placebo.

Cough and cold
The AAP has not supported the use of dextromethorphan as an antitussive because of the lack of evidence demonstrating efficacy, potential for adverse effects, and the absence of published pediatric dosing studies [12]. In an attempt to fill the gap in the literature, investigators compared a single nocturnal dose of dextromethorphan with diphenhydramine and placebo in children who had upper respiratory infections (URI) and evaluated their effects on nocturnal cough, sleep quality, and parental sleep quality [13]. The findings of this study, which used parent-completed subjective rating scales of symptoms, showed that neither drug was superior to placebo for any of the outcomes studied. Similar to the AAP statement, the American College of Chest Physicians published guidelines that cited this study and others in recommending against the use of over-the-counter (OTC) cough suppressants for children [14].

Other OTC cough and cold products were also newsworthy, as the FDA mandated that manufacturers cease production of unapproved products containing the sedating antihistamine carbinoxamine because of safety concerns and a lack of proven efficacy in treating the URI symptoms for which they were being marketed [15]. Similarly, safety concerns led to the voluntary withdrawal of Triaminic Vapor Patch products by Novartis [16]. The topical patches, which contain camphor, eucalyptus oil, and menthol, posed the risk of adverse health effects if ingested by children.

One cause of cough for which an effective treatment is available is croup, or acute laryngotracheobronchitis. A new study expanded on the current evidence by studying oral dexamethasone for mild croup [17]. For children presenting to emergency departments with mild symptoms of croup, a single oral dose of dexamethasone (0.6 mg/kg) was significantly better than placebo for symptom resolution and at preventing return to medical care, lost sleep, and parental stress. This effective treatment for mild symptoms is timely given the results of another study that dispelled the long-held belief that humidified air is helpful for croup symptoms, but clinicians should consider
carefully whether this relatively large dose of corticosteroids is necessary for mild symptoms [18].

Sore throat
Another condition that may benefit from oral dexamethasone is moderate-to-severe pharyngitis [19]. Compared with placebo, children given a single dose of 0.6 mg/kg demonstrated improved pain relief and fewer hours until resolution of sore throat, particularly for those subjects who tested negative for group A β-hemolytic streptococci. Treatment with corticosteroids is an alternative to inappropriate antibiotic prescriptions for those testing negative, a practice that still occurs frequently [20].

Vomiting and diarrhea
Another drug that received an FDA warning is the antiemetic promethazine. Commonly used in children for over 50 years, reports describing an association of the drug with fatal respiratory depression led the agency to add a new black box label warning recommending against its use in children younger than 2 years [21]. In a letter to the editor published in the New England Journal of Medicine, the FDA explained its actions and described all cases of serious adverse events reported to the FDA that involved children receiving any formulation of promethazine. Of the 125 children who had serious adverse events, included were 38 cases of respiratory depression (22 of the 38 were in children younger than age 2 years, of whom seven died), apnea, or cardiac arrest. Additionally, there were 29 cases of extrapyramidal dystonic reactions, 24 cases of other central nervous system reactions, 15 cases of seizures or seizure-like activity, 12 cases of dermatologic reactions, and five cases of the neuroleptic malignant syndrome [3].

In contrast to the reports with promethazine, another common antiemetic, ondansetron, demonstrated good safety and efficacy when it was tested in children aged 6 months to 10 years who presented to a pediatric emergency department with gastroenteritis and dehydration [22]. Compared with placebo, children treated with the active compound were less likely to vomit, took fluids by mouth better, and were less likely to receive intravenous rehydration. They also had shorter emergency department stays, something that could help to offset the cost of the drug.

INFECTIOUS DISEASES
Streptococcal Pharyngitis
Streptococcal pharyngitis traditionally has been treated with either a 10-day course of oral penicillin VK or amoxicillin or with a single injection of penicillin G benzathine, but over the past several years there has been increased interest in the efficacy of shorter courses and those with less frequent dosing. Addressing this issue, a meta-analysis was conducted to analyze shorter courses of treatment [23]. Although shorter courses of penicillin did not have equal bacteriologic cure rates as the traditional 10-day course, 4- to 5-day courses of oral cephalosporins (eg, cefdinir, cefpodoxime, or cefuroxime) did achieve
superior bacteriologic cure rates compared with the traditional penicillin course.

Another study examined the use of injected ceftriaxone for treatment of streptococcal pharyngitis [24]. Because previous studies had shown that a single dose was not adequate, the authors examined the pharmacokinetics and pharmacodynamics of the drug, and determined that it would require two injected doses of 50 mg/kg/dose to achieve acceptable bacteriologic cure rates.

Acute otitis media and otitis externa
Although high-dose amoxicillin (80 to 90 mg/kg in two divided doses for 10 days) has become the standard first-line treatment for acute otitis media, the re-emergence of *Haemophilus influenzae* that is often resistant to amoxicillin as the leading bacterial cause of this condition in some communities has led some investigators to study other drugs for acute otitis media. One such study compared the efficacy of this standard treatment with a single dose of azithromycin (30 mg/kg) [25]. Interestingly, the clinical and bacteriologic cure rates were not different between the two treatment groups, but the azithromycin group had significantly fewer adverse events such as onset of diarrhea. Another study compared high-dose amoxicillin/clavulanate (90/6.4 mg/kg/d in 2 divided doses for 10 days) with azithromycin (10 mg/kg for 1 day followed by 5 mg/kg for 4 days), and found amoxicillin/clavulanate to be superior as determined by clinical assessment and bacteriologic cure rate assessed with tympanocentesis [26]. More adverse events occurred in the amoxicillin/clavulanate arm, however.

For otitis externa, the evidence regarding topical antimicrobial therapy recently reviewed was and published simultaneously with a clinical practice guideline from the American Academy of Otolaryngology-Head and Neck Surgery Foundation (AAO-HNSF) [27,28]. In the review article, the authors reported that topical antimicrobial or antiseptic therapy is highly effective for treatment of acute otitis externa, but that the choice of topical antibiotic does not have a great impact on cure rates. Topical antimicrobial choices described in the article included neomycin (combined with either polymyxin B/hydrocortisone, colistin/hydrocortisone, or polymyxin B/dexamethasone), quinolones, or aminoglycosides, and antiseptics included acetic acid with either aluminum acetate or corticosteroids. Also, the addition of corticosteroids to the antibiotic drops did not result in a significant difference in cure rates. The guidelines supported the use of topical antibiotics for most cases of acute otitis externa, and suggested that oral analgesics also should be a mainstay of treatment. Notably included and relevant for children, if the tympanic membrane is perforated, the AAO-HNSF cautioned against the use of ototoxic medications such as aminoglycosides and neomycin, those containing alcohol, or those that have a low pH (most acidifying/antiseptic agents).

Pneumonia
Children who have moderate-to-severe pneumonia often are given parenteral antibiotics even when they are able to tolerate medications by mouth. To determine the necessity of this practice, the World Health Organization
(WHO) led a multicenter, international study of 1702 children aged 3 to 59 months admitted to the hospital with severe pneumonia [29]. Children were randomized to receive either injectable penicillin or oral amoxicillin for 48 hours followed by oral amoxicillin. Despite using a relatively low dose of oral amoxicillin (45 mg/kg/d), the treatment failure rate was equivalent in the two groups at 19%, and the authors concluded that there was no advantage to using the intravenous medication for the first 48 hours.

Urinary tract infection
Patients who have primary vesicoureteral reflux frequently are placed on prophylactic doses of antibiotics to prevent urinary tract infections (UTIs), pyelonephritis, and renal scarring, but data supporting this practice are limited. Therefore a multicenter trial was conducted comparing randomly assigned patients to either antibiotic prophylaxis (trimethoprim/sulfamethoxazole or nitrofurantoin) or no treatment for 1 year [30]. At the end of this year, there were no differences between the groups for rate of UTIs or pyelonephritis or for the development of renal scarring as determined by dimercaptosuccinic acid renal scans.

Infectious diarrhea
Though relatively uncommon in the United States, cholera remains a major global health problem and cause of infectious diarrhea. The standard treatment for this condition is a 3-day, 12-dose course of erythromycin, but recently this treatment was compared with a single dose of ciprofloxacin (20 mg/kg) in children aged 2 to 15 years with cholera [31]. Although the bacteriologic cure rate was less in the ciprofloxacin treatment arm, the clinical cure rates were comparable, and the ciprofloxacin group vomited less often and had less stool volume than those treated with erythromycin.

Tinea capitis
Traditional treatment of tinea capitis has been a 6- to 8-week course of oral griseofulvin, but recently alternative antifungal treatments such as terbinafine have been studied with positive results. To summarize the data, a meta-analysis was conducted that compared the traditional treatment with 2- to 4-week courses of terbinafine [32]. The results showed that when the condition is caused by *Trichophyton* species, which occurs in most United States cases, terbinafine is at least as effective and well-tolerated and potentially less costly than a griseofulvin treatment course. One further study examined the pharmacokinetics of terbinafine and found that daily doses of 125 mg for children weighing less than 25 kg and 187.5 mg for those 25 to 35 kg were safe and effective [33].

Hepatitis C
The hepatitis C virus causes a chronic hepatitis in most people it infects and can lead to cirrhosis or hepatocellular carcinoma over time. Previous treatment options for this condition demonstrated limited success, but trials with children with hepatitis C have followed the lead of those conducted with adults and now are including combination treatment regimens. As such, investigators
studied the efficacy and safety of the combination approach using interferon alfa-2b plus ribavirin for children who had chronic hepatitis C infections [34]. Although adverse events were common, nearly half of the study subjects achieved a sustained virologic response, defined as undetectable serum virus levels 24 weeks after completing the 48-week treatment course.

PULMONARY

Asthma prevention

Early childhood wheezing often portends subsequent asthma, particularly for children who have family histories of asthma, allergen sensitization, or other atopic features. Because children who have a history of wheezing and these additional features often can be identified early, a multicenter trial evaluated whether toddlers given maintenance treatment with inhaled corticosteroids (ICS) could interrupt the natural history of the illness and prevent the subsequent development of asthma [35]. In this study, the children at high risk for developing subsequent asthma received either fluticasone 88 \( \mu \)g twice daily or placebo for 2 years. Although the children receiving ICS had fewer asthma symptoms during the treatment period, during the subsequent observation year where the children stopped taking ICS, there were no significant differences between groups, indicating that early treatment with ICS did not affect the natural history of asthma. Another prevention trial investigated whether 400 \( \mu \)g of budesonide were superior to placebo when given to infants whose mothers had asthma for 2 weeks following their own first episode of wheezing [36]. At age 3 years, early intervention with ICS after the first episode of wheezing was shown to have no impact on the development of persistent wheezing.

Inhaled corticosteroids versus montelukast for asthma

Persistent asthma in children by definition requires maintenance controller medication in addition to the bronchodilators used for acute symptom relief. Currently, two classes of controller medications commonly are used in children, ICS and leukotriene receptor antagonists (LTRA), and several recent studies compared the two classes of drugs. Although clinically some patients appear to respond better to one class of medications compared with the other, little has been done to characterize the phenotypic features of children with asthma who respond to both, one, or neither of the medication classes. In the first study, children ages 6 to 17 years with mild-to-moderate persistent asthma were randomized to one of two crossover sequences that both included 8 weeks of an active ICS (fluticasone 100 \( \mu \)g twice daily) plus an oral placebo and 8 weeks of an inhaled placebo plus age appropriate doses of an LTRA (montelukast, 5 mg for those ages 6 to 14 years and 10 mg for 15- to 18-year-old children). Because the study used a crossover design, it allowed for within-subject characterization of children that responded to both, neither, or only one of the study drugs [37]. The investigators found that while a large portion of the children with persistent asthma had similar responses to both medications, children with low pulmonary function or markers indicative of allergic...
inflammation are more likely to respond to ICS. Alternatively, those without such features may benefit from a trial of either class of medication. A subsequent analysis of the data from this trial, and a second study evaluating persistent asthma in 6- to 12-year-old children both demonstrated that clinical outcomes, pulmonary responses, and inflammatory biomarkers improved more with fluticasone than montelukast, leading to the conclusion that ICS should be the preferred first-line treatment for children who have mild-to-moderate persistent asthma [38,39]. One additional study that was sponsored by a pharmaceutical company demonstrated that montelukast was not inferior to fluticasone for children who had mild persistent asthma at preventing rescue medication use, but use of systemic corticosteroids was greater in those treated with montelukast [40].

**Long-acting beta agonists**

Long-acting beta agonists (LABA) have been used with increased frequency over the past decade in pediatric asthma, particularly when combined with inhaled corticosteroids. The FDA, however, issued an advisory and added a black box warning to this class of drugs after finding an increased chance of severe asthma episodes with the use of these medications, and an increased risk of death when those episodes occur [41]. Importantly, this risk did not result in the withdrawal of these drugs from the market, because the advisory continued to note that LABA can be added safely to maintenance medications such as ICS to effectively control asthma symptoms.

**NEUROLOGY**

**Seizures**

Tonic–clonic seizures often are treated with rectal diazepam when they occur outside of a medical setting, but there have been few studies comparing this treatment with other routes of benzodiazepine administration. Midazolam can be given in multiple forms, among which are the buccal and sublingual routes. One recent study compared buccal midazolam with rectal diazepam for the emergent treatment of tonic–clonic seizures in children 6 months of age or older who presented to emergency departments [42]. The buccal midazolam treatment was superior for stopping seizures and was not associated with an increased risk of respiratory depression. The doses given were approximately 0.5 mg/kg to children of all ages included in the study. A similar study found that intranasal lorazepam (0.1 mg/kg) was effective at stopping seizures for children 2 months of age or more presenting to an emergency department [43].

**Migraines**

There is little evidence regarding the treatments available for migraine headaches in children, but a recent practice parameter from the American Academy of Neurology (AAN) summarized the published literature recently and offered recommendations, which were endorsed by the AAP [44]. For children younger than 12 years, acetaminophen and ibuprofen were recommended for acute treatment, while sumatriptan should be considered for those 12 years or older.
For preventive therapy, there unfortunately was insufficient evidence for the AAN to support any drugs available in the United States, but limited data do support the use of cyproheptadine, beta blockers, amitriptyline, and some anticonvulsants.

**ONCOLOGY**

Although many great advances have been made in the treatment of pediatric leukemias and lymphomas over the past several decades, some cases remain refractory to conventional treatments. For those who have T cell acute lymphoblastic leukemia (T-ALL) or T cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to chemotherapy or has relapsed following at least two chemotherapy regimens, a new drug, nelarabine, recently was approved as a last resort treatment through the FDA’s accelerated approval program [45]. This program allows the FDA to approve products for cancer and other serious or life-threatening diseases based on preliminary evidence because of the difficulty accruing subjects for clinical trials meeting study inclusion criteria. The caveat for this is that the manufacturer must agree to complete studies to verify the drug’s benefit. Nelarabine is a novel purine nucleoside analog that has exhibited significant antitumor efficacy in adult and pediatric patients with neurotoxicity as the main dose-limiting adverse effect [46].

One of the drugs traditionally used to treat ALL is doxorubicin, but its use carries the well-known adverse effect of cardiotoxicity manifested by impaired left ventricular contractility, congestive heart failure, high-grade ectopy, or sudden death due to cardiac causes. Dexrazoxane is a free-radical scavenger that has been shown to be cardioprotective for adults given chemotherapy, and this drug was studied in children with ALL receiving doxorubicin [47]. Those randomized to the dexrazoxane group demonstrated a significantly reduced occurrence of troponin T elevation, indicating an acute protective effect, but the authors cautioned that these promising findings must be studied further to determine long-term benefits.

**CARDIOLOGY**

**Hypertension**

Despite the plethora of drugs approved to treat adults with hypertension, there are few approved options for treating the condition in children. A multicenter study recently examined the calcium channel blocker amlodipine in children who have hypertension [48]. In this, the largest prospective, randomized study of an antihypertensive agent ever conducted for 268 children who had hypertension of numerous etiologies including primary hypertension, amlodipine was shown to be significantly better than placebo at lowering systolic and diastolic blood pressure when given at doses of 2.5 or 5 mg daily.

**Kawasaki syndrome**

Although most patients with Kawasaki syndrome respond to a single dose of intravenous immunoglobulin (IVIG), 10% to 20% of patients are resistant to
treatment and are at risk for complications including coronary aneurysms. To better understand which patients will be resistant, one study evaluated data on 320 patients with Kawasaki syndrome that included 41 nonresponders [49]. Risk factors for nonresponse included age of no more than 6 months, being ill less than or equal to 4 days, a platelet count under $30 \times 10^{10}/L$, an ALT of 80 IU/L or more, and a CRP of at least 8 mg/dL. Another study found that the brand of IVIG used also contributes to resistance, with those prepared with β-propiolactone associated with poorer acute response and long-term outcomes [50]. Fortunately, for these patients who remain refractory, alternative treatment approaches are being studied. For example, infliximab treatment results in tumor necrosis factor-α (TNF-α) blockade after administration and was found to be successful in treating Kawasaki syndrome in one small series of patients who remained symptomatic after IVIG treatment [51].

Although some new therapies are being evaluated, a meta-analysis of one older therapy, corticosteroids, was conducted for the initial management of Kawasaki syndrome [52]. The authors found that coadministration of these drugs with IVIG and aspirin resulted in a significant reduction in the occurrence of coronary aneurysms when compared with IVIG and aspirin alone.

**DERMATOLOGY**

**Atopic dermatitis**

The topical immunosuppressant calcineurin inhibitors, tacrolimus and pimecrolimus, have become standard treatments for atopic dermatitis in children, and many practitioners have found them to be preferable to topical corticosteroids for this condition. A warning from the FDA, however, cautioned that these agents should be used only as second-line treatment because of a possible association of these drugs with lymphoma and skin cancer [53]. Although the studies describing this association were conducted using higher doses with a long duration of use, the FDA advised that tacrolimus and pimecrolimus be used intermittently and for short periods of time in immunocompetent patients over 2 years of age.

**Acne**

Isotretinoin is the most effective treatment available for severe nodular and scarring acne, but the vitamin A analog carries significant adverse effects such as depression and birth defects if the drug is taken by a pregnant woman. In July 2005, the FDA issued a warning regarding the risk of depression and suicide in patients taking isotretinoin that led to a label change [54]. In addition to discontinuing the medication if symptoms appear, patients must be instructed to contact their health care professional right away if symptoms appear, because discontinuation of treatment may be insufficient to improve symptoms, and further evaluation may be necessary.

The risk of birth defects in infants born to women taking isotretinoin has been known for many years, and a new program, iPLEDGE, was introduced recently by the FDA and manufacturers of isotretinoin to reduce the likelihood
of this tragedy occurring [45]. The new program links negative pregnancy testing with the actual dispensing of the drug. To obtain the drug, women must register with the program, complete an informed consent, obtain counseling about the risks and requirements for safe use of the drugs, and comply with monthly pregnancy testing. In addition, prescribing physicians and dispensing pharmacies must register with the program to participate in the care of these patients. The entire process is administered by means of a technology-based, closed system that monitors each patient’s adherence to the requirements, accessible at https://www.ipledgeprogram.com/.

OBESITY AND POLYCYSTIC OVARY SYNDROME

As the childhood obesity epidemic worsens in the United States and worldwide, obesity-related complications for children such as type 2 diabetes mellitus are occurring more frequently. For both the primary condition and the complications, new therapies are being tested in children. In March 2004, an international consensus statement on childhood obesity was published that discussed the problem, its causes and associated risks, and also treatment options that had been studied to that point [55]. Included in the treatment options was a section on pharmacotherapy, which reviewed treatments such as stimulants, anorectic agents, drugs that limit nutrient absorption, insulin sensitizers and suppressors, metformin, and octreotide. Those given the most favorable reviews by the committee included the anorectic agent sibutramine, a drug that limits fat absorption, orlistat, and the oral biguanide metformin, particularly for use in patients who have concurrent insulin resistance.

Two recent studies have been published supporting the use of sibutramine. This drug acts as a nonselective inhibitor of neuronal reuptake of serotonin, norepinephrine, and dopamine. In the first study, adolescents were randomized to receive either 10 mg/d of sibutramine or placebo in addition to a calorie-restricted diet plus exercise [56]. Although the placebo group lost a mean of 2.4 kg in 6 months, the treatment group lost an average of 10.3 kg. The second study, which was conducted with Mexican adolescents, showed similarly encouraging findings, and in both trials the medication generally was well-tolerated [57].

A large multicenter study conducted in the United States and Canada evaluated orlistat (120 mg/dose) or placebo given three times daily plus a reduced calorie diet, exercise, and behavioral therapy to adolescents [58]. For this study, outcomes were followed for 1 year, and although the adolescents who received the orlistat gained an average of 0.5 kg over that time, their body mass index (BMI) decreased by 0.5. This was significantly better than the 3.1 kg weight gain and 0.3 increase in BMI found in the placebo group. The orlistat group, however, reported gastrointestinal (GI) symptoms more commonly that included nausea, diarrhea, and flatulence.

Although metformin has an established therapeutic benefit for patients with type 2 diabetes, it increasingly is being used to treat polycystic ovary syndrome [59], which is characterized by menstrual dysfunction and hyperandrogenism, often in overweight young women. Because evidence suggests that insulin
resistance may play a role in the pathophysiology of this condition, adolescents who had polycystic ovary syndrome were randomized to receive 12 weeks of metformin (750 mg twice daily) or placebo in conjunction with healthy lifestyle counseling. The results demonstrated that metformin was more effective at decreasing serum testosterone and restoring menstruation compared with placebo.

**ADOLESCENT MEDICINE AND GYNECOLOGY**

**Contraceptives**

The last several years have seen several advances in the area of contraception, particularly with the changes in delivery devices. In addition to oral and injectable forms, contraceptive patches and insertable vaginal rings have become available. The latest to be approved is Implanon, a single rod contraceptive implant that contains 68 mg of etonogestrel. The drug is released over 3 years at a rate of 30 μg/d, and is about the size of a matchstick. Implanon has been used outside of the United States for several years with good success, with the most frequent complication appearing to be irregular bleeding, which occurs in about 11% of women [60].

One of the other relatively new contraceptives, the Ortho Evra (norgestrel/ethinyl estradiol) Patch underwent a label change mandated by the FDA [61]. The label change warns health care providers and patients that the product exposes women to higher levels of estrogen than most birth control pills. This increased exposure potentially could increase the risk of blood clots, although the current data are mixed as to whether such a risk exists.

One older contraceptive, depot medroxyprogesterone (DMPA), was the subject of two recent papers. In the first, weight gain was compared between adolescents receiving DMPA, an oral contraceptive, or no hormonal contraceptive method, and those receiving DMPA were found to have significantly greater weight gain over the 18-month study period for both obese and nonobese girls [62]. The second study reported a decline in bone mineral density in adolescents receiving DMPA, but this loss reversed upon the discontinuation of the drug [63].

**Emergency contraception**

After a long period of discussion and debate, the FDA approved the OTC placement of Plan B (levonorgestrel) for women 18 years of age and older in August 2005 [45]. Plan B is a progestin-only contraceptive that inhibits ovulation and can prevent pregnancy when taken by women within 72 to 120 hours of unprotected intercourse, and it does not require a pregnancy test. It has been shown to be generally well-tolerated by adolescent women, with minor adverse effects such as nausea, fatigue, and vomiting [64]. The change in accessibility was supported by the AAP, although the AAP supported improved availability for all teens and young adults in its policy statement [65]. Plan B remains available as a prescription-only product for women age 17 and under. Importantly, one recent study showed that access to emergency contraception from
pharmacies did not change women’s sexual behavior, frequency of unprotected intercourse, or acquisition of sexually transmitted infections even for those women 16 years of age or less [66,67].

PSYCHIATRY
Attention-deficit hyperactivity disorder
Psychostimulant medications are the first-line therapy for the common neurobehavioral condition, attention-deficit/hyperactivity disorder (ADHD), because they have been shown to reduce the inattention, impulsivity, and hyperactivity that characterize it [68,69]. In February 2005, the safety of one of these medications, extended-release mixed amphetamine salts (Adderall XR), came into question when Health Canada, the drug regulatory agency for Canada, temporarily withdrew the drug from the market [70]. Heath Canada’s actions stemmed from an analysis showing an association of sudden cardiac deaths, heart-related deaths, and strokes in children and adults taking recommended doses of Adderall XR. The FDA immediately issued a statement recognizing that it was aware of Health Canada’s decision, but did not feel that the current evidence warranted a change in labeling or withdrawal from the United States market [61]. The FDA analysis showed that the cases of sudden death reported with Adderall were only slightly greater, per million prescriptions, than for other stimulants and not greater than the number of sudden deaths that would be expected to occur in the population without treatment as a whole [71]. Two FDA committees then reviewed the available data, and the agency ultimately decided to add a black box label to Adderall products, cautioning against misuse of the drug, and including warnings regarding the potential danger of taking stimulants in patients who have pre-existing cardiovascular conditions.

One recent study did contribute to the evidence on this subject when the authors evaluated the short- and long-term cardiovascular effects of once-daily Adderall XR [72]. A post-hoc analysis of two multicenter clinical trials involving over 600 children aged 6 to 12 years was performed, where participants were followed for up to 2 years while taking between 10 and 30 mg of the extended-release compound. The authors discovered minimal cardiovascular effects caused by short- or long-term usage of the drug. With short-term use, no adverse events were reported, and there were no statistically significant effects on blood pressure, pulse, or QT interval corrected for heart rate (QTc) on the electrocardiogram. With long-term use of up to 2 years duration, changes in mean blood pressure and pulse were modest and clinically insignificant. Additionally, group mean QTc values did not significantly change from baseline, and no serious cardiovascular adverse events were detected over 2 years.

Another drug used for the treatment of ADHD, atomoxetine, also received attention from the FDA, which issued a public health advisory regarding a risk of suicidal ideation for children and adolescents taking the drug [73]. This risk was noted to be greater during the initial few months of therapy or when the dose is changed.
Depression
Analysis and discussion of data regarding the risk of suicide in patients taking antidepressants continued over the past 2 years despite new evidence showing the effectiveness of fluoxetine, particularly when used in combination with cognitive–behavioral therapy (CBT) for adolescents with depression [74]. In a multicenter trial, four different treatments were compared: (1) fluoxetine alone, (2) CBT alone, (3) fluoxetine plus CBT, or (4) placebo. The best treatment for the symptoms of depression in this study was combined treatment, with 71% of patients in this group responding as measured by the Children’s Depression Rating Scale–Revised. Also notable, the fluoxetine alone group did significantly better than those receiving CBT alone or placebo treatments.

These positive benefits must be balanced with the new black box warning from the FDA regarding the risk of suicidal thoughts and behavior when antidepressants are taken by children and adolescents [75]. The data that led to this decision and the rationale behind the labeling change were summarized in one recent publication that also called for further research on the positive and negative effects of antidepressant drugs [76]. Since this label change was made, two publications with somewhat different findings further complicated the evidence regarding suicidality and antidepressants. In the first, a health plan’s computerized records were analyzed, showing that the risk of suicidal behavior was highest in the month before the initiation of antidepressant therapy, and decreased progressively over the first several months of treatment [77]. The effect was most pronounced for the newer antidepressants that are not approved for use in children and adolescents, while the older antidepressants were associated with an increased risk after starting antidepressant therapy. The second paper reviewed data from 23 previous studies that had been submitted by pharmaceutical companies to the FDA [78]. This meta analysis found a modestly increased risk of suicidality in pediatric patients taking antidepressants, but there were no completed suicides in any of the trials. To help clinicians juggle the benefits and risks of antidepressant therapy, clinicians may find a recently published note from the Association of Medical School Pediatric Department Chairs, Inc. useful as a guide to treatment and monitoring of patients with depression who are using medications to treat their symptoms [79].

Pervasive developmental disorder
Children who have pervasive developmental disorders (PDD) can be particularly challenging for their families and for physicians trying to help them with some of their more difficult behaviors. Risperidone has emerged as one of the best drugs to treat disruptive behavioral symptoms for children who have PDD, and two recent studies have added to the supportive evidence. In the first, the short-term benefits of the drug were studied in a placebo-controlled trial with 5- to 12-year-old children [80]. The mean dose used was 0.04 mg/kg/d over 8 weeks, and the treatment was significantly better than placebo at improving irritability, conduct, and hyperactivity among other symptoms, but the drug was associated with somnolence in most of those who took the
In a second study with 5- to 17-year-old children who had PDD with disruptive and aggressive behaviors, a 24-week administration of risperidone was followed by a double blind discontinuation period of 8 weeks [81]. During this period, those who discontinued the drug were significantly more likely to have a relapse than those who continued to take the risperidone. The weight gain seen in those taking the drug over this study may limit its use for long durations of time.

**NEONATOLOGY**

**Drug development and medication use**

Despite being a unique population with numerous physiologic and metabolic differences compared with all other populations, many medications are used in neonates that never have been tested adequately in this population. Recognizing this problem, the FDA and the National Institute of Child Health and Human Development (NICHD) established the Newborn Drug Development Initiative (NDDI) to identify obstacles in the way of conducting drug trials in neonates and to suggest strategies to overcome them [82,83]. The first workshop of this group occurred in March 2004, and addressed scientific, clinical, and ethical concerns in the development of drugs for this population.

A related manuscript detailed the most common medications used in neonatal ICUs (NICUs) by examining a large national data set [84]. Although it was not surprising that ampicillin, gentamicin, and ferrous sulfate were the most commonly used drugs, the study also detailed the drugs given most frequently to patients who subsequently died. These included drugs used to treat hypotension, fungal infections, and seizures, as well as paralytic agents. The knowledge gained from this study complements the goals of the NDDI.

**Bronchopulmonary dysplasia**

Caffeine often is given to premature neonates as a treatment for apnea of prematurity, but the duration for which the treatment effect lasts and the long-term benefits of such treatment have been questioned. An international multicenter trial investigated caffeine therapy for infants born between 500 and 1250 g who were candidates for treatment in the first 10 days of life [85]. Compared with placebo, those randomly assigned to receive caffeine until it was deemed no longer necessary were less likely to require oxygen at a postmenstrual age of 36 weeks and were weaned from positive airway pressure an average of 1 week earlier. The authors therefore concluded that caffeine therapy reduces the risk of bronchopulmonary dysplasia (BPD).

In contrast to the results found with caffeine, another multicenter study evaluated the effect of lowdose hydrocortisone (1 mg/kg/d) for extremely low birth weight neonates and found no improvement in survival without BPD [86]. Infants in this study began their treatment in the first 2 days of life and completed a 15-day course. Notably, this trial was stopped because of an increased rate of spontaneous GI perforation found in the treatment group, particularly for those concomitantly treated with indomethacin.
Hypotension
Hydrocortisone also is used for the treatment of hypotension and adrenocortical insufficiency in preterm neonates, and this therapy was the subject of two recent papers. In the first, infants younger than 7 days old being treated with dopamine received either stress doses of hydrocortisone (1 mg/kg every 8 hours for 5 days) or placebo [87]. The short-term outcomes were improved in the treatment group, which was weaned from vasopressor support earlier and received less volume expansion therapy. These promising results must be tempered, however, by a report from the California Perinatal Quality Care Collaborative, which evaluated data from multiple centers and found that hydrocortisone treatment for hypotension was associated with a significantly higher incidence of intraventricular hemorrhage, periventricular leukomalacia, and death [88].

Neonatal infections
Neonatal sepsis continues to be a source of significant morbidity and mortality, particularly for preterm infants. Shortly after birth, group B Streptococcus traditionally has been the leading cause of serious bacterial infections, but maternal screening and appropriate treatment reduces this risk. A common clinical issue is the timing of antibiotic administration for mothers, because deliveries may occur in an unpredictable manner. Therefore, a study was performed to determine the time necessary to achieve and maintain bactericidal concentrations of ampicillin in the cord blood of the neonate after drug administration to the delivering mother [89]. The study found that bactericidal levels of ampicillin were achieved within 30 minutes of administration of the drug to the mother, and remained at bactericidal levels for at least 5.6 hours after treatment.

For infants displaying signs of sepsis, ampicillin typically is combined with an aminoglycoside, although some clinicians have opted for treatment with third-generation cephalosporins as the complementary drug. For infants treated with both combinations in NICUs in the first 3 days of life, outcomes were evaluated using a multicenter database [90]. The study found an increased likelihood of death in those treated with cefotaxime than those who received gentamicin. Although the cause of this difference was unknown, it has been reported that cephalosporin use in the NICU is associated with an increased risk of fungal sepsis, something that may be prevented by prophylaxis with fluconazole for high-risk preterm infants [91].

Neonatal pain
Increasingly, knowledge about neonates has led to better understanding of how they experience pain, and with this knowledge has come increased efforts to minimize the discomfort they feel, particularly for those who undergo complicated stays in the NICU. As part of the NDDI, these issues recently have been considered and reviewed extensively [92]. Although there was a call for additional research, among the conclusions of the group was the recommendation that morphine and fentanyl be used as sedation during mechanical ventilation, since they reduce behavioral and physiologic measures of pain and stress for
preterm neonates [93]. One adverse effect of using narcotics may be a longer
duration of mechanical ventilation, and one recent study suggested that the
use of morphine can worsen respiratory outcomes for preterm neonates who
have respiratory distress syndrome [94].

Another area that included recommendations from the NDDI was the use of
analgesia and local anesthesia during invasive procedures [95]. In this article,
many different analgesic classes were reviewed, and this literature recently
has been expanded by two studies. In the first, a loading dose of morphine
(100 µg/kg) followed by a morphine infusion was found to provide inadequate
analgesia for heel stick-induced acute pain for preterm infants [96]. The second
paper contrasts somewhat with the first in that morphine (100 µg/kg) and tet-
racaine (0.5 g of 4% gel applied to insertion site) plus morphine were found to
provide superior analgesia to tetracaine alone for preterm neonates undergoing
central line placement [97].

Necrotizing enterocolitis
Previous research has demonstrated that acidification of infant feeds resulted in
a decreased incidence of necrotizing enterocolitis in preterm neonates. There-
fore, to determine if an association exists between antacid use (histamine-2 re-
ceptor antagonists) and the occurrence of this condition, data from the
NICHD-sponsored Neonatal Research Network were analyzed [98]. The au-
thors found a significantly greater likelihood of the occurrence of necrotizing
enterocolitis among infants who had used the medications.

TOXICOLOGY AND TRANSFER OF DRUGS
BETWEEN MOTHERS AND INFANTS

Selective serotonin reuptake inhibitors
Selective serotonin reuptake inhibitors (SSRIs) have become the first-line drug
treatment for depression in adults, including those who are pregnant, but it has
become increasingly apparent that maternal use of these medications is associ-
ated with adverse effects on the developing fetus and withdrawal symptoms in
their newborns. The more severe neonatal withdrawal syndrome from SSRIs is
characterized by convulsions, irritability, abnormal crying, and tremor, and the
relationship between maternal use of these drugs and withdrawal was charac-
terized further through an analysis of the World Health Organization’s Collab-
orating Centre for International Drug Monitoring database [99]. Although
several drugs had an association with the syndrome, most neonatal withdrawal
cases occurred following maternal paroxetine use, and the authors advised
against prescribing the drug for pregnant women.

In addition to the more severe symptoms of the withdrawal syndrome, other
symptoms, including respiratory distress, cyanotic events, feeding difficulty,
sleep disturbance, and increased motor activity have been reported in neonates
exposed in utero to SSRIs. Because the prevalence of these symptoms was un-
known, investigators analyzed 120 term infants, 60 of whom had prolonged in
utero exposure to SSRIs [100]. The authors reported that about 30% of the
exposed group had some symptoms of withdrawal, and 13% had severe symp-
toms. These findings led the authors to recommend a minimum nursery stay of
48 hours to evaluate these newborns for withdrawal symptoms. A third study
found that the risk of these symptoms is much more likely for those exposed to
SSRIs in the third trimester through the time of delivery, and that the symp-
toms are typically mild and self-resolving for neonates by 2 weeks of age
[101]. One further study did suggest that some less-obvious effects of SSRI ex-
posure may persist in exposed infants as they demonstrated diminished facial
and cardiac autonomic responses to pain following a heel stick blood draw
at 2 months of age when compared with control infants [102].

Finally, one report described an additional severe morbidity associated with
prenatal exposure to SSRIs, persistent pulmonary hypertension of the newborn
(PPHN) [103]. In comparing infants who had PPHN in utero with control in-
fants, the authors found that SSRI exposure after the 20th completed week of
pregnancy was associated strongly with the development of PPHN, but use be-
fore the 20th week or use of other antidepressants was not associated with this
risk in offspring.

Congenital malformations
Angiotensin-converting enzyme (ACE) inhibitors are used commonly to treat
adults who have hypertension, but their use is contraindicated in the second
and third trimesters of pregnancy because of their known association with
a group of fetal effects that include oligohydramnios, intrauterine growth retar-
dation, hypocalvaria, renal dysplasia, anuria, renal failure, and death. It previ-
ously was thought that ACE inhibitors were safe to use in the first trimester of
pregnancy, however, because fetal urine production does not begin until later
in pregnancy, but a new study suggests that infants exposed to these drugs in
the first trimester have an increased risk of major congenital malformations
[104]. By analyzing Tennessee Medicaid data, the authors determined that
other antihypertensive medications were not associated with major anomalies,
but ACE inhibitor use was associated with major cardiovascular and central
nervous system fetal anomalies, suggesting that this class of drugs should be
avoided during pregnancy.

One class of drugs commonly taken to support early pregnancy for those
with luteal phase dysfunction, progestins, recently was studied to determine
the relationship between maternal use of these drugs and subsequent hypospa-
dias in offspring [105]. It has been hypothesized that these drugs interfere with
fetal androgen production necessary for normal urethral closure, and the cur-
rent study did find that such a risk existed when progestins were taken by
mothers during the fourth through 14th weeks of pregnancy.

Transfer of anesthetics through human milk
New mothers frequently undergo procedures requiring sedation in the postpar-
tum period, and lactating women often are told to discard their milk for the first
24 hours following these procedures. The evidence behind this recommenda-
tion is limited, however, so investigators studied the pharmacokinetics and
transfer to human milk of three commonly used anesthetic medications in lactating women [106]. The investigators discovered that very little midazolam, propofol, or fentanyl appear in human breast milk in the 24 hours following the procedures, suggesting that the recommendation to discard this milk out of fear for neonatal harm may be unnecessary.

**Antibiotic adverse effects**

Dental fluorosis is a common developmental defect in tooth enamel caused by excessive fluoride consumption during enamel formation, but modifying features have been debated. Recently, investigators examined the relationship between amoxicillin use during early childhood and the development of fluorosis [107]. As part of the Iowa Fluoride Study, the authors found that amoxicillin use from 3 to 6 months of age significantly increased the risk of fluorosis on the maxillary central incisors even after adjustment for fluoride intake and otitis media in the data analysis.

**Acetaminophen overdose**

In 2006, the American Association of Poison Control Centers published a practice guideline for the out-of-hospital management of acetaminophen poisoning, a relatively common occurrence for pediatric and adolescent patients [108]. Among the group’s recommendations are:

Activated charcoal should be considered if a toxic dose of acetaminophen has been taken, and fewer than 2 hours has progressed since the ingestion, particularly when acetylcysteine cannot be given within 8 hours of ingestion. Patients younger than 6 years always should be referred to an emergency department for an acute ingestion of 200 mg/kg or more, 150 mg/kg/d over 48 hours, or 100 mg/kg/d over 72 hours or more, while patients 6 years of age or older should go to the emergency department if they have taken similar weight-based amounts as described for younger children or after ingesting acute doses of 10 g or more in 24 hours, 6 g per day over 48 hours, or 4 g per day over 72 hours or more. Importantly, lower doses may also require emergency treatment, but may be examined on an individual basis.

**Clonidine overdose**

Clonidine frequently is given to patients who have ADHD, particularly for symptoms of sleep difficulty, tics, or aggression. Two recent papers describe toxic ingestions of this drug in children. In the first, 24 cases over 5 years were described from a single emergency department in Australia where a mean dose of 46.6 µg/kg was ingested [109]. In these cases, two thirds of the children overdosed on the medicine that had been prescribed for their own ADHD, and the most common presenting symptoms were impaired consciousness and bradycardia. In 3 of the 24 cases, the impaired consciousness and respiratory depression required mechanical ventilation. Activated charcoal was administered to most patients.

In the second report, 113 children who had toxic clonidine ingestions were described [110]. Although the symptoms described and adverse effects were
similar, the larger sample size allowed the authors to make age-based recom-
mendations for treatment. These included direct medical evaluation for:

- All children 4 years of age and less taking at least 0.1 mg
- Children 5 to 8 years of age who ingested doses of 0.2 mg or more
- Children older than 8 years of age following ingestions of 0.4 mg or more

They recommended that these children be observed following ingestion for
at least 4 hours to determine if adverse effects will occur.

References


The past 10 years have seen a rapid advancement in the understanding of idiopathic scoliosis. Physicians now are informed better about the natural history and specific curve behavior. It is now easier to determine which curves are likely to progress and put the child or adolescent at risk. Treatment can be more selective.

ETIOLOGY OF IDIOPATHIC SCOLIOSIS

The etiology of idiopathic scoliosis remains elusive. There are several areas of research that have enticing observations. These include neural axis abnormalities such as hydromyelia, cerebral asymmetry [1], and vestibular dysfunction. Pineal gland and melatonin secretion have been implicated [2]. There may be abnormalities of intracellular levels of calcium and phosphorus as evidenced by elevated calmodulin levels in patients who have idiopathic scoliosis [3]. Genetic studies are playing an increasing role in idiopathic scoliosis. Linkage analyses have identified several candidate regions on chromosomes 6, 9, 16, and 17 [4]. This supports a multifactorial etiology with different familial patterns. In the future, there may be distinct subtypes of idiopathic scoliosis based on genetic analysis. This could guide treatment by separating out progressive curves from nonprogressive based on chromosomal analysis. Osteopenia also may play a role in progressive curves [5].

DETECTION OF SCOLIOSIS

Scoliosis is as least a three- and at times a four-dimensional deformity [6]. The first and most obvious deformity is a lateral curvature of the spine in the frontal or coronal plane. As the spine curves, the second dimension is introduced, a twist or rotation that produces an axial plane deformity. In the thoracic region, this expresses itself as a rib hump, which is the most cosmetically objectionable element of scoliosis. The Adam’s forward bend test detects this...
element of the deformity and alerts the primary care examiner that a scoliosis is present. These two deformities must be present to constitute a structural scoliosis. The third dimension is present in the sagittal plane. This is a lack of normal thoracic kyphosis (hypokyphosis) or presence of kyphosis in the lumbar region when there should be some amount or lordosis [7]. Finally, the fourth dimension may be present. This is decompensation; the head is not centered over the pelvis when the patient is standing erect. This may be due to a lack of compensating curves above and below the pathologic curve or the presence of obliquity of lower lumbar spine in its relationship to the sacrum and pelvis.

Early detection of significant curves remains the common goal of all health care providers. School screening programs were instituted in the past to achieve this goal. Expense, overidentification, and overtreatment have blunted the enthusiasm for these efforts, however. A recent review by Bunnell covers this subject very well [8].

The most important method of detection remains the routine well-child physical examination performed by the pediatrician or primary care giver. Preseason sports physicals are also an important method of scoliosis detection. The Adam’s forward bend test is designed to detect the rotational abnormality of scoliosis (Fig. 1). The scoliometer (Fig. 2) is still a useful tool to separate mild scoliosis, which needs no referral from more severe forms in which prompt referral may

Fig. 1. The Adam’s forward bend test allows for detection of the rotational dimension of scoliosis as evidenced by the rib hump.
be of benefit. A measurement of greater than 7 degrees with the scoliometer warrants orthopedic referral [9]. If the child has significant hypokyphosis, the rib hump may not be as prominent, and the scoliometer may convey a false sense of security. Furthermore, the heavyset child also may mask a significant curve. When in doubt in a child with growth remaining, referral to an orthopedic specialist is never discouraged. Severe scoliosis should be referred at any age. It is recommended that the orthopedic consultant be allowed to obtain the initial radiographs. This permits the initial documentation of the scoliosis to be accomplished with a single standing posterior-anterior and lateral radiograph to include the brim of the pelvis to show the Risser stage.

**TYPES OF IDIOPATHIC SCOLIOSIS**

Idiopathic scoliosis is divided somewhat arbitrarily into three categories: infantile (birth to 3 years), juvenile (3 to 10 years), and adolescent.

**Infantile scoliosis**

In the United States infantile scoliosis is rare, and most spontaneously correct, especially if the rib–vertebral angle difference described by Mehta is less than 20 degrees [10]. If the infantile scoliosis exceeds 20 degrees at time of diagnosis or demonstrates progression, bracing is indicated. A careful search for an underlying diagnosis should be sought in an infant who has progressive infantile scoliosis [11].

**Juvenile scoliosis**

Juvenile scoliosis is of particular concern for two reasons. The first reason is the high incidence in neural axis abnormalities in this group. Twenty percent to 25% of children who present with a juvenile scoliosis of greater than 20 degrees are likely to have an intraspinal abnormality evidenced on MRI [12]. Most of these are asymptomatic hydromyelias. At times, in association with
hydromyelia, a Chiari 1 malformation of the brain stem is also seen. This may require neurosurgical decompression of the foramen magnum. After decompression, some scoliosis curves may improve spontaneously. Any juvenile scoliosis presenting at initial evaluation with a curve that exceeds 20 degrees should have an MRI.

The second concern is the likelihood of progression of the curve, especially when the child reaches the adolescent peak growth velocity. Irrespective of the presence of intraspinal abnormality, 18% to 50% of juvenile curves will progress [13]. Any juvenile curve exceeding 25 degrees, or a 20-degree curve with greater than 5 degrees documented progression should be braced. Fortunately, this age group is far more amenable to bracing than the adolescent group.

When the curve exceeds 45 degrees, surgery is recommended irrespective of age of the child. If fusion of a significant portion of the spine is necessary prior to age 10, there can be an arrest of ultimate trunk height and thoracic cage volume. There are also the crank shaft phenomena, wherein the vertebral bodies continue to grow and rotate out from beneath the fusion of the posterior elements of the spine. As a temporizing measure, a growing rod can be placed without formal fusion with bone graft. The rod will halt progression but allow growth until skeletal maturity is near. About every 6 months, a lengthening of the rod is necessary to keep up with growth. When skeletal maturity is achieved, a definitive spine fusion is performed. A decade ago, a Harrington rod was modified for this purpose with mixed results. The Luque trolley is also an attempt to prevent progression of the curve but permit simultaneous growth [14]. A more recent growing rod developed by Akbarnia has been used with success (Fig. 3).

Fig. 3. Five-year-old boy with spondylometaphyseal dysplasia unresponsive to brace. A growing rod was placed. This hopefully will delay definitive fusion until at least age 12.
Another innovative approach to managing severe juvenile idiopathic curves is vertebral body stapling [15]. The results recently reported are encouraging.

Adolescent scoliosis
Adolescent idiopathic scoliosis is still the most common form of scoliosis. It is defined as a lateral curve exceeding 10 degrees when measured on a radiograph by the Cobb method. The incidence of Cobb measured curves between 10 and 30 degrees is 2% to 3% [12]. The incidence for curve exceeding 30 degrees is 0.3%. Most of these curves are in girls. It is also presumed that before calling the scoliosis idiopathic, a thorough search has been conducted for other etiologies such as neurofibromatosis, Marfan’s syndrome, tethered cord, and other causes.

TREATMENT OF ADOLESCENT IDIOPATHIC SCOLIOSIS
The treatment of adolescent scoliosis still falls in three groups: observation, bracing (Fig. 4), and surgical spine fusion. Curve severity and skeletal maturity are still the main determinants of treatment. Greatest progression of curve occurs during rapid growth. Skeletal maturity is determined clinically by the menarchal status in females and peak growth velocity/voice change in males. Radiographically, the Risser sign continues to be helpful (Fig. 5). The visibility of the

Fig. 4. This Thoraco-lumbar spinal orthosis has internal pads to push either through the rib cage or on the paravertebral lumbar muscles to affect some correction of the curve while the brace is worn. Although comfortable and well covered by clothing, its acceptance by the adolescent is variable.
triradiate cartilage in the acetabulum is also helpful. Unfortunately, none of these commonly used indicators can establish the exact position of a given child within the growth cycle. Has the child not yet reached peak growth velocity? Is the child in the midst of it? Or has the child now past it and therefore largely out of danger to progress? The goal is to brace the patient in a timely manner but avoid treating a child who is near the end of growth and out of danger.

A child with a Risser of 0 or 1 and a curve between 10 and 20 degrees has a 22% chance of progression prior to maturity. If the curve is 20 to 29 degrees, the likelihood of progression increases dramatically to 68%. If this same child has a Risser of 2, 3, or 4, the risk of progression is only 2% for the curve less than 20 degrees and 23% for the curve from 20 to 29 degrees [7]. Thus skeletal immaturity and curve severity are the main determinants for instituting brace management (Fig. 6). The break point appears at 25 degrees or any curve less than that with documented 5 degrees progression. Hence a Risser 0, 25-degree curve should be braced, but the same curve in a Risser 2 or 3 child may involve some discussion with the parents regarding their comfort level with continued observation. Brace treatment does nothing more than arrest further progression of the curve. What is lost in observation is never regained. At maturity and completion of brace wear, the curve reverts to the magnitude at commencement of treatment. Is a 30-degree curve more visible than a 25-degree one? Probably not. The long-term studies indicate that even curves of less than 50 degrees do not produce disability in adulthood [16,17]. There is consensus that any curve of 30 to 40 degrees at presentation and at least a year of growth remaining should be braced.

Success of brace treatment is influenced most largely by brace compliance [18]. Full-time brace wear is the desired goal but is somewhat ephemeral in
the adolescent population. The reality is that most adolescents will comply with part-time, (evening and night) brace wear but not full-time or at school. Fortunately, results from this level of treatment show that the effort is still worthwhile [18]. Although not a perfect study, the results from brace wear appear to have a favorable influence on what currently is regarded as the natural history of untreated adolescent idiopathic scoliosis (Fig. 7) [19].

Surgical spine fusion is offered to any adolescent with a curve greater than 40 degrees. Bracing is not effective beyond this degree of curvature. Despite the study by Weinstein [16,17], curves of this magnitude can progress in adulthood and become painful. The ideal time to undergo a spine fusion is when the adolescent is in optimal good health, can afford the time for the recovery process, and is most likely to be covered by some form of third-party payer.

**ADVANCES IN SURGICAL CORRECTION OF SCOLIOSIS**

Prior to 1948, severe scoliosis was regarded as surgically untreatable. The attempt at fusion frequently yielded nonunion and failed to halt the progression on the curve. Paul Harrington developed the first practical implant, a single distraction rod, which served as a temporary supporting strut while the fusion mass consolidated. Autologous iliac crest bone graft was used routinely (see Fig. 7). A postoperative cast was required; modest correction was achieved, and the fusion rate was high enough to make the surgery a creditable procedure (Fig. 8).
Fig. 7. Eleven-year-old, premenarchal, Risser 0 female commenced part-time brace treatment of 30-degree curve in 2003. Menarche occurred 1 year later. Curve has not progressed. She is now 18 months since onset of menarche and Risser 3 (2005). Part-time brace treatment will continue until at least 2 years post menarche, Risser 4, and no further documented change in height.

Fig. 8. Now of historical interest, this is a single Harrington distraction rod used for partial correction and stabilization of an adolescent spine fusion.
The single Harrington distraction rod was the standard of surgical care for 20 years. It corrected only the frontal (coronal) dimension of the deformity. It had little influence on axial rotation (the rib hump) or hypokyphosis. At times it made the sagittal deformity worse. The several iterations of spinal instrumentation since Paul Harrington’s pioneering work have all been attempts to correct all dimensions of the deformity. Currently, anterior fusion with disketomy has given a measure of increased correction, especially in thoraco–lumbar curves (Fig. 9). Severe stiff curves can be made more flexible, and an anterior fusion can be accomplished by video-assisted thoracostomy and interbody fusion [20,21]. Rod placement can be done thoracoscopically but is technically demanding and time-consuming.

With the advent of pedicle screws, the posterior spinal fusion is now a very effective form of surgical treatment. Dual rods, with pedicle screws at multiple levels, are used. Intraoperatively, a combination of rod contouring, distraction, and derotation are used to obtain maximal, neurologically safe correction. Intraoperative monitoring of spinal cord function has reduced the incidence of neurologic sequelae to less than 1%. Allograft now has supplanted the harvesting of autogenous iliac crest bone graft much to the delight of the patient [22]. Correction of the preoperative Cobb curve routinely exceeds 50%. Both sagittal balance and the axial rotation are improved. This is important, as the greatest desire of the adolescent is cosmetic improvement of the rib hump (Fig. 10).

**Fig. 9.** (A) Preoperative posterior-anterior radiograph of a 12-year-old male with juvenile scoliosis and a Chiari I malformation that required decompression. Scoliosis continued to progress, and when it reached 55 degrees, an anterior spine fusion was performed. (B, C) Note restoration of sagittal and coronal plane deformities.
Furthermore, newer instrumentation methods allow shorter fusion levels, thus preserving motion segments. This conceptionally reduces the chance of degenerative changes later in life. Contemporary surgical instrumentation corrects more aspects of the complex deformity and provides improved internal stability. Consequently, postoperative morbidity and complications have been reduced. The result is earlier postoperative ambulation, a shortened hospital stay, and a more rapid return to normal activities. It is the expectation that once a spinal fusion for idiopathic scoliosis has healed (about 6 months), the patient may return to all preoperative activities. The long-term outcomes indicate that most spine fusions done in adolescence result in a satisfied patient. Residual back pain is no more frequent or severe that what is generally found in the nonscoliotic adult population [23]. Appearance and self-image and activity level are likewise favorable [24].

**SUMMARY**

The understanding of idiopathic scoliosis continues to evolve. At some time in the foreseeable future the term will be oxymoronic. It may eventuate, based on a series of laboratory and genetic tests, that there will be three groups:

- One in which the curve will never be of significance, and regular follow-up is unnecessary
- A second group with predictable response to a brace
- A third group in which spine fusion is an inevitability

**Fig. 10.** Preoperative and postoperative radiography of posterior spinal fusion with dual rods and multiple pedicle screws. Note not only significant curve correction but restoration of sagittal contour in the lateral film. (Courtesy of Erickson M, MD.)
This latter group should be allowed to enjoy childhood and early adolescence unfettered by treatment until such time as surgery is necessary. Until then, efforts must be directed toward early detection, comprehensive evaluation, and best efforts at preventing progression of the curve. To this end, a referral to an orthopedic surgeon for suspected scoliosis never is disparaged.

References


Evaluation of the Quality of Care in Congenital Heart Surgery: Contribution of the Aristotle Complexity Score

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It is only in the last decade that surgeons, particularly cardiac surgeons, became aware that the evaluation of quality of care is a fundamental aspect of their practice. Even today, the most read reports about the quality of care in hospitals or departments are produced by media, insurance companies, or institutions trying to define centers of excellence. Under the auspices of the Society of Thoracic Surgeons (STS) in North America and the European Association of Cardio–Thoracic Surgery (EACTS) in Europe, a strong international movement was initiated by cardiac surgeons to place the evaluation of quality of care under the governance of the health care delivery team [1–12]. Initially considered a research issue, the evaluation of quality of care today must answer a legitimate growing demand from patients, families, hospital managers, referring physicians, insurance companies, government agencies, courts, and the media. A rapid shift in the mentality of many surgeons has occurred. In the past, the quality evaluation process was perceived by most surgeons as an unpleasant questioning of one’s practice. Today, for a rapidly increasing number of cardiac surgeons, quality evaluation has become a legitimate scientific necessity. Evaluation of quality of care is a new chapter of modern medicine, which

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follows a different rhetoric and demands the need to measure and compare. “One cannot evaluate what is not measured” is a classical statement of business management. Many instruments used in the past to describe results are now obsolete. New methods, parameters, and vocabulary are needed to measure quality of care. A new mentality is emerging; it is a climate of self-evaluation of quality of care driven by scientific methods.

WHY EVALUATE QUALITY OF PRACTICE?

The better question is “Why let others do it?” It is self-evident that the practitioners possess or can acquire all the information needed to judge their outcomes and evaluate the quality of care that they deliver. When other parties try to evaluate outcomes, they either inquire about physician data from clinical databases, or unfortunately, they are reduced to work from administrative databases, which are often erroneous, incomplete, and not verified [13]. Historically, most evaluations performed were limited to raw hospital mortality. This practice leads to inaccurate and unfair evaluation of performance. Some hospitals control their mortality by refusing to treat high-risk patients and thereby receive high performance marks unfairly. Many surgeons who deal with high-risk patients have a higher mortality and become frustrated when given a negative evaluation by some officials. The introduction of risk stratification in the STS database by adult cardiac surgeons, and more recently the complexity score by pediatric cardiac surgeons [4,5,8], allows a fair comparison between centers.

Since 2000, the members of the STS and EACTS who send their data to their respective congenital databases receive a report ranking their center in comparison with other participating centers and the overall database average performance. Over 100 centers in the STS and EACTS sent data in 2006 [14]. It is expected that this number will increase in the future, as will the scientific expertise of the quality evaluation. This self-evaluation process of quality of care is underway and will be carried on with respect for confidentiality inside scientific societies, and in collaboration with hospital managers and public and private insurance companies.

QUALITY OF CARE EVALUATION MUST LOOK AT MULTIPLE OUTCOMES

Operative mortality

In the past, most performance evaluations were based exclusively on hospital mortality. Currently, the preferred parameter is operative mortality, which has been defined precisely [12]. It includes all deaths occurring during the first 30 days following a surgical procedure or those occurring before patients are discharged home. The new definition considers that a patient dying at home in the first 30 days is an operative death and that a patient dying after transfer to another hospital is also an operative death.

Importantly, the mortality rate now is calculated by dividing the number of deaths by the number of surgical patient admissions and not by the number of
procedures. In congenital heart surgery specialty, approximately 15% of the patients have multiple procedures. After retroactive correction of this factor, the operative mortality observed in the STS database increased from 4.0% to 4.4% overall and from 10.5% to 12.2% in neonates [12].

The Joint EACTS/STS Congenital Database Committee has established a new index of mortality based on objective mortality data from 53,750 patients. One hundred procedures (representing 95.4% of the patient population) received an index value from 0.1 to 5.0 (Fig. 1). The new mortality index will be developed further on objective data, and will combine the Aristotle Basic Complexity Score (ABCS) and the Risk Adjustment in Congenital Heart Surgery (RACHS-1) methods [15].

The great limitation of reducing the quality evaluation to only operative mortality is that it allows evaluating approximately 5% of the patients, leaving 95% of the patients without evaluation.

Operative morbidity
Performance evaluation in the past for the most part has neglected operative morbidity. The Aristotle complexity score is one of few tools that measures this crucial factor [4,5,8,9]. Morbidity is defined as a state of illness or a lack of health or a physical disability. Operative morbidity is defined as the temporary or permanent disability observed after a surgical procedure. Importantly, the most successful operative procedure still is associated with some degree of temporary disability. Therefore, zero operative morbidity is impossible to achieve. The operative morbidity of an atrial septal defect device closure is

![Mortality Index (53,750 patients, 95.4%)](image-url)

**Fig. 1.** The Joint EACTS and STS Congenital Database Committee has established a new index of mortality based on objective operative mortality data derived from 51,295 patients corresponding to 95.4% of the population. One hundred procedures have been assigned an index value from 1 to 5, corresponding to a mortality ranging from 0% to 26% and over.
less than a surgical closure, but it is not nil, and it can be estimated through length of hospital stay. Occurrence of complications is the main factor of morbidity. The Joint EACTS and STS Congenital Database Committee, working in collaboration with the Multi-Societal Database Committee for Pediatric and Congenital Heart Disease, has initiated a comprehensive study to define and list the complications observed in the specialty, which will be used for the quantification of morbidity. The same group is developing an index of morbidity that will be correlated with cost. It will include numeric values based on the sum of postoperative length of stay (LOS) and postoperative length of ventilation time (Fig. 2). Each procedure will receive a morbidity value from 0.1 to 5 based on real harvested data from the STS and EACTS. When a patient dies, he or she will be assigned a maximum morbidity value. In order to assess and discuss morbidity, a name is needed for the antonym of morbidity; the authors have proposed the new term “optivival” (analogous to the term survival, the antonym of mortality).

Occurrence of complications is an important contributor to morbidity. Unfortunately, the nomenclature is defined poorly, and up to now data collection has been inconsistent. Although most complications can be measured by their contribution to ventilation time and LOS, occurrence of complications associated with either severe temporary disability (unplanned reoperation, extracorporeal membrane oxygenation, or others) or permanent disability (myocardial dysfunction, atrioventricular block, phrenic nerve palsy, neurological deficit, 

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**Fig. 2.** The Joint EACTS and STS Congenital Database Committee is establishing a new index of morbidity based on objective morbidity data derived from 51,295 patients; 100 procedures have been assigned an index value from 1 to 5. The operative morbidity is the sum of postoperative ventilation time and postoperative LOS), ranging from 6 hours to 30 days and over. In 2007, this index also will include quantitative values to account for complications with either permanent or severe temporary disability.
dialysis dependent renal failure, or others) deserve additional recognition. When data become available, these will be added to the measurement of morbidity.

Long-term functional results
Achieving a normal long-term quality of life is the ultimate goal of surgical practice. It is achieved only partially in pediatric cardiac surgery. Many patients require reoperation. Others are only palliated and remain with significant limitation, like many patients with functionally single ventricles. Cardiac surgeons have limited access to long-term results, because the cardiologists assume responsibility for all the long-term follow up. Ideally, the evaluation of quality of care should be pursued during the entire lifetime of the patient; otherwise, information on late deaths frequently will be incomplete. Quantification of long-term functional status is necessary. Collaboration with referring cardiologists should allow enriched surgical databases with long-term results, concerning not only survival but also long-term functional status. This project is not addressed today by surgical scientific societies and represents a goal for the future.

Cost
Health care cost is a central aspect of this highly technical specialty. Private or public health insurance companies and hospital managers are expecting more information about cost from the medical community. So far, most cardiac surgeons have neglected this aspect. Today, only a few institutions have a clear understanding of the cost per operation in congenital cardiac surgery. Cost clearly is correlated with morbidity. The STS leadership recently asked the cardiac surgeons to develop precise quantification of the cost, based on a modern evaluation of morbidity. This important task must be carried out in collaboration with hospital financial departments applying analytic accounting resources.

Patient and family satisfaction
The satisfaction of the families is not correlated entirely with survival and op-tivival (antonym of morbidity). Satisfaction of the patients is evaluated through questionnaires given to the family at the time of discharge. This evaluation is helpful to improve hospital service and amenities and delivery of the therapeutic team.

The five different categories of performance
According to the different outcomes that the authors have defined, various categories of performance can be studied (Table 1).

THE FIVE COMPONENTS OF THE EVALUATION OF THE QUALITY OF CARE
The Joint EACTS and STS Congenital Database Committee and the Multi-Societal Database Committee for Pediatric and Congenital Heart Disease consider that the evaluation of quality of care in this specialty requires five components.
A common language: the international nomenclature

Pediatric cardiac surgery is a complex specialty. The pediatric cardiac surgical community has long felt that the *International Classification of Diseases, Ninth Revision (ICD9)* and *Current Procedural Terminology (CPT)* codes, currently used by administrative databases, are not sufficiently accurate to define a precise evaluation of the quality of care [1,2]. In 1998, under the leadership of Constantine Mavroudis, the International Congenital Heart Surgery Nomenclature and Database Project was created in collaboration between the STS and the EACTS. A comprehensive nomenclature with long lists and a limited nomenclature with short lists were adopted by the STS and EACTS and published in a 2000 supplement of the Annals of Thoracic Surgery [1]. The short lists include 200 diagnoses and 150 procedures; they form the basis of the language required to evaluate quality of care and are shared by the STS and EACTS congenital databases [1,2].

A data collection system: the registry

The database to be used for quality evaluation should be a registry. A registry as defined by Bill Williams will contain “some data on all patients” [16]. It is essential to limit the data entries to be able to ensure their completeness and accuracy without imposing too strenuous a workload on the surgical team. Several software packages have been produced to organize and implement the database, the most popular being CardioAccess [17]. Following the creation of the common nomenclature, the STS and EACTS registries have accumulated data since 2000. In 2006, each registry contained more than 40,000 patients and, when combined, contained over 80,000 patients. Figs. 3 and 4 illustrate the progression of the STS database. It is expected that in 2007, the combined databases will have accumulated 100,000 patients.

A data verification process

Verification of the accuracy and the completeness of the data is crucial, because it has been shown that patients not included in a database have a worse outcome than those included [18]. A report from the United Kingdom Central Cardiac Audit Database [19] revealed that hospital-based databases underreported 42 hospital deaths out of a total of 194. Similarly, the EACTS

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### Table 1

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Category</th>
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<tr>
<td>Mortality/survival</td>
<td>Safety</td>
</tr>
<tr>
<td>Morbidity/optimivialis</td>
<td>Efficiency</td>
</tr>
<tr>
<td>Long-term survival</td>
<td>Quality</td>
</tr>
<tr>
<td>Cost</td>
<td>Economy</td>
</tr>
<tr>
<td>Patient satisfaction</td>
<td>Reputation</td>
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</table>

*Optivival is a new proposed term to name the antonym of morbidity.*
implemented a data verification process and reported that seven hospital deaths out of 68 were missed [20]. These three reports [18–20] illustrate that there is a need for verification of both the completeness and the accuracy of data in pediatric cardiac registries. Using a common protocol, the data verification process now is organized officially at both the EACTS and STS under the leadership of Bohdan Maruszewski of the EACTS and David R. Clarke of the STS, respectively.

A multisocietal congenital heart diseases network Jeffrey P. Jacobs, the current chair of the STS Congenital Database Taskforce, has created The Multi-Societal Database Committee for Pediatric and Congenital Heart Disease. This important network has gathered together all parties interested in the diagnosis, treatment, and evaluation of quality of care for congenital heart disease (CHD). This network includes cardiac surgeons, cardiologists, intensivists, anesthetists, nurses, and government administrators. The
The purpose of this network is to elaborate common definitions of CHD outcomes, sharing the same methods of evaluation of quality of care across all subspecialties and governmental agencies. These definitions and classifications are meant to standardize terminology, find broader acceptance, and be useful in all forms of quality of care analyses. It is inside this group that the index of mortality, the index of morbidity, and the evaluation of complications are discussed.

A fair method to compare outcomes between centers and surgeons

This last component is essential in a modern system of quality of care evaluation. In 2000, the Joint EACTS and STS Congenital Database Committee initiated in Oslo, Norway, a new method of risk stratification, under the leadership of the Francois Lacour-Gayet. It is a method based on the complexity of the procedures called the Aristotle complexity score.

**THE ARISTOTLE COMPLEXITY SCORE**

For the past 15 years, the standard method of benchmarking in quality of care has been risk stratification. The literature has recognized one factor almost exclusively to evaluate the quality of care in surgery: the risk of operative mortality. Hazard curves popularized by Eugene Blackstone [21] demonstrate the time-adjusted hazard function and compare patient’s survival or freedom from a given complication over time, according to recognized risk factors. This technique is the gold standard to evaluate a surgical method or procedure for a series of patients undergoing surgery in a given center. The risk of performing a given procedure is essentially similar in a given center; it is exceptional when a study recognizes risk according to an individual surgeon [22].

Risk depends on performance. Complexity, defined as the sum of the operative mortality, the operative morbidity and the technical difficulty, does not

When comparing outcomes between centers, a stratification based on risk alone is insufficient and possibly erroneous. Centers have different capabilities and resources, and variable expertise according to procedures. A given center can have excellent results in simple procedures and decide to send away patients who are more complex, while another center may be excellent in some challenging procedures and not in others. When comparing congenital heart surgery to sport or music (for example, ice skating, alpine ski, golf, or piano), the difficulty (or complexity) of performing optimally a challenging task is precisely ranked by judges. The ranking depends on a constant that is established by the party judging the competition. The risk of failure of the sportsman or musician depends on his or her ability to perform a task as perfectly as possible. The risk of failure depends on the level of performance. An analogy can be made to the perfect realization of a surgical procedure without near-miss or complication. In fact, performing a surgical procedure may be far more complex than many individual sports, while similar to an orchestra or many sports, the surgeon relies on a complex team for optimizing performance.
The fundamental principle of the complexity–Aristotle concept is to define a constant for the challenge presented by a given surgical procedure in a given surgical specialty. It is different from the severity of a disease, which is defined by intensivists [23], because various procedures may be indicated for the same disease. A patient presenting with a Taussig-Bing heart, ventricular septal defect (VSD), and aortic coarctation can be treated by coarctation repair with pulmonary artery banding or preferentially by a one-stage repair with arterial switch, aortic arch repair, and VSD patch closure. The complexity of the former operative procedure is less provided there is no contraindication to the latter.

The authors postulate along with the Aristotle committee [5] that the complexity of given procedure in pediatric cardiac surgery is the sum of three factors or indices (and not risk): the operative mortality, the operative morbidity and the technical difficulty. Such complexity is different according to surgical or medical disciplines. Ophthalmologists, orthopedists, or neurosurgeons have limited hospital mortality (excluding trauma), while morbidity and permanent disability may be more frequent.

Why include technical difficulty in the equation?
This question has been, and still is a source of controversy. Technical difficulty is useless when dealing with nonchallenging procedures, and the technical difficulty index for simple procedures is very low. On the other hand, when dealing with long-lasting and complex procedures requiring speed, precision, and accurate intraoperative judgment, the technical difficulty of the operation becomes an important factor. These complex procedures require a challenging learning curve. A given operation, for a given surgeon and with a given team, can be very simple with minimal mortality and morbidity, and can be very different for a different surgeon and team in another institution. How does one evaluate this human factor? In surgery, interventional cardiology, and also in interventional radiology, (neuroradiology, vascular radiology, visceral radiology and others), human behavioral factors are central to the final result. For many colleagues, including many medical and some surgical specialties, this human factor is very limited. The medical treatment of a patient with Hodgkin’s disease, Crohn’s disease, or essential hyperlipidemia, and even the combined treatment of a patient with a breast tumor, does not depend on the physical skill of the practitioners, but instead patient outcomes depend on an optimal protocol confirmed by multicentric randomized clinical trials (which are nearly absent in pediatric cardiac surgery). It is not likely, that in the near future, all surgeons will be equal in performing an operative procedure. The ability of reconstructing an anatomy in three dimensions is specific to surgeons. This concept is why surgery remains a form of art as well as science. The mortality after an arterial switch operation (ASO) with intact septum and after isolated VSD patch closure are similar in the STS database. The ASO operation requires a long learning curve to be able to transfer safely all coronary anatomy, while the isolated VSD patch closure is far simpler. In fact, when mortality and even morbidity are quite similar, the only way to
differentiate the technically complex procedures is to introduce a technical diffic-
ulty factor. Practically, a surgeon’s compensation for two procedures of differ-
ing technical difficulty will become similar if the rating is based only on potential for mortality and morbidity.

The initial period: complexity based on subjective probability

In 2000, when harvesting patient information with the new international no-
mencature began, there was no database available. Congenital heart surgeons were facing a dilemma. Many prominent surgeons dealing with the most com-
plex patients were very reluctant to send data, because their mortality was higher than the average mortality observed. It was urgent to establish a fair benchmarking tool of complexity to adjust the mortality. It was decided to rely on expert opinion using a subjective approach.

This complexity stratification was named the Aristotle score, following Aristot-
elle’s belief in the importance of current opinion:

“When there is no scientific answer available, the opinion (Doxa) perceived and admitted by the majority has the value of truth.” (Aristotle, Rhet-
oric, Book I, 350 BC).

As explained in detail elsewhere [4,5,8,9], the authors sent a questionnaire to 50 international centers asking their opinion as to what was the potential for mortality, the potential for morbidity, and the technical difficulty of a basic surgical operation, using the procedure short list from the EACTS-STS no-
mencature. This resulted in the Aristotle Basic Complexity Score (ABC Score). Each of the 150 primary procedures was scored on a scale of 15 points (Fig. 5). The ABC Score was simple. Its accuracy was limited, however, be-
cause the challenge raised by a given operation like arterial switch for Trans-
position of the Great Arteries can vary from a straightforward operation with normal coronary to a very technically challenging procedure with intramural coronary arteries. Many anatomical variations can co-exist in a single procedure. Moreover, comorbidities are frequent and potentially can add very haz-
ardous conditions. To meet these variations, the authors created the Aristotle Comprehensive Complexity Score (ACC Score) that includes associated anomalies, associated procedures, and comorbidity. The ACC Score allowed for the addition of 10 points to the ABC Score; therefore, the ACC Score is calculated on a total of 25 points (see Fig. 5). The additional 10 points were calculated by expert opinion, potentially adding five points for procedure-
dependent factors and five points for procedure-independent factors. The ACC Score has been used in several publications to score complex procedures [24–28].

This subjective approach has been criticized by several prominent authorities [29]. Subjective probability analysis, however, was initiated by Thomas Bayes (1702–1761) in the 18th century. Bayesian statistics are a classical and quite complex mode of probability, taught in business schools and scientific univer-
sities and extensively used in medicine [30,31]. As stated by Ashby [31],
Bayesian statistics has now permeated all the major areas of medical statistics, including clinical trials, epidemiology, meta-analyses and evidence synthesis, spatial modeling, longitudinal modeling, survival modeling, molecular genetics and decision-making in respect of new technologies.

Bayesian statistics may be needed to further validate the Aristotle score [32].

Two principles of the Aristotle complexity score

The first principle is that complexity is a constant. The complexity of an operation to be performed on a given patient at a given time is a global constant. The complexity is a calculated value that was estimated initially through a subjective approach.

The second principle is that a logical relationship exists between performance, complexity and outcomes. The authors postulate, as their first hypothesis, that Performance = Complexity × Outcome, where complexity is a constant, and performance and outcome are variables.

Figs. 6–8 show graphs documenting the results from 80 centers (40 STS centers and 40 EACTS centers), comparing average complexity with either survival or performance. The performances are quite similar, with slightly more complex patients receiving operations in North America because of a greater number of Norwood procedures.
The relationship of the volume of operations to outcomes performed was studied. The 80 centers were divided in three groups: small-volume (<100 cardiac operations per year), medium-volume (100 to 250 cardiac operations per year) and large-volume (>250 cardiac operations per year). Fig. 8 shows that good results can be achieved in medium- and even small-volume centers; excellence is not the exclusive privilege of large centers.

**Fig. 6.** The graph compares the STS and EACTS centers with regards of survival and complexity. The optimal quadrant is in the upper right one; the worst one is the inferior left one.

The relationship of the volume of operations to outcomes performed was studied. The 80 centers were divided in three groups: small-volume (<100 cardiac operations per year), medium-volume (100 to 250 cardiac operations per year) and large-volume (>250 cardiac operations per year). Fig. 8 shows that good results can be achieved in medium- and even small-volume centers; excellence is not the exclusive privilege of large centers.

**Fig. 7.** The graph compares the STS and EACTS centers with regards of performance and complexity. The highest performing centers are those on the upper right part of the graph.
Limitations of the Aristotle score

Evidently, the subjective approach can be wrong. When calculating mortality and morbidity indices using observed data, the authors discovered that their subjective values were wrong in approximately 30% of operations. The authors over-ranked some procedures (ASO, Ross procedure, and other rare procedures) and undervalued others (systemic to pulmonary shunts, patent ductus arteriosus surgical closure, and other rare procedures). These errors will be corrected when the authors combine objective data with subjective probability where objective data are lacking.

Another limitation is that the ABC Score, like the RACHS-1 method [15], does not optimally predict mortality. The authors believe that predicting mortality with certainty for a given patient is impossible. The ABC Score predicts mortality and morbidity fairly well in large samples. To address this issue, the authors have created new indices of mortality and morbidity (see Figs. 1 and 2).

The limitation of the predictability of the Aristotle score also relates to the fact that morbidity is undervalued, because the most complex patients may die earlier, therefore having a shorter LOS. In the future, the authors will assign a maximum morbidity for a patient who died.
Validation of the Aristotle scores
The ABC Score finally was validated by using a large sample of patients from a collaborative study performed by the Duke Research Clinical Institute (DCRI), the STS Congenital Database Taskforce, and The Joint EACTS and STS Congenital Database Committee [31]. Procedure-specific probabilities of hospital mortality and prolonged postoperative LOS greater than 21 days were estimated in a hierarchical model for 83 congenital cardiac procedures (excluding procedures with N <50) using both the EACTS congenital database (17,545 operations, 56 centers) and the STS congenital database (17,382 operations, 32 centers). The ability of the ABC Score to discriminate low-risk versus high-risk procedures was quantified by calculating the area under the receiver operating characteristics curve (C-index). The ABC score generally differentiates low-risk and high-risk procedures (C = .70 for mortality; C = .67 for LOS >21 days) (Fig. 9) [33].

The validation of the Comprehensive Aristotle score was studied on 2655 patients from 12 centers sending their data to the Aristotle Institute (http://www.aristotleinstitute.org/). Fig. 10 shows the excellent correlation between the ACC score and discharge mortality, with a risk of mortality over 40% when the score reaches or exceeds 20.

The second period: complexity based on indices calculated on observed data
Only when data on 100,000 patients are available potentially after 2007, will one be able to calculate mortality and morbidity on all operations. Today,

Fig. 9. The Aristotle Basic Score predicts well the risk of operative mortality (C = .70) and the risk of prolonged LOS >21 days (C = .67). (Data from O’Brien SM, Clarke DR, Jacobs JO, et al. Accuracy of the Aristotle basic complexity score for classifying the mortality and morbidity potential of congenital heart surgery procedures. Presented at the 2006 Meeting of The Society of Thoracic Surgeons (STS). San Diego, CA, January 29, 2007.)
one can evaluate safely mortality and morbidity for 95% of the congenital cardiac operations if limit the calculation is limited to operations where the database contains 32 occurrences by case. Figs. 1 and 2 represent the values of the new indices of mortality and morbidity.

The next period of data analysis starts in 2007, when performance will be calculated based on these new indices. The new complexity score, based on real data, is the sum of: Mortality Index + Morbidity Index + Technical Difficulty Index (subjectively derived).

The first results, coming from the group in Warsaw that manages the EACTS database, were presented at the Congenital Heart Surgeons Society (CHSS) in Chicago in October 2006 [34]. This data revealed an optimal correlation with mortality and morbidity, allowing a fair comparison between centers.

Future developments
Starting in 2007, the authors will develop the following sets of data:

- A mortality index, based on objective data
- A comprehensive but limited listing of complications, ranked according to their degree of disability
- A morbidity index based on objective data
- A new Aristotle basic score based on objective data
- A new comprehensive Aristotle score and a cost index correlated with the morbidity index

References


Advances in the Diagnosis and Treatment of Osteoporosis

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Osteoporosis is defined as a systemic skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fractures. Osteoporosis historically has been considered an adult condition because of its increasing incidence with age, affecting one in five postmenopausal women [1]. Osteoporosis is also costly, as the US Surgeon General reported that the estimated annual cost to the United States health system for all osteoporosis-related fractures ranged from $12.2 to $17.9 billion in 2002 [2].

In contrast, there are no data regarding prevalence or cost of osteoporosis in the pediatric population. In the past, osteoporosis in the pediatric population was reported in small numbers of children with rare conditions. Over the last decade, however, the problem has received increasing recognition as a common complication of several chronic conditions, as well as a consequence of therapies utilized to treat them.

PEDIATRIC-SPECIFIC BACKGROUND

More than 90% of adult bone mass is attained during the first two decades of life, with peak bone mass achieved by age 25 to 30 years. Periods of very rapid accretion occur during both infancy and puberty (Table 1) [3], and optimizing accretion has significant long-term effects upon prevention of osteoporosis and fracture risk later in life [4]. Bone mass accretion reflects the balance of bone formation, mediated by osteoblasts, and bone resorption, mediated by osteoclasts. The cycle of bone turnover occurs throughout life and is necessary for normal homeostasis. During childhood and adolescence, bone formation dominates bone resorption, leading to a net increase in bone mass and size.

Both intrinsic and extrinsic factors determine the rate of both mass accretion and attainment of peak bone mass (Box 1). Although intrinsic, essentially...
unmodifiable factors constitute the major influence on bone mass, the alteration of extrinsic factors can have a dramatic effect on short- and long-term bone health. Adverse effects on bone formation during rapid periods of pediatric bone accrual can lead to a continuum of presentations ranging from acute, symptomatic osteoporosis in childhood to reduced peak bone mass and a theoretical increased fracture risk in old age.

**CONTRIBUTIONS TO BONE MASS**

Intrinsic factors affecting accrual of peak bone mass include factors such as gender, ethnicity, and specific gene contributions. Males on average have a higher

<table>
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<th>Table 1</th>
<th>Lifetime patterns of bone calcium deposition</th>
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<td>Age years</td>
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<tr>
<td>Premature infants</td>
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<tr>
<td>Full-term infants</td>
<td>&lt;1.0</td>
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<tr>
<td>Prepubertal girls</td>
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<td>Postpubertal girls</td>
<td>15.4</td>
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<tr>
<td>Adults</td>
<td>30–60</td>
</tr>
</tbody>
</table>

The rate of bone mineral accretion varies throughout life, with the most rapid phases occurring during infancy and puberty.

From Abrams SA. Normal acquisition and loss of bone mass. Horm Res 2003;60(Suppl 3):72; with permission.

There are multiple influences on accretion. Intrinsic factors represent dominant and unchangeable influences, whereas extrinsic factors represent less dominant and highly changeable influences.
bone mass than females (Fig. 1), reflecting gender differences in bone size, bone calcium content, and bone geometry [5]. Ethnic differences also have been observed, with African Americans (both male and female) having higher bone mass than peers in other ethnic groups (Fig. 2) [6].

There is evidence for more specific genetic determinants of bone mass also. Elderly women and men with a family history of osteoporosis are at higher risk of being affected by osteoporosis than those without such a history. Similarly, premenopausal daughters of women who have postmenopausal osteoporosis have lower bone mineral densities than premenopausal daughters of women without osteoporosis [7].

Multiple studies have been performed to evaluate additional candidate genes in osteoporosis risk and bone mass determination. Linkage analysis studies have identified multiple candidate genes such as the vitamin D receptor, insulin-like growth factor-1 (IGF-1), estrogen receptor alpha, and the calcitonin receptor [8]. Attempts to identify specific monogenic contributors to bone mass determination have been mostly unsuccessful, with a few exceptions. The gene-encoding low-density lipoprotein (LDL) receptor-related protein 5 has been identified as a strong determinant of bone accretion. Loss-of-function mutations result in osteoporosis–pseudoglioma syndrome [9], and gain-of-function mutations result in a familial elevation of bone mass [10].

Extrinsic factors (Fig. 3) are less important than genetics in determining overall bone mass accretion; however, unlike genetic factors, these factors are modifiable. Perturbations of extrinsic factors account for most of the cases of abnormal bone mass encountered in pediatrics. In addition, interventions...
designed to change extrinsic factors offer opportunities for promoting optimal bone accrual.

Calorie and nutrient intake have significant effects on bone health. Calcium and vitamin D intake are particularly important and have been studied extensively as a factor in bone mass accretion. Among adults [11–13], it is clear that short-term supplementation improves bone mass, but the results of pediatric studies have been conflicting [14–16]. There has been particular concern about the effect of lower calcium consumption combined with higher phosphate intake caused by consumption of carbonated beverages by children and adolescents. For example, a recent study demonstrated that the consumption of cola beverages by physically active girls was associated with a higher risk for

Fig. 2. Ethnic differences in bone mass at various sites. Ethnic differences can be seen in bone mass, with African Americans having on average a higher bone mass at all sites relative to other ethnic groups. (From Bachrach LK, Hastie T, Wang MC, et al. Bone mineral acquisition in healthy Asian, Hispanic, Black, and Caucasian Youth: a longitudinal study. J Clin Endocrinol Metab 1999;84:4708; with permission.)
Improving the dietary practices and health of children is particularly important, given that the average dietary calcium intake of most adolescents is about 50% to 75% of the Recommended Dietary Allowance, which is 1300 mg/d for people between the ages of 9 to 18 years [18,19]. Vitamin D is critical for normal calcium absorption from the diet. There have been an alarming number of recent reports of vitamin D deficiency rickets in breastfed infants in Chicago [20], New Haven, Connecticut [21], and New York City [22], as well as severe vitamin D deficiency in schoolchildren in Beirut [23] and Greece [24]. The United States government has recognized the impact of calcium and vitamin D on bone health and has issued guidelines for recommended daily intake levels of these nutrients (Table 2) [25].

Vitamins C and K also have been shown to play important roles in bone health. Vitamin C is a required cofactor in the hydroxylation of lysine and proline necessary for collagen formation, and it has been demonstrated to have a positive effect on bone mass in adults [26]. Vitamin K is an important cofactor in enzymatic carboxylase reactions. It is known mainly for its role in blood clotting proteins, but it also participates in the carboxylation of osteocalcin, matrix Gla protein, and protein S (bone matrix proteins). Intervention studies in adults using vitamin K have shown improvement in bone mass [27].

Mechanical force strongly influences bone mass accretion, with immobilization having detrimental effects, while impact exercise is beneficial. Multiple

![Fig. 3. Extrinsic factors in bone mass determination. There are overlaps in all the major areas of extrinsic factors that influence bone mass. Perturbations in one area will influence other areas.](image)

**Table 2**

<table>
<thead>
<tr>
<th>Age group</th>
<th>Adequate daily calcium intake</th>
<th>Adequate daily vitamin D intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth through 6 months</td>
<td>210 mg</td>
<td>200 IU vitamin D</td>
</tr>
<tr>
<td>7 through 12 months</td>
<td>270 mg</td>
<td>200 IU vitamin D</td>
</tr>
<tr>
<td>1 through 3 years</td>
<td>500 mg</td>
<td>200 IU vitamin D</td>
</tr>
<tr>
<td>4 through 8 years</td>
<td>800 mg</td>
<td>200 IU vitamin D</td>
</tr>
<tr>
<td>9 through 18 years</td>
<td>1300 mg</td>
<td>200 IU vitamin D</td>
</tr>
</tbody>
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Dietary calcium and vitamin D intake guidelines recommended by the National Academy of Science.

short-term studies have demonstrated improvement in bone mineral density in pediatric patients undertaking weight bearing, impact exercise [14,28–30], and postmenopausal women who regularly performed weight-bearing exercise when they were adolescents have increased bone density, regardless of the amount of exercise during the intervening years [31]. A recent study showed improvement in bone mineral density at the lumbar spine and femoral neck over a 20-month period in early pubertal girls who participated in a circuit of varied jumping activities for 10 minutes, three times per week (Fig. 4) [29].

Smoking and excessive alcohol use have been associated with increased fracture risk in adult populations [32,33]. A recent meta-analysis that included 40,753 subjects showed reduction in bone mineral density in smokers compared with nonsmokers at all measured sites [34]. Similarly, a recent study of adolescent males (mean age 18.9 plus or minus 0.6 years) demonstrated that smokers had lower bone mass in multiple body sites measured using dual x-ray absorptiometry (DEXA) than nonsmokers. Measurement of bone parameters in this same study using peripheral quantitative CT demonstrated lower cortical thickness of the radius and tibia in adolescent male smokers compared with nonsmokers [35].

Despite studies showing the effects of variation in extrinsic factors on bone mass and bone mass accrual, however, it is important to emphasize that osteoporosis in an otherwise healthy child is extremely rare. Idiopathic juvenile osteoporosis and milder forms of osteogenesis imperfecta may present in this fashion, but these cases represent a minority of children who present with symptomatic osteoporosis. Rather, most children encountered will have osteoporosis as a complication of a chronic condition. The next sections will address specific conditions with osteoporosis as a prominent feature.

**Fig. 4.** Activity intervention effects on bone mass. (From MacKevie KJ, Khan KM, Petit MA, et al. A school-based exercise intervention elicits substantial bone health benefits: a 2-year randomized controlled trial in girls. Pediatrics 2003;112(6):e451; with permission.)
Osteogenesis imperfecta

Osteogenesis imperfecta (OI) is an inherited disorder caused by a mutation in one of the two genes that encode alpha chains of type I collagen (COL1A1 and COL1A2) [36]. The mutation causes abnormal and/or inadequate collagen formation, resulting in formation of diminished amounts of abnormal bone prone to accelerated resorption. The diagnosis of OI often is made based on a phenotypic basis. There are typical extraskeletal manifestations of OI, but they are present to a variable degree; these include blue sclera, dentinogenesis imperfecta, hyperlaxity of ligaments and skin, hearing impairment, and the presence of Wormian bones on skull radiographs [37].

Additional testing by skin biopsy to look for abnormal collagen in skin fibroblasts or DNA extraction from lymphocytes for mutation analysis has been used as an adjunct to clinical evaluation. Both of these approaches are reported to detect up to 90% of cases of abnormal collagen [38]. Inability to find a mutation in one of the implicated genes does not exclude the diagnosis of OI, as some mutations are not detected in standard gene analysis, and mutations in genes other than type I collagen have been reported in forms of OI [39–41].

OI can present with varying degrees of severity, although it always is associated with bone fragility (Table 3). The first classification of OI was published in 1979 and distinguished four clinical types, OI types I to IV [42]. Recently three additional OI types have been named, types V, VI, and VII [39–41]. These newer types are moderately to severely deforming, but are not associated with known mutations.

Gastrointestinal disease

Gastrointestinal (GI) diseases associated with reduced bone mass include inflammatory bowel disease, celiac disease, and liver diseases. The etiology of poor bone density in these disorders is multifactorial and varies with the particular disease process. Overlapping risk factors seen in all of these conditions include poor nutrition and malabsorption of both calcium and fat-soluble vitamins [43,44]. Direct detrimental effects on bone of inflammatory cytokines, such as interleukin (IL)-6, have been reported in celiac disease and inflammatory bowel disease [45]. Reduced fat mass and serum leptin concentrations have been correlated with low bone mass in celiac disease [46]. Lastly, glucocorticoid treatment used in both liver disease and inflammatory bowel disease may worsen bone mineral status further.

Endocrine disorders

Reduced bone mass and frank osteoporosis have been reported in association with multiple endocrine disorders. Growth hormone (GH), acting mainly through locally produced IGF-I, has important anabolic effects on bone. Growth hormone deficiency is associated with reduced bone density [47,48]. Estradiol in both males and females potently inhibits osteoclast-mediated bone resorption. Hypogonadism seen in Turner syndrome [49] and constitutional delay of puberty [50] has been associated with low bone density.
Osteoporosis also has been documented in hypothyroidism and hyperthyroidism, although the pathophysiology of osteoporosis in these two conditions is distinctly different. Thyroid hormone nuclear receptors are present in both osteoclasts and osteoblasts. IGF-I levels are stimulated at physiologic levels of triiodothyronine [51], and bone formation occurs; therefore, hypothyroidism results in poor bone formation. Hyperthyroidism increases osteoclastic-mediated bone resorption with association of elevated cytokines [52]. Treatment of each of these endocrine problems is essential for peak bone mass accrual.

Cushing syndrome is rare in children; however, pharmacologic doses of glucocorticoids used routinely in numerous pediatric conditions including rheumatologic conditions, inflammatory bowel disease, and immune suppression after organ transplantation reproduce many of the detrimental effects observed in Cushing syndrome including osteoporosis and fracture. A sustained excess of glucocorticoid has detrimental effects on bone by means of numerous different mechanisms, including alteration of calcium homeostasis [53], alteration in other hormones that influence bone [54], decrease of osteoblast-mediated bone formation [55], and increase of osteoclast-mediated bone resorption [56]. Pharmacologic glucocorticoids both reduce intestinal calcium absorption and increase renal calcium excretion, leading to depletion in total body calcium. In addition, glucocorticoids reduce growth hormone secretion and production of gonadal steroids. A biphasic pattern described in adults receiving chronic glucocorticoid treatment is characterized by an initial phase of increased bone resorption followed by decreased bone formation.

### Table 3

<table>
<thead>
<tr>
<th>Osteogenesis imperfecta type</th>
<th>Characteristics</th>
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<tr>
<td>Type I</td>
<td>Mild, typically no bone deformities, may have vertebral compression fractures</td>
</tr>
<tr>
<td>Type II</td>
<td>Lethal in perinatal period, usually caused by respiratory compromise/rib fractures</td>
</tr>
<tr>
<td>Type III</td>
<td>Extreme short stature, limb and spine deformities caused by multiple fractures</td>
</tr>
<tr>
<td>Type IV</td>
<td>Moderate bone deformities and variable short stature</td>
</tr>
<tr>
<td>Type V</td>
<td>Autosomal dominant, moderate-to-severe bone fragility, calcification of interosseous membrane at the forearm, and a predisposition to develop hyperplastic calluses</td>
</tr>
<tr>
<td>Type VI</td>
<td>Moderate-to-severe, unknown inheritance pattern; bone histology shows increased amount of osteoid and an abnormal pattern of lamellation.</td>
</tr>
<tr>
<td>Type VII</td>
<td>Has only been observed in a community of Native Americans in northern Quebec, bone fragility, rhizomelia, coxa vara, autosomal recessive</td>
</tr>
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The classification of types of osteogenesis imperfecta have expanded since the original classification scheme for Type I to Type IV to include newer types with variable phenotypes.
Parathyroid hormone has anabolic and catabolic effects on bone. Intermittent, pulsatile exposure leads to net bone formation through stimulation of anabolic factors such as IGFI [57,58], decreased osteoblast apoptosis [59], and a decrease in receptor activation of nuclear factor-kappa B (NF-KB) ligand (also known as receptor activator for NF-KB ligand [RANKL]), an osteoclast-enhancing cytokine [60,61]. Chronic elevation of parathyroid hormone levels, however, results in net bone resorption that can lead to osteoporosis, as occurs in severe primary hyperparathyroidism; the mechanisms of this resorption are understood poorly [62]. Fortunately, primary hyperparathyroidism is extraordinarily rare in pediatrics, with few cases reported in the literature [63–65]. Hyperparathyroidism can occur in patients who have multiple endocrine neoplasia (MEN) types I and II, and familial hyperparathyroidism without other endocrinopathies. Secondary hyperparathyroidism is encountered in pediatric patients who have chronic renal failure; appropriate treatment with vitamin D decreases this occurrence.

Oncologic and/or organ transplants
Patients who have malignancies or organ transplants are also at increased risk of osteoporosis, as a consequence of high-dose glucocorticoid therapy, aggressive chemotherapy, immunosuppression, cranial irradiation [66], poor nutrition, and decreased physical activity, as well as the effects of the underlying illness itself. Thirty-four percent of young adult survivors of solid tumors in childhood were found to have osteopenia or osteoporosis of the total body, lumbar spine, total hip, or femoral neck, and an additional 16% had isolated osteopenia or osteoporosis of the upper extremity. There is a direct relationship between osteoporosis or osteopenia and number of chemotherapy agents administered [67]. Decreased bone density compared with controls also has been documented in patients who have been treated for acute lymphoblastic leukemia (ALL) [68]. It has been shown that ALL patients have decreased bone density at diagnosis, and therefore the disease process itself likely has a negative effect [69]. Other studies have not found decreased bone densities in long-term survivors of ALL [70,71], perhaps because of newer treatment regimens using less cranial irradiation and decreased glucocorticoid dosing. Pediatric patients treated for bone sarcomas are also at risk of having decreased bone density [72].

Anorexia nervosa/malnutrition
Anorexia nervosa is associated with reduced bone mass. Some of the factors cited as causes for this reduction have included body mass index (BMI) [73], low estrogen levels [74], and possibly hypercortisolemia [75].

Bone fractures have been reported in cases of anorexia nervosa with severe reduction in bone mass [76]. The mainstay of treatment is improvement of caloric intake and restoration of body weight. Unfortunately, women with anorexia who attain a normal adult BMI and have regular menses, but who had long-standing anorexia during childhood/adolescence have decreased
bone mineral density, presumably because of failure to achieve an adequate peak bone mass [77].

Other disorders
Those patients with impaired mobility, and decreased weight bearing caused by neuromuscular disease have decreased bone density, likely because of the lack of mechanical stress needed for optimal bone formation [78]. Chronic anticonvulsant medications increase the risk of vitamin D deficiency. Chronic renal disease can lead to impaired vitamin D hydroxylation, resulting in impairment of bone formation because of a relative deficiency of vitamin D, as well as increased bone resorption as a consequence of secondary hyperparathyroidism.

EVALUATION OF BONE HEALTH
Much effort has been expended in examining the diagnosis, treatment, and prevention of osteoporosis in adults. The accurate diagnosis of osteoporosis in at-risk adults is critical in directing further evaluation and treatment resources. Features such as ease of use, safety, and accuracy are important in evaluating diagnostic modalities available to assess bone mass. All of the currently available modalities translate bone mass into a quantifiable measure of bone mineral density—a measure of bone calcium content within a defined area or volume of imaged bone. Modalities have included DEXA, quantitative ultrasound, and various types of CT imaging studies.

Dual-energy X-ray absorptiometry
The most common radiographic study used to evaluate bone health is dual-energy x-ray absorptiometry (DXA). This technology measures the transmission of radiographs of two different photon energies through the body. The attenuation of these transmitted energies depends upon the composition of the tissues through which the beam passes. A detector measures the energies passing out of the body, and computer-calculated values of bone mineral content and bone mineral density are reported. This technology can be used to measure the bone density of the whole body, as well as specific regions, such as the lumbar spine, hip, and distal radius. There are significant differences between brands of DEXA machines, and direct comparisons cannot be made between machines on an individual patient.

The World Health Organization (WHO) Study Group established diagnostic criteria for osteoporosis in older women using bone mineral density (BMD). Osteoporosis was defined as a T-score (the number of SDs above or below the average BMD of young healthy white women) of -2.5 SD on DEXA. Osteopenia was defined as a T-score of -1 SD [79]. These definitions have clinical utility in the adult patient population, because they ultimately are associated with fracture risk in outcome studies.

Z-scores, which express the number of SDs that a patient’s BMD deviates from age- and sex-matched controls, are more appropriate for use in pediatrics given the dramatic changes in normal bone density with age and change in
Neither studies indicate whether Z-scores predict fracture risk, however. Additionally, the studies on which reference ranges for pediatric bone density are based included relatively small numbers of patients, and these reference populations were predominantly Caucasian. The International Society of Clinical Densitometry has published an official position paper recommending that the diagnosis of osteoporosis in young people not be made on densitometric criteria alone [80]. The society recommends the use of Z-scores and proposes that patients with a Z-score below -2.0 be classified as having “low bone density for chronological age” [80].

Interpretation of DEXA results in the pediatric population is complicated further by several factors that may affect the calculated result, including short stature, delayed skeletal maturity, and delayed puberty. Short stature and therefore lower bone height will give a patient a lower bone mineral density by DEXA than is truly present. This is because bone mineral density is reported in two-dimensional units of grams of hydroxyapatite per cm² area of a particular bone region. Also, patients who have delayed puberty or delayed skeletal age can be expected to have a BMD more appropriate for skeletal maturation than for chronologic age.

Approaches to correction of artifacts have been proposed. Calculation of a three-dimensional volumetric bone mineral apparent density (BMAD) value (grams of hydroxyapatite per cm³ of a particular bone region) using a mathematical model based on the bone width has been used to correct for short stature bias. Another option is to analyze bone mineral density relative to height age (the age at which the child’s height would be at the 50th percentile) to mitigate the problems resulting in patients who have short stature. Analysis of BMD readings relative to the gender-specific normal values for the patient’s bone age rather than chronologic age may correct for the biases of delayed skeletal maturation or delayed puberty. Although these corrections are accepted widely as being clinically useful, there are no studies supporting their reliability in correctly predicting fracture risk.

Other measurements of bone density
In 2000, the diagnosis of osteoporosis shifted from a condition of low bone mass to one of compromised bone strength; this shift takes into account that resistance to bone fracture is determined by geometry, quality, and material properties of bone in different compartments, as well as bone mass [4]. Operationally, however, this has proven difficult, as technology is not yet advanced enough to permit clinically relevant measurement or calculation of bone strength, particularly in pediatrics, where bones are continuing to change and grow. Although DEXA provides a measurement of bone density, with the aforementioned caveats, it cannot provide a direct measure of bone geometry or strength.

Quantitative CT
Quantitative CT (QCT) uses standard body CT scanners and assesses bone in three dimensions [81]; this method can measure volumetric bone directly.
irrespective of bone size, and distinguish cortical from trabecular bone. It is much less readily available, however, and requires a radiation exposure approximately 10 times that of DEXA. Therefore, pediatric reference norms remain less readily available than they are for DEXA [82].

Peripheral quantitative CT
Peripheral QCT (pQCT) is promising, as it can measure volumetric BMD and bone geometry and can differentiate between cortical and trabecular components of bone, similar to QCT. This method evaluates long bones, however, such as the radius or tibia [83], and therefore requires far less radiation exposure than QCT [82]. In experiments using radii from cadavers, correlations between the geometric parameters derived from pQCT and the strength of bone and bending and simulated fall testing ranged from $r = 0.85$ to $r = 0.96$ [84]. This method has the possibility of being much less expensive than QCT, but it is not yet readily available for clinical use, and pediatric norms are lacking [82].

Quantitative ultrasound
Quantitative ultrasound has the advantage of being inexpensive and requiring no ionizing radiation. It can be used in areas where there is no underlying soft tissue, such as the radius, calcaneus, and phalanges. Bone mass and parameters of bone quality and strength can be measured [85]. There are fewer pediatric reference data available than DXA, and the normative values vary by manufacturer [82].

EVALUATION OF FRACTURE RISK IN PEDIATRIC PATIENTS

Various studies have been performed in an attempt to define fracture risk in pediatric patients, but they have had varying results. Goulding and colleagues [86] demonstrated that girls who had forearm fractures between ages 3 and 15 years had lower bone mineral content (BMC) and BMD (measured by DEXA) in the hip, spine, forearm, and total body than a control group without forearm fractures, supporting the view that a low BMD may contribute to fracture risk in children. In a 4-year follow-up study of the same cohort, the group found that low total body BMD, low spinal volumetric BMAD, and high body weight independently increased the risk of new fractures [87]. Skaggs and colleagues [88], however, used QCT and found that there were no differences in cancellous, integral, and cortical bone densities in girls who had a forearm fracture compared with those without a fracture. Those who had fractures had an 8% smaller cross-sectional area at the distal radius, and the authors concluded that small cross-sectional area, not bone density, affected fracture risk. Several other small studies have been performed in an attempt to correlate a low BMD and fracture risk in conditions such as cerebral palsy [89], Duchenne muscular dystrophy [90], and cystic fibrosis [91]. These studies have found an association between fracture risk and low BMD, but they have been unable to define a fracture threshold because of low numbers of patients.
EVALUATION OF PEDIATRIC PATIENTS WITH LOW BONE MASS WITH OR WITHOUT FRAGILITY FRACTURES

The authors’ approach to assessing and treating patients who have low bone mass is summarized in Fig. 5. A thorough history is obtained focused on evaluation of current health status, current medical treatments, dietary history, and family history of bone disorders. A physical examination is performed evaluating for evidence of underlying disease such as evaluation for joint laxity seen in OI and other collagen disorders. Laboratory investigation begins with basic measures including a serum calcium, magnesium, and phosphorus, alkaline phosphatase, vitamin D 25-OH level, vitamin D 1,25-OH level, intact

**Fig. 5.** A proposed algorithm for evaluation and treatment of children presenting with low bone mass, with or without bone fragility fractures.
parathyroid hormone, free T4, TSH, IGF-I, and spot urine for urine/creatinine, primarily to evaluate for otherwise treatable causes of poor bone density.

Laboratory measures of bone metabolism markers in serum or urine, believed to reflect the activity of either osteoblasts or osteoclasts, have been studied in adults as a means of screening for osteoporosis and monitoring osteoporosis treatment [92–94]. Adult studies have shown that the accuracy of these markers for osteoporosis diagnosis and monitoring is inferior to BMD measurements [95]. Bone metabolism markers also can be measured in the pediatric population, but the accuracy concerns noted in adult studies, and other problems, hamper their widespread use. Many of the markers have diurnal variation, and all are influenced strongly by puberty. Furthermore, there are no pediatric reference ranges for many of the newer markers.

Measurement of these markers in conjunction with clinical evaluation and radiologic findings may aid in the initial investigation of pediatric osteoporosis and possibly assist in monitoring therapy. Because of their multiple limitations in pediatrics, bone metabolism markers should not be relied on exclusively to make important clinical decisions. Measurement of several indices at once, and serial measurements, may help to overcome some of these limitations. Table 4 summarizes several laboratory assays for bone metabolism markers.

Radiology studies are done if not performed previously. The authors prefer to obtain a DXA scan of the lumbar spine and femoral neck, as well as a bone age radiograph, to adjust Z-score, BMD, and BMAD calculations for physiologic age.

TREATMENT
Clear guidelines regarding which pediatric patients to treat and large, well-designed randomized studies of treatment options are lacking. Identification of any underlying medical condition associated with low bone mass is an imperative and will determine in large part therapy. Before undertaking any specific treatment of osteoporosis, it is important to consider risks and benefits of any proposed treatment. A general therapeutic approach that can be applied in almost 100% of cases of low bone mass in children is the optimization of vitamin D and calcium intake. This intervention has potential benefit with very little risk. For example, ensuring at least 200 IU of vitamin D daily combined with 1300 mg of calcium daily for ages 9 to 18 years will provide the minimal requirement.

However, calcium and vitamin D optimization by themselves are often not enough to correct more severe reductions in bone mass especially when associated with fragility fractures. The benefits of some of the possible treatments often may outweigh the potential risks. It is therefore particularly important to evaluate each patient’s clinical condition when determining whether to initiate pharmacologic therapy.

BISPHOSPHONATE THERAPY
Bisphosphonates are used widely in the treatment of osteoporosis in the adult population. Bisphosphonates inhibit osteoclast function and therefore decrease
bone resorption, while allowing bone formation to continue. The biologic half-life of bisphosphonates is 8 to 10 years in adults, but the exact half-life in children is unknown [96]. Bisphosphonates are also the most frequently used medications for the treatment of low bone mass with associated fragility fractures in pediatrics. There is now roughly a 20-year experience of published reports of use of bisphosphonates in children.

There are case reports and small studies regarding the use of bisphosphonates in various conditions in pediatric patients including OI [97,98], glucocorticoid-induced osteoporosis [99], cerebral palsy [100], and fibrous dysplasia [101]. These studies have demonstrated that bisphosphonates can reduce bone pain, increase mobility, reduce fractures, improve grip strength

| Table 4 | Bone metabolism markers |
|---|---|---|
| Marker | Location | Notes |
| Bone formation | Serum | Most widely used test; 80% of activity is derived from bone. |
| Alkaline phosphatase | Serum | Assay not widely available |
| Bone-specific alkaline phosphatase | Serum | Product of osteoblast function; specificity of test reportedly is good. |
| Osteocalcin | Serum | Cleavage product from formation of type I collagen; other sources of type I collagen besides bone hamper test specificity. |
| Procollagen type I carboxyterminal propeptide (PICP) | Serum | Cleavage product from formation of type I collagen; other sources of type I collagen besides bone hamper test specificity. |
| Procollagen type I amino terminal propeptide (PINP) | Serum | Produced by osteoclasts; assay not widely available; data on normal values are scarce. |
| Bone resorption | Serum | Amino acid component of collagen; wide variation in day-to-day values and effects from dietary sources hamper specificity. |
| Tartrate-resistant acid phosphatase | Serum | Cross-linking peptides within collagen; specificity reported to be good. |
| Hydroxyproline | Urine | A fragment from cross-linking peptides within collagen; values strongly affected by puberty; specificity reported to be good. |
| Pyridinoline/deoxypyridinoline (DPD) | Urine | A fragment from cross-linking peptides within collagen; values strongly affected by puberty; specificity reported to be good. |

Table 4 lists descriptions of the different bone turnover markers available for measure in children. Normative values may not be available for all of the tests.
These studies have been limited in size and duration; however, the largest study involved 165 patients, and duration of follow-up is typically 1 to 2 years. Bisphosphonates have been used in infants as young as 2 weeks old.

**TREATMENT PROTOCOLS FOR BISPHOSPHONATES**

Bisphosphonates can be given by either oral or intravenous routes, with both methods being studied in children. Studies have not been placebo-controlled, nor have they compared dosing regimens. Therefore, definitive data on best route of administration, optimal dosing regimen, and treatment interval still are being defined.

The most commonly studied bisphosphonate in pediatrics is pamidronate given by intravenous infusion. The typical protocol reported in use of intravenous pamidronate in OI treatment is administration of pamidronate on three consecutive days. There is some variation of dosing frequency (typically every 1 to 4 months, depending upon the age of the patient, with younger patients receiving more frequent infusions). Therapy options for intravenous pamidronate are summarized in Table 5.

Treatment requiring three consecutive days of intravenous therapy every several months can cause a significant burden of both time and cost. The efficacy of cyclic single-day intravenous pamidronate infusions in a heterogeneous group of patients between 6 to 21 years of age was studied and demonstrated similar improvements in bone density and in fracture rate as reported with 3-day infusions in patients with OI. A direct comparison of 3-day to single-day infusion of pamidronate has not been published in the pediatric population. Zoledronic acid is a newer bisphosphonate with higher potency than pamidronate. It has the advantage of being given as a brief infusion over 30 minutes. Reports of intravenous zoledronic acid use in children are limited, and the optimal dosing frequency is not known.

Oral bisphosphonates have not been studied well in the pediatric population for various reasons, including requirements to swallow whole pills and

<table>
<thead>
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<tr>
<td><strong>Therapeutic options for administering intravenous pamidronate</strong></td>
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</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>First cycle, day 1</th>
<th>First cycle, days 2 &amp; 3</th>
<th>Subsequent cycles, days 1–3</th>
<th>Interval between treatments</th>
</tr>
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<tbody>
<tr>
<td>&lt;2 years</td>
<td>0.25 mg/kg/d</td>
<td>0.5 mg/kg/d</td>
<td>0.5 mg/kg/d</td>
<td>2 months</td>
</tr>
<tr>
<td>2–3 years</td>
<td>0.38 mg/kg/d</td>
<td>0.75 mg/kg/d</td>
<td>0.5–0.75 mg/kg/d</td>
<td>3 months</td>
</tr>
<tr>
<td>&gt;3 years</td>
<td>0.5 mg/kg/d</td>
<td>1 mg/kg/d</td>
<td>1 mg/kg/d</td>
<td>4 months</td>
</tr>
<tr>
<td>Alternatively, in patients &gt;6 years of age</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>&lt;50 kg</td>
<td>30 mg</td>
<td>—</td>
<td>—</td>
<td>4 months</td>
</tr>
<tr>
<td>&gt;50 kg</td>
<td>45 mg</td>
<td>—</td>
<td>—</td>
<td>4 months</td>
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Numerous regimens have been described in administering intravenous pamidronate, including the recommended 3-day cycle based on dosing for Paget’s disease. A newer single-day regimen also has been reported.
stringency in dosing method. Because many of the patients at risk for childhood osteoporosis have complicated medical histories and frequent behavioral and physical limitations, it has been assumed that many of these patients would not be good candidates for oral therapy. Oral, continuous treatment with a bisphosphonate, however, may have a more uniform effect on bone, as suggested by radiographs. Wide, dense metaphyseal bands are seen in long bones in patients undergoing continuous therapy, as opposed to the pattern of thin sclerotic metaphyseal bands seen in patients undergoing intermittent therapy [110]. This uniform effect may be associated with stronger bones.

The results of a small 2-year study evaluating oral alendronate versus intravenous pamidronate were recently published [111]. In this prospective randomized clinical trial of 18 pediatric OI patients, half of whom received oral alendronate and half of whom received intravenous pamidronate, both groups had steady and equivalent improvement over baseline in total body and lumbar spine BMD Z-score, with decrease in bone turnover markers after 2 years of therapy. The fracture incidence showed a trend toward a decrease, and height Z-scores showed a trend toward an increase in both groups. When both groups were pooled, there was a statistical decrease in fracture incidence compared with pretreatment rates and an increase in height Z-scores compared with normal children. In addition, subjects in the oral treatment group had no GI problems. Though this study was too small to prove equivalence of treatment, it does suggest that oral therapy may be tolerated well and potentially equivalent to intravenous therapy, while being clearly less expensive. The next sections will address bisphosphonate therapy in specific conditions.

**Osteogenesis imperfecta**

Physical therapy, rehabilitation, and orthopedic care are essential in the treatment of OI to maximize mobility and other functional capabilities [112,113]. These, however, often do not alter the extreme bone fragility that results in frequent fractures [36]. Therefore, the use of cyclic pamidronate in pediatric patients who had OI first was reported in 1998 [97]. Since then, several groups have reported upon the use of bisphosphonates in this patient population [102,112,114–117], but most series have been small. Most studies of cyclic pamidronate given every 1 to 4 months have found decreased bone pain, a rise in vertebral bone mineral mass, and an increased sense of well-being [37]. Improved mobility [97,102,106] and grip force [106] have been shown. The main effect demonstrated by histomorphometric studies of iliac bone samples is an increase in cortical thickness with an additional increase in number of trabeculae [117,118].

Generally, it is reported that those patients with OI who have long-bone deformities, vertebral compression fractures, and frequent fractures are candidates for bisphosphonate therapy [37], although some investigators feel that a low BMD reading alone in a patient who has OI should suffice [119]. It has been shown that pamidronate given to patients who have OI within the first 2 years of life can be beneficial, particularly at improving bone strength.
and gross motor function [117], but the cycles need to be repeated more frequently because of bone pain [98]. Bone turnover is suppressed markedly in these infants, and therefore treatment in infants should be limited to those with a moderate-to-severe phenotype [117].

It is currently unclear how long pamidronate should be administered in children who have OI, as well as what effects discontinuation of treatment may have. Studies seem to show that the greatest improvements in BMD and bone geometry occur in the first 2 to 4 years of treatment [104,120]. A recent study evaluated the effects of discontinuation of pamidronate treatment in a group of patients who had OI types I, III, or IV, all of whom had been receiving pamidronate for a minimum of 3 years. During a 2-year observation period off pamidronate therapy, markers of bone metabolism increased but remained lower than pretreatment levels, suggesting that pamidronate continues to have biologic activity 2 years after treatment is discontinued. Areal BMD Z-scores decreased in those patients off pamidronate therapy, although they remained much greater than pretreatment Z-scores. Patients who remained on pamidronate therapy had continued increase of BMAD Z-scores. There were no differences in fracture rates or functional status, although the numbers of patients were low. This study suggests that discontinuation of pamidronate therapy results in an incomplete reactivation of bone metabolism [120].

Chronic glucocorticoid use
Bisphosphonates are considered a mainstay in the prevention of glucocorticoid-induced osteoporosis in adults [121]. Glucocorticoids promote osteoblast apoptosis and decrease osteoclast inhibition. Therefore, osteoclastogenesis and increased bone resorption occurs with decreased bone formation. Conversely, bisphosphonates promote osteoclast apoptosis and increase osteoclast inhibition, thereby opposing the effects of glucocorticoids and decreasing glucocorticoid-induced bone resorption. There have been very limited data regarding treatment of glucocorticoid-induced osteoporosis, likely because of heterogeneity of the patient population and frequent variation of glucocorticoid dosing with an unpredictable pattern of remission and relapse of the patient’s underlying condition. A recent article was published specifically regarding the difficulty recruiting potential subjects into a study comparing vitamin D and calcium supplementation with cyclical pamidronate infusions. The study was stopped after 4 years because of difficulty with recruitment [122].

The authors compared a group of subjects who had ongoing glucocorticoid exposure (n = 6) with subjects without glucocorticoid exposure (n = 7); all patients had clinical evidence of bone fragility and reduced BMD by DXA. Both groups were treated with single-day pamidronate therapy for a minimum of 6 months. The median improvement in lumbar BMD Z-score was 13 plus or minus 5% in the glucocorticoid-exposed group, with an improvement of 33 plus or minus 10% in the group without glucocorticoid exposure. Although the study involved few subjects, it suggests that those with ongoing glucocorticoid exposure improve bone density while on pamidronate therapy, but to a lesser
extent than those without glucocorticoid exposure [109]. Another study, performed by Bianchi and colleagues, demonstrated a 15% annual increase in BMD with bisphosphonate therapy in 38 glucocorticoid-treated patients with connective tissue disease [99].

Hypotonia or nonambulatory status
Patients who are hypotonic or nonambulatory are at risk for poor bone density and increased fracture risk; many such patients are at an even greater risk of poor bone density because of the use of anticonvulsant medications and resultant vitamin D deficiency. Therefore, Plotkin and colleagues [123] treated 23 nonambulatory pediatric patients with severe spastic quadriplegic cerebral palsy and low BMD with cyclic intravenous pamidronate for 12 months. The researchers demonstrated an increase in lumbar spine and femoral neck Z-scores compared with baseline values. They were not able to determine a statistically significant difference in fractures.

A second study evaluated 10 nonambulatory pediatric patients who were treated with 35 mg alendronate per week for an average of 23 months per patient. There were 18 fractures in the patient population before alendronate, and 1 during the follow-up period. Half of the patients had nociceptive behaviors/pain complaints that resolved after starting alendronate. Seventy percent of the patients had gastroesophageal reflux disease (GERD), but there were no changes in GI adverse effects on medication. No patient stopped the medication due to side effects. Only half the patients had a premedication DXA scan, and there were no follow-up DXA scans. This small retrospective study suggests that oral bisphosphonate therapy is associated with an improvement in pain symptoms in patients presumed to have disuse osteopenia, a decrease in fracture rate, and no worsening of GI symptoms. No bone density measurements were provided, however [124].

BISPHOSPHONATE ADVERSE EFFECTS
Most adverse effects of oral and intravenous bisphosphonates have been documented well [125]. Adverse effects of oral bisphosphonates include mainly GI upset and risk for erosive esophagitis. Both oral and intravenous bisphosphonates carry risks for nephritis, GI upset, uveitis, and hypocalcemia [125]. Treatment with an intravenous bisphosphonate often causes an acute-phase reaction of fever, bone pain, and headache in patients receiving the first dose. A retrospective case review of 27 pediatric patients receiving pamidronate evaluated the effectiveness of pretreatment in decreasing the acute-phase reaction. Patients who received either or both ibuprofen or acetaminophen had less fever or bone pain than those who received no pretreatment. Seventeen percent of patients who were given ibuprofen as pretreatment had an acute-phase reaction compared with 89% of patients who were given acetaminophen [125, 126].

There have been ongoing concerns regarding the effects of bisphosphonates on fracture and osteotomy healing. Between 1984 and 2003, 131 patients with
moderate-to-severe OI treated with pamidronate at the Shriners Hospital for Children in Montreal (Canada) were evaluated. Delayed healing was diagnosed when a fracture or osteotomy line was at least partially visible 12 months after the event. The authors evaluated 197 fractures that occurred either more than 12 months before pamidronate was started or after initiation of pamidronate therapy. Pamidronate was not associated with delayed healing; instead, the strongest predictor of delayed healing was improved mobility, along with male gender, increased age, and lower height Z-score. However, delayed healing was seen in patients who were receiving pamidronate at the time of osteotomy compared with those patients who were not receiving pamidronate. Mobility was not a factor in this population. Although retrospective, these results confirm the results of previous case series [127]. Therefore, pamidronate should not be stopped if a patient fractures, but it should be stopped before a planned osteotomy.

Two recent reports of adverse bisphosphonate effects need to be mentioned. First, there have been multiple reports of osteonecrosis of the jaw in adults on bisphosphonate therapy [128]. This complication has yet to be reported in children. Second, there was a recent report of a 12-year-old patient who had hyperphosphatasia and bone pain who was treated for 3 years with high-dose intravenous pamidronate and developed osteopetrosis [129]. This case report, in a high profile journal, stirred concern in the pediatric community. A careful review of this case demonstrates several key points. The patient was treated with pamidronate for no generally recognized indication, with no clear treatment target, and at a dose and frequency vastly exceeding any current treatment protocol in use for childhood osteoporosis. This case highlights the importance of having a strong rationale for starting bisphosphonate therapy, monitoring of therapy, and clear end-points to stop therapy.

**MONITORING OF BISPHOSPHONATE THERAPY**

There are currently no clinical guidelines for monitoring therapy in children on bisphosphonates. Therefore, the treatment of these patients should be supervised by clinicians experienced in the evaluation of childhood osteoporosis. The patients should receive the smallest dose adequate to provide improvement in bone density, treatment should be continued for a limited period of time, and treatment should be accompanied by careful monitoring. Suggested parameters for monitoring are summarized in Fig. 6.

**ANABOLIC AGENTS**

There is significant interest in agents that may stimulate bone formation in children who have osteoporosis. These agents are appealing for use in all age groups, because they promote formation of new bone, unlike bisphosphonates, which act by suppressing bone resorption. Unfortunately, these agents primarily have only been studied in the adult population or are contraindicated for pediatric use.
Growth hormone/insulin-like growth factor

Growth hormone (GH) and IGF-I are potential anabolic agents; GH works through locally produced IGF-I, which promotes chondrocyte and osteoblast differentiation and growth [130]. Most of the studies using GH on bone mass in patients with postmenopausal osteoporosis have been disappointing, with minimal changes demonstrated in bone mass [131]. IGF-I administration has been shown to increase markers of bone formation in young women who have anorexia nervosa [132]. Improvements in fracture risk, however, have not been well-defined.

---

**Fig. 6.** A proposed algorithm for monitoring children on either oral or intravenous bisphosphonate Therapy.

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Interval History</th>
<th>Beneficial Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular complaints</td>
<td></td>
<td>Fracture history</td>
</tr>
<tr>
<td>Non-healing areas in mouth</td>
<td></td>
<td>Improvement in mobility</td>
</tr>
<tr>
<td>GI complaints</td>
<td></td>
<td>Improvement in bone pain</td>
</tr>
<tr>
<td>Electrolyte disturbances</td>
<td></td>
<td>Upcoming surgical procedures</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physical Examination</th>
<th>Labotary Assessment</th>
<th>Radiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular examination</td>
<td>Intact PTH</td>
<td>Bone age x-ray</td>
</tr>
<tr>
<td>Oral examination</td>
<td>Serum osteocalcin</td>
<td></td>
</tr>
<tr>
<td>Joint and spine examination</td>
<td>Urine calcium</td>
<td></td>
</tr>
</tbody>
</table>

- Serum electrolytes and serum creatinine
- Complete blood count
- Vitamin D studies
- Urine creatinine

-Bone mineral density measurement
- Skeletal survey (if applicable)

**Unacceptable acute side-effects from therapy?**
- Strongly consider stopping therapy

**Majority of clinical endpoints achieved?**
- Bone mineral density within 1 SD of mean
- Improvement in bone pain and mobility
- Reduction in fracture rate

**Evidence of over-treatment?**
- Bone mineral density within 1 SD of mean
- Hyperdense bones on x-ray
- Bone turnover markers below 25th percentile for age and gender

**Reduce dose and/or frequency of therapy**
- Yes
- No

**Continue therapy**
- Yes
- No
One study has been performed using GH therapy in prepubertal subjects who had cystic fibrosis. Those treated with GH therapy for one year had an increase in bone mineral content as well as an increase in height, weight, and lean tissue mass, compared with a placebo-treated group [133]. The same group also found improvements in the bone mineral content of adolescents with cystic fibrosis treated with GH compared retrospectively with an untreated group [134].

Parathyroid hormone
Continuous parathyroid hormone (PTH) secretion causes a catabolic response in the skeleton, as is seen in hyperparathyroidism, but low-dose, intermittent PTH has an anabolic effect. The mechanisms by which this occurs are not understood completely, but they may be related to stimulation of growth factors, such as IGF-I [57] or to inducing gene expression of bone-forming genes such as osteocalcin and tartrate-resistant acid phosphatase [135]. Parathyroid hormone also may prevent osteoblast apoptosis [59] and/or increase the receptor activator of NF-κB ligand (RANKL), an osteoclast-enhancing cytokine [61]. PTH has been demonstrated to be effective at increasing BMD and decreasing fracture risk in the adult population with osteoporosis, either in postmenopausal women as monotherapy [136] or in combination with estrogen replacement [137]. It also has been shown to be beneficial in men [138] and to improve bone density in patients who have glucocorticoid-induced osteoporosis [139]. It has not been studied in pediatric subjects, however, as studies (18 to 24 months) with high-dose h-PTH (1 to 34 amino acids) administered to 6-week-old Fisher 344 rats demonstrated an increased risk of osteogenic sarcoma. The effect is dose-dependent. Primate studies have failed to find an association between intermittent administration of PTH and osteogenic sarcoma [135], but an understandable fear has limited research in the pediatric population.

Strontium
Strontium is a divalent cation that chemically resembles calcium and appears to participate in bone mineralization [140]. It appears to stimulate osteoblast formation and inhibit osteoclast formation [141]. In a randomized, placebo-controlled trial, 1649 postmenopausal women with at least one vertebral fracture were treated with strontium ranelate daily or placebo for 3 years. The strontium group had a 41% reduction in relative risk of a new vertebral fracture, and lumbar BMD was increased in the treatment group by 11.4% (uncorrected for the presence of strontium in bone). The treatment group also had increases in bone-specific alkaline phosphatase (bone formation marker) and decreases in serum C-telopeptide (bone resorption marker) [142]. Strontium therefore is thought to have anabolic properties and the ability to inhibit resorption. There has been no experience with its use in the pediatric population, however.

Other potential anabolic agents
3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (statins) have been associated with a modest increase in BMD and a significant fracture risk reduction in adults [143,144], with both anabolic [145] and
antiresorptive effects theorized \[146\]. Studies, however, have not been placebo-controlled but have rather been epidemiologic and cross-sectional, and therefore subject to ascertainment bias. This effect has not been studied or reported in the pediatric population.

Sodium fluoride in a low-dose, slow-release formulation also has been shown to have potentially beneficial anabolic properties in postmenopausal osteoporosis \[147,148\], with reductions in vertebral fractures and increases in vertebral BMD from 3% to 6% per year \[148\]. Another formulation of fluoride, monofluorophosphate (MFP), has shown even greater benefit when administered with antiresorptive therapies such as hormone replacement therapy \[149\] or a bisphosphonate \[150\]. There have been no reports on the effect of fluoride use on bone density in the pediatric population, however. There have, however, been concerns regarding an association between exposure to fluoride in drinking water during childhood and the incidence of osteosarcoma in the pediatric population \[151\].

**SUMMARY**

Although severely low bone density is relatively rare in the pediatric population, it can be a significant problem in many patients with chronic illness. As peak bone formation occurs during adolescence, it is crucial that pediatricians and other care providers for this patient population recognize the significance of attainment of adequate bone. Dietary intake of vitamin D and calcium should be optimized, and correction of underlying causes of poor bone density should occur whenever possible. Assessment of bone density is difficult, as each technology available has problems, and none of the technologies are well-associated with fracture risk in pediatric patients. Once diagnosis of severely low bone density is established, treatment options are limited and poorly studied. The benefits of bisphosphonate therapy appear to outweigh the risks in patients with low bone density and frequent fragility fractures, and it appears that most improvement with bisphosphonates occurs within the first 2 to 4 years. Evidence, however, is emerging that once off therapy, bone turnover remains decreased for at least several years. During that time, improvements in bone density are decreased. Many questions remain regarding duration of therapy with bisphosphonate therapy and the long-term effects on the children who receive this medication. Anabolic therapies may become important in the future, but there is currently extremely limited information regarding their use in pediatrics.

**References**


Van Staa TP. The pathogenesis, epidemiology, and management of glucocorticoid-induced osteoporosis. Calcif Tis Int 2006;75(3):129–137.


In 1966, in an article entitled The Disappearance of Rickets, Harrison reported that vitamin D deficiency rickets had become so rare as to be a “medical curiosity” in children [1]. A number of reports suggest, however, that the recent worldwide prevalence of the disease is increasing [2]. In the United States, over 100 cases of rickets have been reported in the last 10 years. These occur primarily in dark-skinned, breast-feeding infants and toddlers with little sun exposure whose intake of dietary vitamin D is low. Not infrequently, they are exclusively breast fed by a mother who receives insufficient dietary vitamin D from milk, meat, eggs, or fish, or who ingests an unsupplemented vegetarian diet [3,4]. Hypovitaminosis D is also common in older children, adults, and the elderly. Vitamin D deficiency may also result from malabsorptive conditions, such as celiac disease, biliary obstruction, gastric resection, or pancreatic insufficiency, as well as from accelerated metabolism by anticonvulsants, such as phenytoin, that degrade vitamin D to rapidly excreted water-soluble forms.

In the end of the nineteenth century in such cities as Boston in the United States, 80% to 90% of children were found to have rickets at autopsy [5]. In this same period, investigators first realized the role of sunlight in preventing the disorder. In the early years of the twentieth century, the introduction of cod liver oil as a dietary supplement reduced the frequency of vitamin D deficiency, and treatment with mercury arc lamps was first employed as an antirachitic remedy. In the midtwentieth century, fortification of milk with vitamin D substantially reduced the incidence of the disease. As the century drew to a close, however, the movement of agrarian populations to more polluted urban settings; large-scale immigration from southern to northern latitudes, especially among people whose religious and cultural traditions require the body to be extensively covered; lifestyle changes, including more indoor dwelling and increased use of sunscreen, have all contributed to a resurgence of vitamin D deficiency.
Measurement of circulating levels of calcidiol (25(OH)D) best define total body vitamin D stores. Serum levels <11 ng/mL are very low and a minimum normal concentration for infants and neonates should exceed 20 ng/mL [6]. However, values <25 to 30 ng/mL may be inadequate to ensure optimal bone mineralization [7]. The World Health Organization has defined an “international unit” of vitamin D as the activity of 0.025 μg or 65 pmol of international standard preparation of crystalline vitamin D₃.

**BIOCHEMISTRY OF VITAMIN D METABOLISM**

The absorption of sunlight in the ultraviolet range (280–305 nm) converts dehydrocholesterol (DHC) in basal epidermal cells of the skin to provitamin D₃, which is then gradually thermally isomerized (37°C) to cholecalciferol (vitamin D₃) (Fig. 1) [8]. Total body exposure to one minimal erytherma dose of sunlight is equal to the intake of approximately 250 μg or 10,000 units of vitamin D, which is 17 to 50 times the daily adequate intake of 200 to 600 IU (5–15 μg) established by the Institute of Medicine [9]. Increased melanin in darker skin competes with 7-DHC for UV-B photons, reducing photosynthesis and circulating vitamin D levels. A dark-skinned individual requires about six times more sun exposure than a light-skinned person to produce the same cutaneous concentrations of vitamin D [10]. The topical use of sunscreen with protection factors of ≥8 may also reduce synthesis by over 95% [11]. Ergocalciferol (vitamin D₂) is formed in nature in small quantities in plants and fungi by the opening of the B-ring of ergosterol. The vitamin is synthesized commercially and used to fortify a variety of foods (Table 1) [12]. However, vitamin D₂ is less than one third as potent as vitamin D₃ and has a shorter duration of action [13].

As individuals age, unesterified epidermal concentrations of 7-DHC decline. An older person synthesizes <30% of the vitamin D₃ of a young adult with identical simulated solar exposure [14]. Latitude, time of day, and season of the year also influence cutaneous vitamin D₃ production. For example, in Boston, at 42°N latitude, sun exposure between November and February is insufficient to generate vitamin D₃ synthesis in skin. In many northern countries wavelengths from 239 to 310 nm are not present in sunlight from the end of October to the end of March [15]. In Boston, vitamin D₃ photosynthesis occurs between 7 AM and 5 PM in summer but only between 9 AM and 4 PM in spring and autumn because of the higher angle of the sun [2]. Air pollution has also been shown to inhibit cutaneous synthesis of vitamin D.

Vitamin D₃ produced in the skin is transported to the liver bound to vitamin D binding globulin (VBG), a protein present in high concentration in serum but only minimally (2%) saturated [16]. In hepatocytes, vitamin D is 25 hydroxylated to calcidiol by the P450c27 mitochondrial enzyme vitamin D-25 hydroxylase (encoded by *CYP27Al, CYP3A4, CYP2Rl, CYP2J3*) (Fig. 2). Because calcidiol only minimally inhibits its own synthesis, its concentration in serum closely reflects total body vitamin D stores. Biologically inert, calcidiol, whose circulating half-life is 2 weeks, is then carried by VBG to the proximal convoluted and straight renal tubules where it is converted to the active hormone...
Fig. 1. The photoproduction and metabolism of vitamin D and the various biologic effects of 1,25(OH)2D on calcium (Ca), phosphorus (P), and bone metabolism. Vitamin D is either produced in the skin by exposure to UV-B radiation or is ingested in the diet. Vitamin D (D represents vitamin D2 or vitamin D3.) is converted by the vitamin D-25-hydroxylase (25-OHase) in the liver to 25(OH)D. In the kidneys, 25(OH)D is converted by 1-OHase to 1,25(OH)2D. Once formed, 1,25(OH)2D enhances intestinal calcium and phosphorus absorption and stimulates the expression of receptor activator of nuclear factor-κB (NF-κB) ligand (RANKL) on the osteoblasts to interact with its receptor activator of NF-κB (RANK) on preosteoblasts to induce mature osteoclastic activity, which releases calcium and phosphorus (HPO42-). In addition, 1,25(OH)2D inhibits the renal 1-OHase and stimulates the expression of the renal 25(OH)D-24-hydroxylase (24-OHase). The induction of the 24-OHase results in the destruction of 1,25(OH)2D into a water-soluble inactive metabolite calcitroic acid, previtamin D (PreD3). DBP, vitamin D binding protein; PTH, parathyroid hormone. (From Holick MF. Resurrections of vitamin D deficiency and rickets. J Clin Invest 2006;116(8):2062–72; with permission.)

calcitriol (1,25-dihydroxyvitamin D) by 1,a-hydroxylase (CYP 24, 20q13.2), a mixed-function oxidase active on the inner mitochondrial membrane of renal cells. 25(OH)D-1,a-hydroxylase activity is increased by hypocalcemia and hypophosphatemia, parathyroid hormone (PTH), PTH-related protein (PTHrP), calcitonin, 24,25(OH)2D, growth hormone, insulin-like growth factor I , prolactin, cyclic adenosine monophosphate, and protein kinase A. Elevated calcium
and phosphate values and calcitriol itself inhibit the activity of 25(OH)D-1,α-hydroxylase [17]. Calcitriol is inactivated in bone, intestine, liver, and kidney through glucuronidation, sulfation, hydroxylation, and lactone formation to water-soluble calcitroic acid excretable in urine and bile [18].

Calcitriol raises serum calcium and phosphorus concentrations by binding to intranuclear vitamin D receptors (VDRs) in intestine, bone, and kidney. The VDR is a 427 amino acid member of the steroid/thyroid superfamily of nuclear-transcription transactivating molecules [19]. The calcitriol-VDR complex combined with a retinoic acid X receptor in the nucleus activates vitamin D response elements in target cells, such as cells in the gut epithelial calcium channel. Increased calcium flux into gut epithelium is followed by calcium binding to 9K calbindin and delivery into the circulation. In states of vitamin D deficiency, only 10% to 15% of dietary calcium and 50% to 60% of dietary phosphorus are absorbed [6]. VDR polymorphisms, such as the BB genotype, have been associated with subtle alterations in bone mineral density as well as with differences in birth length and growth in early childhood [20].

Calcitriol’s biologic role is to maintain the appropriate serum and tissue concentrations of calcium and phosphorus needed to achieve normal bone mineralization [8]. In bone, calcitriol increases calcium outflux by indirectly stimulating formation of bone resorbing osteoclasts. Osteoclasts and osteoblasts develop from common progenitor cells and their interaction is necessary for osteoclast differentiation and function. Osteoblasts and stromal cells express the

Table 1
Dietary sources of vitamin D

<table>
<thead>
<tr>
<th>Source</th>
<th>Vitamin D content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fortified milk</td>
<td>100 IU/8 oz</td>
</tr>
<tr>
<td>Fortified orange juice</td>
<td>100 IU/8 oz</td>
</tr>
<tr>
<td>Infant formula</td>
<td>100 IU/8 oz</td>
</tr>
<tr>
<td>Fortified yogurt</td>
<td>100 IU/8 oz</td>
</tr>
<tr>
<td>Fortified butter</td>
<td>56 IU/3.5 oz</td>
</tr>
<tr>
<td>Fortified margarine</td>
<td>429 IU/3.5 oz</td>
</tr>
<tr>
<td>Fortified cheese</td>
<td>100 IU/3 oz</td>
</tr>
<tr>
<td>Fortified breakfast cereal</td>
<td>~100 IU/serving</td>
</tr>
<tr>
<td>Egg yolk</td>
<td>~20 IU/yolk</td>
</tr>
<tr>
<td>Shiitake mushrooms, fresh</td>
<td>100 IU/3.5 oz</td>
</tr>
<tr>
<td>Tuna, canned</td>
<td>236 IU/3.5 oz</td>
</tr>
<tr>
<td>Mackerel, canned</td>
<td>~250 IU/3.5 oz</td>
</tr>
<tr>
<td>Sardines, canned</td>
<td>~300 IU/3.5 oz</td>
</tr>
<tr>
<td>Salmon, canned</td>
<td>~300–600 IU/3.5 oz</td>
</tr>
<tr>
<td>Salmon, fresh</td>
<td>~400–500 IU/3.5 oz</td>
</tr>
<tr>
<td>Shiitake mushrooms, sun-dried</td>
<td>1,600 IU/3.5 oz</td>
</tr>
<tr>
<td>Drisdol (Vitamin D2) liquid</td>
<td>8,000 IU/cc</td>
</tr>
<tr>
<td>Cod liver oil</td>
<td>400 IU/teaspoon</td>
</tr>
</tbody>
</table>

cytokine mediator, receptor activator of nuclear factor-κB (NF-κB) ligand. Through cell-to-cell interaction, binding of this factor to receptor activator of NF-κB on prefusion osteoclast membranes induces osteoclast activation, fusion, and initiation of bone resorption [21]. Calcitriol also stimulates osteoblast synthesis of osteocalcin, osteopontin, and alkaline phosphatase and inhibits osteoblast expression of PHEX, whose endopeptidase gene product inhibits phosphate reabsorption in the kidney [22]. Calcitriol action at the parathyroid cell inhibits PTH transcription, restricting synthesis and release of PTH. While calcitriol mobilizes calcium from the renal tubule and the bone, these effects are of less physiologic significance than its action on calcium absorption in the gut [23].

**Fig. 2.** Metabolism of vitamin D. Vitamin D can be metabolized to the active form, 1α 25-dihydroxyvitamin D or to an inactive form, 24,25-dihydroxyvitamin D. (From Hochberg Z. Vitamin D and rickets. Basel [Switzerland]: S. Karger AG; 2003. p. 20; with permission.)
BONE MINERALIZATION AND THE HISTOLOGY OF RICKETS

Type I collagen comprises 85% to 90% of the organic matrix proteins of bone. A coiled triple helix of two polypeptide alpha I chains and an alpha 2 chain are cross-linked by disulfide bonds and bound by telopeptide-pyridinium links into bundles of collagen fibrils united into fibers [24]. Ten percent to 15% of bone matrix is noncollagenous protein products of the osteoblast, including chondroitin sulfate, heparin sulfate, growth-promoting and cell-attachment proteins, cytokines, and growth factors. As the calcium x phosphorus product exceeds solubility, primarily passive calcification of extracellular matrix proceeds [25]. Rickets represents a deficit in endochondral calcification of the cartilaginous growth plate in children with open epiphyses. Thus, active linear growth is required for the development of rickets. When vitamin D stores are deficient, mineralization of preformed osteoid of the trabecular, endosteal, and periosteal bone surfaces is delayed. Cartilage cells in the hypertrophic zone become disorganized with enlargement of the zone of maturation and the appearance of a chaotic and irregular process of provisional calcification [26]. The osteoid seam widens [27]. Rickets is usually accompanied by osteomalacia, impaired mineralization of the bone matrix.

Mineralization of cartilage is required for growth of metaphyseal blood vessels into the growth plate. When deficits of calcium or phosphorus impede cartilage mineralization, vascular invasion and subsequent removal of cartilage is delayed, growth plate tissues accumulate, and the border between the growth plate and metaphysis is obscured. The primary spongiosa becomes inadequately mineralized and the haversian systems in cortical bone fail to develop properly [27].

CLINICAL PRESENTATIONS OF RICKETS BY AGE

Neonates of severely vitamin D deficient mothers may present with “congenital rickets” manifest by hypocalcemia and/or radiographic evidence of rickets or fractures, sometimes detected incidentally on chest films [28]. Osteopenia of prematurity is discussed below. In infants <6 months of age, symptomatic hypocalcemia causes seizures and, on occasion, stridor or cardiomyopathy with cardiac dilatation. Softened bones of the skull may result in a persistently enlarged anterior fontanel, widened sutures, and craniotabes. Other associations may include iron deficiency anemia, the von Jacksch-Luzet syndrome of anemia, leucocytosis, thrombocytopenia, and hepatosplenomegaly that remits rapidly with vitamin D replacement. In the first year of life, widening of the wrists and ankles and prominence of the costochondral junctions (“rachitic rosary”) result from accumulation of unmineralized cartilage, and an exaggerated demarcation below the rib cage (“Harrison’s groove”) forms when the diaphragm contracts against the softened ribs. As weight-bearing begins, bow legs (genu varum) or knock-knees (genu valgum) result (Fig. 3) [29]. Skeletal anomalies usually reflect long-standing disease. Dental eruption is delayed and enamel hypoplasia may occur. Rickets is generally encountered before a year and a half of age, with a peak frequency between 4 and 12 months [6]. Researchers
recently described a group of breast-fed African-American infants with nutritional rickets in North Carolina. Their median age was 15.5 months, and they presented with failure to thrive, skeletal changes, hypocalcemic seizures, and tetany [30].

Older children with rickets complain of bone pain and fatigue, or present with pneumonia secondary to limited ventilatory effort and respiratory obstruction [6,31]. In adolescence, especially in girls in early to mid-puberty with low calcium and vitamin D intake, complaints of extremity pain and weakness may progress to hypocalcemic tetany or convulsions. Genu valgum and a waddling gait suggest advanced disease [32].

**Fig. 3.** Clinical signs of calcium-deficiency rickets. (A) Genu varum. (B) Windswept deformity. (C) Genu valgum. (D) Wrist enlargement. (E) Rib beading. (From Hochberg Z. Vitamin D and rickets. Basel (Switzerland): S. Karger AG; 2003. p. 112; with permission.)
BIOCHEMICAL CHANGES IN RICKETS

Biochemical changes of rickets reflect the duration and severity of disease (Table 2). In most infants and children with vitamin D deficiency rickets, serum total calcium levels are borderline-normal or low, phosphate values are reduced, and alkaline phosphatase and PTH concentrations are increased. Initially, serum calcium levels decline, reflecting a lack of vitamin D action on intestinal calcium transport, prompting development of secondary hyperparathyroidism. If calcidiol deficits are not severe, PTH induction of 1,a-hydroxylase activity may raise 1,25(OH)2D levels sufficiently to increase intestinal calcium absorption and transiently reestablish normocalcemia. Elevated PTH levels lower circulating phosphorus concentrations by reducing renal reabsorption of phosphate. Thus, the presence of hypophosphatemia in the hypocalcemic neonate is a key finding for discriminating vitamin D disorders from various forms of hypoparathyroidism with high serum phosphate. Subsequently, serum calcium again declines as reduced osteoclastic resorptive action is insufficient to maintain normocalcemia. Altered tubular reabsorption of bicarbonate results in a mild hyperchloremic acidosis, and increased bone turnover is reflected in elevated levels of alkaline phosphatase, an important marker for following healing once vitamin D replacement therapy is initiated. Low levels of 25-hydroxyvitamin D (calcidiol) (<10–12 ng/mL) confirm vitamin D deficiency rickets in children [33]. Concentrations of 1,25(OH)2D range from low normal to high, reflecting the stimulatory effects of increased PTH on renal 1-alpha hydroxylase activity, but calcitriol values remain inappropriately low given the elevated PTH [29]. Concentrations of serum osteocalcin are low, while levels of carboxy-terminal extension of procollagen type I (PICP), a marker of bone formation, and carboxy-terminal cross-link telopeptide of type I collagen (ICTP), a marker of bone resorption, are increased in infants with vitamin D deficiency rickets, reflecting increased collagen turnover. These values rise transiently when vitamin D supplementation is begun, then normalize as the manifestations of rickets heal [34].

ROENTGENOGRAPHIC DIAGNOSIS OF RICKETS

Early radiologic changes of rickets are best seen in areas of rapid bone growth at the epiphyses in the hands and knees (Fig. 4). In younger children, the distal

---

**Table 2**

<table>
<thead>
<tr>
<th>Vitamin D deficiency</th>
<th>Calcium</th>
<th>Phosphate</th>
<th>Alkaline phosphatase</th>
<th>25OHD</th>
<th>1,25(OH)2D</th>
<th>Parathyroid hormone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>N, ↓</td>
<td>N, ↓</td>
<td>↑</td>
<td>↓</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Moderate</td>
<td>N, ↓</td>
<td>↓</td>
<td>↑↑</td>
<td>↓</td>
<td>↓, N, ↑</td>
<td>↑</td>
</tr>
<tr>
<td>Severe</td>
<td>↓</td>
<td>↓</td>
<td>↑↑</td>
<td>↓↓</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

Abbreviations: N, normal; ↓, low levels; ↓↓, very low levels; ↑, high levels; ↑↑, very high levels.

ulnae are prominently affected while in older subjects the metaphyses above and below the knee are most likely to show rachitic change. There is widening of the radiolucent area separating the metaphyses and epiphyses with metaphyseal fraying and cupping [29], resembling the end of a paint brush [35]. Metaphyseal cupping may be caused by stress upon ligamentous attachments that pull cartilage cells peripherally, causing microfractures of the primary spongiosa [35,36]. Femoral and tibial bowing develop as children begin to crawl and ambulate. Genu valgum reflect softening of bone and poor muscle tone. In the pelvis, coxa vara and protrusion acetabuli occur. In ill preterm infants, rarification of the metaphyseal and metadiaphyseal regions (osteopenia of prematurity) suggests early rachitic disease; more characteristic metaphyseal changes require weight-bearing and normal linear growth. Epiphyseal widening and metaphyseal irregularities appear after several months and acute and healing fractures of the ribs and extremities are not uncommon [35]. With therapy, healing appears as a dense metaphyseal band of provisional calcification.

Several approaches have been studied to diagnose metabolic bone disease in preterm infants. The gold standard is dual energy x-ray absorptiometry (DXA) to measure bone mineral density [37]. Plain radiographs are only useful in diagnosis of fractures, as it takes a reduction of 20% to 50% in bone mineral density before changes are seen [37,38].

PERINATAL PHYSIOLOGY OF CALCIUM AND VITAMIN D
Worldwide, pregnant women have a high prevalence of hypovitaminosis D [39–42]. The causes of maternal vitamin and mineral deficiencies include short
interpartum intervals, deficient vitamin D and calcium intake, decreased exposure to sunlight (due to living in northern latitudes, pollution, using sunscreens, being dark-skinned, wearing cultural attire that covers most of the body, or staying indoors), or a malabsorptive disease. An infant born to a mother deficient in vitamin D can present with congenital rickets. This disorder is treated by providing vitamin D and calcium supplements to the infants titrated to decrease alkaline phosphatase levels and to promote skeletal healing [43,44]. Maternal vitamin D concentrations during pregnancy affect skeletal growth in infancy as well as accretion of bone mass during childhood. For example, deficient maternal 25(OH)D status during pregnancy results in reduced bone-mineral content of children at 9 years of age [45,46]. Transfer of calcium from mother to fetus is vital for bone deposition in the developing skeleton. A total of 30 to 35 g of calcium accrues during normal gestation with 80% of the transfer occurring during the third trimester [47,48].

Maternal 1,25(OH)2D levels rise two- to threefold during gestation as calcitriol is produced by the decidua and placenta. Mothers’ PTHrP concentrations also increase, up-regulating 1α-hydroxylase activity and synthesis of 1,25(OH)2D, increasing intestinal calcium absorption by 33% [36,48]. Calcium is actively transported from the placenta to the fetus via a magnesium adenophosphate-dependent calcium pump while calcium-sensing receptors in the placenta help maintain calcium homeostasis [36]. 1α-hydroxylase activity in the placenta and fetal kidney provide additional supplies of 1,25(OH)2D to the fetus. Functioning receptors for 1,25(OH)2D are present in the fetal intestine by the end of the first trimester. However, their role in fetal calcium metabolism is not essential for skeletal formation, as patients with vitamin D receptor mutations are born with normal bone mineralization [48]. Passive or facilitative transplacental transfer of 25(OH)D and 24,25(OH)2D results in cord levels that are 66% to 80% respectively of maternal levels throughout pregnancy [48,49].

**VITAMIN D AND LACTATION**

Postpartum, maternal 1,25(OH)2D and PTH levels are low to low-normal. Nevertheless, calcium levels in lactating women are higher than in nonpregnant controls as PTHrP promotes calcium resorption from bone for transfer to breast milk. Women nursing for at least 6 months experience a 3% to 10% decrease in bone mineral density. Bone mineral density increases after weaning [48,50]. Calcium supplementation during lactation has minimal effects in increasing neonatal bone mineral density [50]. However, increasing daily dietary vitamin D intake to 4000 IU has been shown to improve 25(OH)D stores in both mothers and nursing infants without toxicity [51].

Once placental transfer of calcium and vitamin D is terminated by delivery, calcium concentrations fall in the first 24 to 48 hours of life, returning to childhood levels by day of life 5 to 8. This relative hypocalcemia stimulates increased secretion of PTH, raising neonatal concentrations of 1,25(OH)2D [36,47,48]. From birth to about 8 weeks of age, infant 25(OH)D levels depend
on maternal concentrations. As breast milk contains inadequate concentrations of vitamin D, a critical source of vitamin D for breast-fed infants is sun exposure [52,53]. To keep an infant’s 25(OH)D levels >11 ng/mL, an exclusively breast-fed infant <6 months of age should conservatively spend 30 minutes per week in the sun wearing only a diaper, or receive 2 hours a week of sunlight fully clothed without a hat to have adequate 25(OH)D levels [54]. However, the American Academy of Pediatrics committee on environmental health recommends that infants under 6 months should avoid direct sunlight [55]. Thus, to maintain appropriate levels of 25(OH)D, infants who are mostly breast-fed and who do not receive requisite sun exposure need dietary supplementation. The American Academy of Pediatrics guideline for prevention of rickets and vitamin D deficiency states that infants consuming <500 mL of vitamin-D–fortified formula should receive a daily supplement of 200 IU of vitamin D. The authors recommend an intake of at least 400 IU of vitamin D daily. Currently, in the United States, infant formula must contain a minimum of 400 IU/L of vitamin D, ensuring that infants drinking 500 mL/d will receive 200 IU/L of vitamin D [56].

**PRETERM INFANTS**

In the first 3 days of life, premature infants may experience hypocalcemia from immature PTH secretion and reduced vitamin D synthesis. Although able to 1α-hydroxylate 25(OH)D, premature infants have lower levels of 25(OH)D. With a shortened gestation time, such infants forego the benefits of mechanical stimulation of bone in utero from kicking against the uterine wall [57]. In sick preemies especially, the stress of intercurrent illnesses, inadequate dietary intake, absence of sun exposure, and poor calcium, phosphate and 25(OH)D stores, create risk for osteopenia of prematurity and metabolic bone disease, often presenting in the first 2 months of age with poor growth and occult fractures detected incidentally on chest radiograph. The incidence of metabolic bone disease is 50% in preterm infants who weigh <1000 g and 30% for infants weighing <1500 g [58]. Because phosphorus and calcium cannot be combined in intravenous fluids because of risk of precipitation, failure to provide sufficient concentrations of phosphorus to parenterally alimented infants may occur. An excess of either mineral leads to urinary excretion and deficient bone mineralization. Thus, for parenteral feeds, a calcium/phosphate ratio of 1.7:1.0 is recommended, and for enteral feeds, the calcium/phosphate ratio should be 2:1 [58]. Exercising of extremities against passive resistance in preterm infants may also be beneficial in increasing bone mineral content [57].

Frequent treatment with glucocorticoids and theophylline contributes to undermineralization of bone. Steroids reduce production of 1,25(OH)₂D and increase bone matrix resorption, while theophylline interferes with calcium absorption from the gut [36]. Maximum calcium transport occurs during the third trimester, and the lack of this critical calcium accumulation leads to a greater need for postnatal calcium intake. Premature infants with feeding intolerance may be unable to tolerate adequate enteral nutrition. Sufficient protein intake
is necessary to assure bone collagen synthesis into which hydroxyapatite is deposited for optimal bone mineralization [58].

**HYPOVITAMINOSIS D AND RICKETS IN OLDER CHILDREN AND ADOLESCENTS**

Vitamin D deficiency, which may be clinically unapparent, is not uncommon among older children and teens. In growing adolescents, attainment of normal peak bone mass may be affected by hypovitaminosis D, resulting in increased bone remodeling that adversely affects bone mineral acquisition. A study of healthy adolescents examined at a Boston health clinic revealed that 40% had vitamin D levels <20 ng/mL, 24% <15 ng/mL and approximately 5% <8 ng/mL [9]. In Maine, 48% of a group of girls aged 9 to 11 sampled at the end of winter were vitamin D deficient [59]. Children adopted by American parents from the former Soviet Union have also been reported at risk [60]. Vitamin D and PTH levels were determined in a cohort of 54 male adolescents enrolled in a training school near Paris. Samples were taken every 6 months over a period of 18 months with the first evaluations in September. Levels of 25(OH)D rose in summer while intact PTH values declined, with the inverse pattern occurring in winter. Intact PTH concentrations varied from 4.18 (±1.18) and 4.11 (±1.35) pmol/L in winter to 2.44 (±0.82) and 2.71 (±0.71) pmol/L in summer. Vitamin D levels measured during the two winter samplings were <10 ng/mL in 72% of subjects during the second year and 68% during the third year. Supplementation with vitamin D eliminated the seasonal variations. Based on a nonlinear regression analysis, intact PTH levels rose sharply when 25(OH)D values declined below 30 nmol/L [61].

Immigrant children living in Western Europe have an increased risk of rickets. Asian adolescents from India, Pakistan, and Bangladesh living in Britain and Turkish and Moroccan children resident in the Netherlands have been particularly susceptible [62]. Risk factors in this population are felt to include high latitude, religious practices that require the body to be extensively covered, staying indoors, and vegetarian diets low in calcium [33].

**THE ROLE OF CALCIUM DEFICIENCY IN CHILDHOOD RICKETS**

Nutritional rickets has been reported in several tropical countries despite high levels of sun exposure and vitamin D sufficiency. In fact, in parts of Africa, India, Asia, and the Middle East, rickets is reported among the five most common disorders of childhood [63]. Studies in South Africa and Nigeria suggest that dietary deficiency of calcium may also cause rickets, a finding that has also been reported in the United States [64]. A genetic predisposition to metabolic bone disease may contribute to rickets and osteomalacia in some of these patients as affected subjects frequently report a greater proportion of first-degree relatives with rickets [65].

Skeletal calcium deposition begins early in fetal life and about 25 g accrue in utero [66]. While breast milk contains less calcium than cow’s milk (340 mg/L versus 1.330 mg/L), the calcium ion in breast milk is more avidly absorbed
from the gut than calcium contained in cow’s milk (55% versus 38%) [63]. A shorter duration of breast-feeding has been reported to reduce calcium content of breast milk [67] and infant feeding with soy-based formulas may also play a role in calcium deficiency. Soy-based formulas may contain phytic acid, a calcium binder, as well as a low calcium/phosphate ratio [68].

By adulthood, the skeleton contains 1300 g of calcium [69]. About 60% of total adult bone calcium is deposited during adolescence, with 26% in the 2 years bracketing peak velocity of bone mineral content accrual. Adolescents require 1300 to 1600 mg of elemental calcium daily to absorb the 220 mg/d of calcium needed to optimize adult bone calcium mass [70]. Bone mineral content achieves 50% of maturational peak and bone size 80% of peak by age 7 years. Femoral and lumbar spine bone mineral content increases 50% to 150% during puberty, during which time volumetric bone mineral density rises by 11% to 30% [71].

Children in the African studies were reported to have calcium intakes of approximately 200 mg/d, normal serum levels of 25(OH)D, and elevated concentrations of 1,25(OH)_{2}D [72,73]. In rachitic children in Nigeria, calcium supplementation with or without vitamin D was more effective at healing radiographic and biochemical manifestations of rickets than treatment with vitamin D alone [74,75]. Following calcium supplementation, serum 25(OH)D levels rose significantly and 1,25(OH)_{2}D values declined, supporting reports suggesting that a low dietary intake of calcium reduces calcidiol levels. The mechanism of this reduction may result from PTH-stimulated increased levels of calcitriol that have been shown to lower circulating 25(OH)D levels by increasing its metabolic clearance rate [76]. In rats, in vivo administration of calcitriol reduces 25(OH)D levels in a time-and-dose–dependent fashion and, in kidney homogenates in vitro, calcitriol increases conversion of 25(OH)D to 24,25(OH)_{2}D sevenfold [77]. Grains that are central to the African diet contain high concentrations of phytates, oxylates, tannates, and phosphates that inhibit calcium absorption [63]. Chapatti and raghif, unleavened breads eaten in South Asia and the Middle East, are also high in phytates [78].

**PREVENTION OF VITAMIN D DEFICIENCY**

Endogenous vitamin D synthesis, long-term storage in fat, and additional effects of mineral intake, along with factors associated with age, sex, skin color, and sun exposure complicate the establishment of an recommended daily allowance for Vitamin D. An intake standard described as adequate defines sufficient ingestion of vitamin D to maintain healthy circulating concentrations [63]. The daily requirements of calcium, phosphorus, and vitamin D as defined by the European Society of Paediatric Endocrinology are shown in Table 3 [63]. In utero, the rate of fetal skeletal mineralization increases from deposition of 100 mg daily of calcium by 28 weeks to 350 mg daily at 35 weeks [79]. Because the concentrations of vitamin D in breast milk are low at 240 to 340 mg/L (15–50 IU/L), and because the vitamin D intake of the breast-feeding mother may be inadequate to prevent rickets in her infant, all breast-fed infants should
receive 400 IU of supplemental vitamin D daily, as should other infants with suboptimal sun exposure or dietary vitamin D supplies. A Centers for Disease Control analysis of data from the Third National Health and Nutrition Examination Survey (NHANES III) revealed that 48% of African-American women aged 15 to 49 had calcidiol levels <15 ng/mL at the end of winter [80]. Vitamin D supplementation should be provided throughout childhood and adolescence for children with suboptimal sun exposure and dietary intake [81].

**TREATMENT OF NUTRITIONAL RICKETS**

Clinically diagnosed rickets may be safely and effectively treated with the daily administration of 1000 to 2000 IU of vitamin D daily for several weeks. When roentgenographic healing is seen by 2 to 4 weeks of treatment, the dosage can be lowered to 400 IU/d [63]. Serum calcium and phosphorus levels generally correct within a few days, while circulating PTH and alkaline phosphatase may require several months to normalize [79]. In situations where compliance or absorption is of concern, subjects may be given 10,000 to 50,000 U/mo for 3 to 6 months or a single intramuscular injection of 300,000 to 600,000 U of vitamin D [82]. Elemental calcium (40 IU) should be coadministered to avoid acute hypocalcemia that may occur as the bone rapidly remineralizes (“hungry bone” syndrome). In addition to following levels of alkaline phosphatase as a biochemical indicator of healing, monitoring to avoid hypercalcemia, hypercalciuria, and nephrocalcinosis is also recommended [34].

**VITAMIN D’S OTHER ROLES (IMMUNITY, BLOOD PRESSURE MAINTENANCE, AND CANCER PREVENTION)**

VDR is present not only in the small intestine, skin, kidney, and bones, but also in many other tissues, including skeletal muscle, colon, breast, prostate, brain,
pancreas, heart, T and B lymphocytes, and monocytes (Fig. 5). Many of these cells are also able to convert 25(OH)D to 1,25(OH)₂D. The latter inhibits cell growth by increased cell differentiation, reduced cell proliferation, apoptosis, and antiangiogenesis [6,83,84]. Epidemiologic data suggest that living in higher latitudes and having a lower 25(OH)D levels lead to increased risk of many types of cancer. Early data show that a vitamin D analog, seoclacitol, was effective in inhibiting progression of hepatocellular carcinoma [85]. The property of 1,25(OH)₂D to inhibit proliferative states is used in treating such hyperproliferative skin conditions as psoriasis [83].

Vitamin D may also have a role in preventing autoimmune diseases, such as type 1 diabetes, rheumatoid arthritis, Crohn’s disease, and multiple sclerosis. A

**Fig. 5.** Noncalcemic functions of 1,25(OH)₂D. Vitamin D coming from the photoproduction of previtamin D or coming from the diet is converted in the liver to 25(OH)D by the vitamin 25-OHase. In the kidneys, 25(OH)D is converted by 1-OHase. 1,25(OH)₂D not only regulates calcium and phosphorus metabolism but can also stimulate the pancreas to produce insulin and to down-regulate the renal production of renin. 1,25(OH)₂D also interacts with its nuclear vitamin D receptor (VDR) in a wide variety of tissues and cells and helps maintain normal cell proliferation and differentiation. 25(OH)D can also be converted to 1,25(OH)₂D in a wide variety of cells, including those of the colon, prostate, and breast, for the autocrine production of 1,25(OH)₂D. It is believed that the autocrine production of 1,25(OH)₂D is important for regulating cell growth and maturation, which decreases the risk of the cell becoming malignant. 25(OH)D also is metabolized in macrophages by the 1-OHase to produce 1,25(OH)₂D. The expression of the VDR and 1-OHase is up-regulated when toll-like receptor 2/1 (TLR2/1) is stimulated by lipopolysaccharide (LPS). This results in an increase in the expression of the VDR and the 1-OHase. The increased production of 1,25(OH)₂D increases the nuclear expression of cathelicidin in the macrophage, which is a cationic peptide that causes the destruction of infective agents, including *Myobacterium tuberculosis*. mRNA, messenger RNA; RXR, retinoid X receptor. (From Holick MF. Resurrections of vitamin D deficiency and rickets. J Clin Invest 2006;116(8):2062–72; with permission.)
large longitudinal birth-cohort study of children showed that children supplemented with 2000 IU of vitamin D daily reduced their risk of developing type 1 diabetes by 80% [86]. Nonobese diabetic (NOD) mice, which typically develop type 1 diabetes, were supplemented with 1,25(OH)₂D throughout their lives. These NOD mice were 80% less likely to develop type I diabetes [83] than NOD mice without the supplement. Vitamin D has also been implicated in regulating blood pressure. A mouse model showed that 1,25(OH)₂D inhibited renin and angiotensin expression and thus lowered blood pressure [83].

SUMMARY

The recent resurgence of the ancient disease of vitamin D deficiency rickets and the widespread presence of hypovitaminosis D across the age spectrum pose significant challenges for today’s clinicians. Furthermore, new research into previously unsuspected actions of vitamin D in multiple cell systems offer the possibility that vitamin D will play an increasingly important role in our understanding of a wide variety of disease states.

References


Immunization remains the most cost-effective method of delivering health care, particularly for children. The National Commission on Prevention Priorities recent update to the 2001 ranking of clinical preventive services listed childhood immunization series as second only to aspirin chemoprophylaxis for the prevention of cardiovascular events in adults [1]. Both 2005 and 2006 saw several changes in the childhood and adolescent immunization schedules with the approval of several long-awaited vaccines. The purpose of this article is to provide readers with a comprehensive overview of the new changes and developments in the already hectic childhood and now adolescent immunization schedules (Figs. 1 and 2). For the sake of this discussion, the authors have divided this article into new vaccines for adolescents followed by new vaccines for children as well as any updates in the vaccination schedules for children.

VACCINES FOR ADOLESCENTS

Adolescents continue to provide health care providers with ongoing challenges for providing preventive health services. Vaccines traditionally recommended for adolescents included booster vaccines for tetanus and diphtheria (Td), as well as mumps, measles, and rubella (MMR) if not given earlier. In the early 1990s, hepatitis B virus vaccine was added to the series as catch-up to the recommended vaccination series for newborns and infants [2]. Since the beginning of 2005, new vaccines approved for adolescents include tetanus, reduced diphtheria toxoids and acellular pertussis vaccines (Tdap), human papilloma virus (HPV) vaccine, and tetravalent meningococcal conjugate vaccine (MCV4). These vaccines represent not only extremely important public health advances but also have the potential to significantly improve health care through prevention for this extremely vulnerable group of young individuals.

Tetanus, Diphtheria Toxoids, and Pertussis Vaccines

Pertussis is the only vaccine-preventable childhood illness for which rates in the United States (US) are increasing. Some of this increase may be due to better

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diagnosis and intensive regional surveillance. Despite the increase, underdiagnosis and lack of intensive national surveillance programs probably still significantly underreport the actual number of cases [3]. Numbers of cases reported to the Centers for Disease Control (CDC) reached 25,616 in 2005 and 25,827 in 2004 in contrast to 11,647 cases reported in 2003 [4–6]. The highest rates of increase are among children and adolescents 10 to 19 years of age [7].

**Fig. 1.** Recommended immunization schedule for persons aged 0 to 6 years—United States, 2007.
Possible causes of this resurgence are several fold [3,8]. Most cases in persons older than 10 years of age are due to waning immunity [9–11]. Disease-induced immunity itself does not last much longer than that induced by vaccination [12]. Mutations in the pertactin and pertussis toxin genes have been documented; however it is not clear at this time if this is playing a significant role [12]. The use of less immunogenic vaccines in the 1990s may also have contributed to this resurgence; but by far the most important reason seems to be increased awareness by public health personnel as well as enhanced

### Fig. 2. Recommended immunization schedule for persons aged 7 to 18 years—United States, 2007.

This schedule indicates the recommended ages for routine administration of currently licensed childhood vaccines, as of December 1, 2006. For children aged 7-18 years, additional information is available at http://www.cdc.gov/nip/rec upd tbl/2007.htm. Any dose not administered at the recommended age should be administered at any subsequent visit, when indicated and feasible. Additional vaccines may be licensed and recommended during the year. Licensed combination vaccines may be used whenever any components of the combination are indicated and other components of the vaccine are not contraindicated and if approved by the Food and Drug Administration for that dose of the series. Providers should consult the respective Advisory Committee on Immunization Practices statement for detailed recommendations. Clinically significant adverse events that have been immunization should be reported to the Vaccine Adverse Event Reporting System (VAERS). Guidance about how to obtain and complete a VAERS form is available at http://www.vaers.hhs.gov or by telephone, 800-822-7967.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Age</th>
<th>Range of recommended ages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tetanus, Diphtheria, Pertussis</strong></td>
<td>7-10 years</td>
<td>Tdap</td>
</tr>
<tr>
<td><strong>Human Papillomavirus</strong></td>
<td>11-12 years Tdap, 16 years for HPV</td>
<td>HPV (3 doses)</td>
</tr>
<tr>
<td><strong>Meningococcal</strong></td>
<td>13-14 years Tdap, 15 years for MCV4</td>
<td>MCV4</td>
</tr>
<tr>
<td><strong>Pneumococcal</strong></td>
<td>15-16 years</td>
<td>PPSV23</td>
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<tr>
<td><strong>Influenza</strong></td>
<td>16-18 years</td>
<td>Influenza (Yearly)</td>
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<tr>
<td><strong>Hepatitis A</strong></td>
<td>17-18 years</td>
<td>HepA Series</td>
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<tr>
<td><strong>Hepatitis B</strong></td>
<td>18-19 years</td>
<td>HepB Series</td>
</tr>
<tr>
<td><strong>Inactivated Poliovirus</strong></td>
<td>19-20 years</td>
<td>IPV Series</td>
</tr>
<tr>
<td><strong>Measles, Mumps, Rubella</strong></td>
<td>21-26 years</td>
<td>MMR Series</td>
</tr>
<tr>
<td><strong>Varicella</strong></td>
<td>27-35 years</td>
<td>Varicella Series</td>
</tr>
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</table>

8. **Hepatitis A vaccine (HepA)**, (minimum age: 12 months)
   - The 2-dose series in the setting should be administered at least 6 months apart.
   - HepA is recommended for certain other groups of children, including in areas where vaccination programs target other children. See MMWR 2008;57 RR-19.
   - A 3-dose series of RotaTeq HIB is licensed for children aged 11-15 years.
   - Inactivated poliovirus vaccine (IPV), (minimum age: 4 weeks)
   - For children who received an all-IPV or all-Hib pertussis (DTP/Hib) 4 dose, the fourth dose is not necessary if the third dose was administered at age 12-15 months.
   - Both IPV and OPV were administered as part of a series. A total of 4 doses should be administered, regardless of the child’s current age.
   - Measles, mumps, and rubella vaccine (MMR), (minimum age: 12 months)
   - If not previously vaccinated, administer 2 doses of MMR during any visit, with 4-6 weeks between the doses.

9. **Varicella vaccine**, (minimum age: 12 months)
   - Administer 2 doses of varicella vaccine to persons without evidence of immunity.
   - Administer 2 doses of varicella vaccine to persons aged ≥13 years at least 4-8 weeks apart. Do not repeat the second dose if administered ≥28 days after the first dose.
   - Administer 2 doses of varicella vaccine to persons aged ≥13 years at least 4 weeks apart.

surveillance and diagnostic facilities leading to greater numbers of recognized cases [4,12].

In the prevaccine era, pertussis was believed to be a disease of preschool-aged children. Less than 10% of known cases reported occurred in infants younger than 1 year of age, and reported rates were even less amongst adolescents and adults [13]. Following routine immunization of children in the 1940s, the number of cases declined dramatically from 200,000 cases annually to 1010 cases in 1976 [4]. Due to this and the belief that the vaccine conferred immunity for a person’s lifetime, no pertussis-containing vaccine was licensed for use in the US in persons aged 7 years and older. Data from Europe and the US support the fact that infections in adolescents and adults were common in the prevaccine era [14,15].

Available data also indicate that *B. pertussis* infections continue to prevail in adolescents and adults of all ages. Studies investigating prolonged cough illnesses in adults and adolescents, as well as studies looking at antibody titer rise to pertussis toxin in populations over time, all support this conclusion [16–23]. Adolescents serve as reservoirs of *B. pertussis* and can be the source of pertussis for young infants who have the highest risk of pertussis-related complications that include hospitalization and death. The current pertussis-related mortality rate among infants in the US is 2.4 deaths per 1 million, and fatal cases in young infants account for more than 90% of all deaths from pertussis [6]. Rates of reported pertussis cases are 40 fold to 160 fold less than actual illness rates, and asymptomatic infections are 4 to 22 times more common than symptomatic infections [12].

Given the evidence, it is clear that adults and adolescents serve as the major source of infection in unvaccinated children, hence the need for a vaccine against pertussis that would protect adolescents as well as adults. A secondary objective is to reduce the reservoir of pertussis within the population at large and thus reduce the incidence of disease in those who are unimmunized, particularly young infants.

The US Food and Drug Administration (FDA) [24,25] licensed two vaccines containing Tdap products in the spring of 2005. Each Tdap product was licensed as a single dose booster immunization against tetanus, diphtheria, and pertussis. Boostrix (GlaxoSmithKline Biologicals, Rixensart, Belgium) was licensed May 3, 2005, for use in people 10 through 18 years of age, and Adacel (SanofiPasteur, Toronto, Ontario, Canada) was licensed on June 10, 2005, for use in people 11 through 64 years of age. No vaccine containing pertussis antigens alone is licensed in the US. A comparison of relevant tetanus and diphtheria toxoids and acellular pertussis (DTaP) and Tdap vaccines is shown in Table 1.

Criteria for Tdap licensure were on the basis of clinical trials demonstrating immunogenicity not inferior to US licensed tetanus, reduced diphtheria toxoid (Td), or pediatric DTaP products and an overall safety profile clinically comparable to US-licensed Td products [4,26,27]. In a noninferiority trial, immunogenicity, efficacy, or safety end points are demonstrated when a new product is
at least as good as a comparator on the basis of a predefined and narrow margin for a clinically acceptable difference between the study groups. The efficacy of the tetanus and diphtheria toxoid component of each Tdap was based on the immunogenicity of the antigens compared with US-licensed Td using established correlates of protection.

In contrast to tetanus and diphtheria, no well-accepted serologic or laboratory correlate of protection for pertussis exists [28]. A consensus was reached at the 1997 meeting of the Vaccines and Related Biological Products Advisory Committee that the efficacy of the pertussis components of Tdap administered to adolescents and adults could be inferred using a serologic bridge to infants vaccinated with pediatric DTaP during clinical endpoint efficacy trials for pertussis [29]. For each Tdap product, the immune response (geometric mean antibody concentration) of adolescents to each vaccine pertussis antigen after a single dose of Tdap was compared with the immune response of infants after three doses of pediatric DTaP that included the same pertussis components as the Tdap being assessed.

Immune responses to tetanus and diphtheria toxoids were comparable between the Boostrix and Adacel groups compared with the Td group [30,31]. The efficacy of the pertussis components of Boostrix was evaluated by comparing the immune response of adolescents vaccinated with a single dose of Boostrix with the immune responses of infants vaccinated with three doses of Infanrix [32]. Boostrix contains the same tetanus, diphtheria toxoids and pertussis antigens as those in Infanrix (pediatric DTaP) but in reduced quantities. For Adacel, the immune responses were compared between adolescents immunized with one dose of Adacel with immune responses of infants vaccinated...
with three doses of Daptacel [33]. Adacel contains the same tetanus, diphtheria toxoids, and pertussis antigens as those in Daptacel but in reduced quantities. The geometric mean antibody concentrations for both Boostrix and Adacel when compared with Infanrix and Daptacel were not inferior.

Aluminum is present as an adjuvant in Boostrix, and the vaccine does not contain any thimerosal. Primary safety studies conducted in the US demonstrated no significant serious adverse events when compared with Td. Pain at the injection site was the most frequently reported local adverse event; 75% of subjects in the Boostrix group and 72% of subjects in the Td group reported some degree of pain [26].

Adacel contains no thimerosal and has aluminum as the adjuvant. Primary safety studies in the US demonstrated no significant side effects amongst adolescents immunized with Adacel in comparison to Td. Pain at the injection site was the most frequently reported adverse event amongst adolescents in both groups. In the group immunized with Adacel, 78% of subjects reported pain at the injection site compared with 71% of those in the Td group. Adverse events reported within 15 days of immunization were similar in both groups except for fever of 100.4°F or higher, which was reported in a greater proportion of adolescents in the Adacel group compared with the Td group (5% versus 2.7%) [27].

Previously, for routine administration, the American Academy of Pediatrics (AAP), CDC, the American Academy of Family Physicians, and the American Medical Association had recommended an adolescent booster dose of Td at the 11- to 12-year visit. A 10-year interval between subsequent routine booster Td doses and a 5-year interval for wound management was also recommended [34,35]. With the licensure of the two Tdap vaccines, the current recommendations are adolescents 11 to 18 years of age, should receive a single dose of Tdap instead of Td for booster immunization against tetanus, diphtheria, and pertussis if they have completed the recommended childhood DTP/DTaP immunization series and have not received Td [35]. Repeat doses may be recommended in the future.

An interval of at least 5 years between Td and Tdap immunization is suggested to reduce the risk of local and systemic reactions after Tdap immunization although Tdap can be given at shorter intervals. The safety of intervals as short as 2 years between Td and Tdap has been reported [36,37].

Although both Tdap and MCV4 contain diphtheria toxoid, both vaccines may be administered at the same visit to adolescents 11 to 18 years of age if indicated [4]. The AAP recommends a minimum interval of 1 month between the two vaccines if not administered simultaneously [38]. Either Boostrix or Adacel may be used in adolescents who have either not completed the childhood DTP/DTaP immunization series or have completed the series without regard to the type or manufacturer of the vaccines used to complete the primary childhood series [38].

Adolescents who require tetanus toxoid as part of wound management should receive a single dose of Tdap instead of Td if they have not previously
received Tdap. Adolescents 11 to 18 years of age who have a history of pertussis generally should receive Tdap because the duration of protection against *B. pertussis* infection is unknown (and may be as brief as 7 years after natural infection) [39]. Administering pertussis vaccines to persons after a history of pertussis infection presents no safety concerns [38].

Pregnancy is not a contraindication to Tdap or Td immunization. The AAP recommends that pregnant adolescents be given the same considerations for immunization as nonpregnant adolescents [40]. If indicated, administration in the second or third trimester (before 36 weeks of gestation) is preferred. The FDA categorizes Tdap and Td vaccines as category C agents. Well-controlled human and animal reproductive studies acceptable by the FDA have not been conducted for Tdap. Both Tdap manufacturers have established registries for women immunized with Tdap during pregnancy.

Vaccination of pregnant women has been proposed as a strategy to protect infants from pertussis passively before they receive active immunization. The rationale for this strategy is based on observations that maternal antibody titers to pertussis antigens are low but when present may provide some protection because they are actively transported across the placenta [41]. Guidance on the use of Tdap during pregnancy to protect against pertussis is under consideration by Advisory Committee on Immunization Practices (ACIP) of the CDC [4]. The ACIP does, however, recommend that Tdap may be given to women right after delivery and before hospital discharge to try to prevent mothers from getting pertussis and mother-to-infant transmission of pertussis in early infancy.

For individuals older than 18 years of age, the CDC had previously recommended Td boosters for adults beginning 10 years after the adolescent dose. The safety and immunogenicity of only Adacel as a single booster immunization against tetanus, diphtheria, and pertussis have been demonstrated for individuals 19 to 64 years of age.

Current recommendations call for immunization with Tdap instead of Td if more than 10 years have elapsed since the last dose of Td. Detailed recommendations for use of Tdap vaccines in adults are available in the December 15, 2006, issue of Morbidity and Mortality Weekly Report [5].

**Tetravalent meningococcal conjugate vaccine**

Following the introduction of universal immunization in the 1990s for *Streptococcus pneumoniae* and *Haemophilus influenzae* type b, *Neisseria meningitidis* has become the leading cause of bacterial meningitis in children in the United States [42]. There are between 1400 and 3000 cases of invasive meningococcal disease each year in the US with an annual incidence of 0.5 to 1.1 per 100,000 population. Data reported by the CDC from 1991 to 2002 showed a biphasic pattern with the incidence of disease being highest among infants and children younger than 1 year of age and a second lower peak from age 15 years through early adulthood. Although infants and children younger than 11 years of age had the highest incidence of invasive meningococcal disease (38%), adolescents
had the highest case-fatality rate (20%) [43]. Adolescents 15 years and older are more likely than infants and children to have meningococcemia without meningitis (40% versus 20%, respectively), shock at presentation (69% versus 27%, respectively), and a fatal outcome (22.5% versus 4.6%, respectively) [44]. The case-fatality rate across all age groups of 10% to 14% does not reflect the significant morbidity associated with this disease, not to mention the inconsolable loss of a young life to the family as well as community. Complications resulting from the disease include but are not limited to cranial nerve palsies, spastic quadriplegia, loss of a limb, and hearing impairment [45].

*Neisseria meningitidis* has 12 serogroups based on the capsular polysaccharide. However the distribution of serogroups causing disease varies with time, age group, and geographic location. Serogroups A, B, and C account for an estimated 90% of meningococcal disease worldwide [46]. In the United States, serogroup A is uncommon, whereas serogroups B and C are responsible for most cases of disease as well as school and community outbreaks [45]. Serogroup Y is also becoming more prevalent [47]. Sporadic cases of meningococcal disease account for 98% of cases, and it is estimated that 75% to 80% of adolescent meningococcal disease can be accounted for by serogroups A, C, Y, and W135 [45].

Development of meningococcal polysaccharide vaccines was catalyzed in the late 1960s and early 1970s because of increased rates of meningococcal disease amongst military recruits. The first vaccine addressed serogroup C [48,49]. A quadrivalent polysaccharide vaccine (MPSV4 [Menomune-A/C/Y/W135; Sanofi Pasteur, Swiftwater, PA]) was licensed in 1981 for use in children older than 2 years of age as well as adults. Quadrivalent polysaccharide vaccine has been routinely used for immunization of all military recruits and has resulted in a sustained reduction in the incidence of meningococcal disease. Quadrivalent polysaccharide vaccine is also recommended by the AAP for use in children over the age of 2 years with certain high-risk conditions [50].

Quadrivalent polysaccharide vaccine consists of 50 ug each of the A, C, Y, W135 purified meningococcal capsular polysaccharides in a single dose. Protective concentrations of antibodies are usually achieved within 7 to 10 days after immunization. The antibody responses to each of the four polysaccharides in the quadrivalent polysaccharide vaccine are serogroup-specific and independent. In children 2 to 5 years of age, measurable concentrations of antibodies against group A and C polysaccharides decrease substantially during the first 3 years after a single dose of the vaccine. Like other polysaccharide vaccines, it does not generate memory T cells, and attempts to boost protection with repeated vaccination may result in a diminished antibody response. This is because the bacterial polysaccharides comprising the capsule of *N. meningitides* are T-cell independent antigens that stimulate mature B cells but not T lymphocytes. Also like other polysaccharide vaccines, this meningococcal vaccine does not prevent mucosal colonization and therefore does not provide herd immunity through interrupted transmission of *N. meningitides*. These drawbacks make its use for broad public health programs limited.
It was not until 2000 that the ACIP issued guidelines concerning “the modestly increased risk for meningococcal disease among college freshmen, particularly those living in dormitories or residence halls” [51]. This was based on studies conducted within the US assessing the risk of meningococcal disease among college students [52–54]. Other groups at high risk and recommended for immunization included those who had certain medical conditions (terminal complement component deficiencies, anatomic and functional asplenia) travelers to countries with epidemic or hyperendemic meningococcal disease or during outbreak situations for control of disease. As of August 2004, 31 states have adopted legislation requiring colleges to provide information on risks of meningococcal disease to matriculating students and students residing on campus. Eleven of these states mandate immunization of students living on campus unless an immunization waiver is provided [55].

The new tetravalent meningococcal A, C, Y, W135 conjugate vaccine (MCV4 [Menactra; SanofiPasteur, Swiftwater, PA]) was licensed by the FDA on January 14, 2005, for use in individuals 11 to 55 years of age [56]. The basis for licensure was demonstration of noninferiority to MPSV4 for immunogenicity and safety. Tetravalent meningococcal conjugate vaccine is also being considered for licensure by the FDA for use in children 2 to 10 years of age [42]. The rationale for choosing 11 to 12 years was based in part because this is the age at which a booster dose of Td is recommended, and it is expected that adolescents will visit their pediatricians during this time. The second cohort, entering high school students or 15 year olds, whichever came first, was based on the peak incidence of invasive meningococcal disease as well as the need for routine medical visits by adolescents at that age. Once adequate vaccine supply is ensured, it is likely that routine vaccination for all adolescents will be recommended [45].

The tetravalent meningococcal conjugate vaccine contains capsular polysaccharides from serogroups A, C, Y, and W135 conjugated to 48 μg of diphtheria toxoid. Protective concentrations of antibodies are achieved within 8 days of immunization. Conjugation (covalent-coupling) of polysaccharide to a protein carrier that contains T-cell epitopes changes the expression of the immune response to the polysaccharide from T-cell independent to T-cell dependant, resulting in an improved primary response to the polysaccharide and a strong amnestic response at re-exposure.

Comparison of the immunogenicity of MCV4 and MPSV4 in a randomized controlled trial of 881 adolescents 11 to 18 years of age 28 days after immunization revealed that immune responses to MCV4 and MPSV4 were similar for all four serogroups [56].

The recommendation to immunize all children between the ages of 11 and 12 years with catch-up immunization at entry into high school or 15 years of age, whichever comes first, is expected to reduce the rate of invasive meningococcal disease by 32%. This has been extrapolated from the British experience with group C vaccine. Since 1999, all children ages 1 to 17 years in the United Kingdom have received serogroup C vaccine leading to an almost total elimination of type C disease in the United Kingdom [57,58]. Although
implementing universal vaccination seems to be an extremely expensive proposition, with the cost approaching $120,000 per life year saved as opposed to most other vaccines whereby the cost is approximately $20,000 per life year saved, recent data from the CDC suggests that this might be more cost effective than was initially thought. The total cost of immunizing a single adolescent includes both direct and indirect costs [59].

Concerns regarding MCV4 vaccination include the fact that a reduction in the transmission of certain serogroups of \textit{N. meningitides} by vaccination may lead to replacement by other groups not covered by the vaccine. Although this has not been observed in the United Kingdom after use of the type C vaccine, this will need to be tracked. Other concerns include the interrupted supply and intermittent vaccine shortages. In fact, shortly after the approval by the FDA, a vaccine shortage was reported in May 2005 leading to the recommendation by the AAP to hold immunizations for the 11- to 12-year group. Since the resolution of MCV4 shortage, routine immunization is recommended again. This does, however, remain a potential concern for the future.

A safety concern has been the development of Guillain-Barré syndrome among vaccine recipients. As of September 22, 2006, the Vaccine Adverse Event Reporting System received 17 confirmed case reports of Guillain-Barré syndrome in adolescents after receipt of MCV4 vaccine. Fifteen people, 11 to 19 years of age, experienced symptoms within 6 weeks after receiving Menactra. Two other reports of Guillain-Barré syndrome among persons 20 years of age and older have also been confirmed. The symptom onset was 2 to 33 days after vaccination. No causal association has been established, and the recommendations for immunization stand unchanged thus far [60]. Vaccine effectiveness and herd immunity as well as evaluation of the duration of protective antibodies and safety will need to be monitored carefully.

Other meningococcal vaccines being used in Europe but not currently available in the US include three different serogroup C conjugate vaccines. These have been incorporated into the routine infant immunization schedule in the United Kingdom since 1999. By the end of 2005, six other European countries including Ireland, Spain, the Netherlands, Belgium, Iceland, and Portugal had all implemented public immunization campaigns with serogroup C vaccine and experienced significant decline in the incidence of serogroup C disease [61].

There is no currently approved vaccine that would prevent serogroup B infection, which is responsible for most neonatal and early childhood disease as well as a good proportion of adolescent disease. Because the capsular polysaccharide is poorly immunogenic in humans perhaps due to a structural similarity to a human glycoprotein found in neural tissue, other approaches to development of serogroup B vaccines are underway including focus on surface proteins and outer surface proteins of certain epidemic strains.

\textbf{Quadrivalent human papilloma virus vaccine}

In the US, HPV infections of the cervix and vagina are the most common sexually transmitted infections among the young sexually active population [62].
Conservative estimates of the prevalence of HPV in the US are close to 20 million individuals. A recent study estimated that 6.2 million sexually active men and women in the US become infected with HPV each year [63,64]. Of these new infections, 74% occur among sexually active Americans between 15 and 24 years of age who represent 25% of the sexually experienced US population between 15 and 44 years of age. The World Health Organization estimates that globally there are approximately 660 million people infected with HPV with the highest prevalence found in Africa [65].

The CDC has reported a lifetime risk of acquiring HPV infection for sexually active men and women in the US of at least 50%. By 50 years of age, at least 80% of women will have acquired genital HPV infection. The lifetime risk of developing genital warts is approximately 10% in men and women [64,66,67]. In 2005 it was estimated that approximately 10 women would die from cervical cancer in the US each day [68].

Although cervical cancer is not amongst the top five leading causes of death in women in the US, it is the second leading cause of death in US women aged 20 to 39 years of age, second only to breast cancer [69]. Globally cervical cancer is second only to breast cancer as the leading cause of cancer in women [70]. The risk of cancer increases with age as with many cancers; however, almost half of the deaths occur in women less than 55 years of age. Data suggest that HPV infections precede the development of cervical cancer by decades [71,72]. Although it has mostly been studied in the context of cervical cancer, HPV is associated with several other types of malignancies including vaginal, penile, vulvar, and anal carcinomas [73]. In places where routine screening has been properly implemented, mortality from cervical cancer has declined considerably. However data from the US show that up to 11% of women older than 21 years of age are not being screened regularly [74]. Use of screening among adolescents is also limited because of issues related to availability of affordable health care, confidentiality, and the fear of being diagnosed with cancer. In addition to this, routine screening may not identify all cervical abnormalities and hence does not always ensure early intervention [75].

There are more than 100 HPV viruses that are fully sequenced and identified. These viruses have been characterized based on nucleic acid sequence homology rather than serologic reactivity resulting in classification of HPV by genotypes rather than on the basis of serotypes. HPV genotypes mapped to certain phylogenetic clades A5, A6, A7, and A9 have been shown in population-based studies to be associated with a high risk for cancer. This includes type 16 and 18 that have been associated with approximately two thirds of all cervical cancers. Other clades include types that may commonly infect the ano/oral/genital tract but are not associated with cancer development. Included in this group are HPV types 6 and 11 that cause anogenital warts in men and women as well as recurrent respiratory papillomatosis but rarely if ever are found in invasive cancers [76–78].

HPV infection is not systemic and thought to occur through mechanical abrasion of an infected epithelial surface with an uninfected epithelial surface.
Most cases of HPV are clinically asymptomatic. The natural history of HPV subtypes with oncogenic potential is not well understood in men. The only notable exception is the high risk for anal neoplasia resulting from anal HPV infection among men who have sex with men, particularly those who have HIV coinfection [79]. Natural history studies of HPV infection in women show that 90% of HPV infections resolve spontaneously lasting an average of 12 months postinfection [80,81]. The presence of persistent infection with the same high-risk genotype, however, has been shown to confer a strong risk for development of subsequent neoplasia [82,83].

Although the strength of association between high risk HPV infection and invasive cervical cancer is unprecedented in cancer epidemiology with odds ratios exceeding 45 in most cases; this must be interpreted in light of the high prevalence of HPV transient infection among sexually active women and the frequent resolution of such lesions [84]. High risk HPV infection is therefore a necessary but insufficient cause of invasive cervical cancer alone. Other risk factors include multiparity, cigarette smoking, and less consistently oral contraceptive use, as well as coinfection with other sexually transmitted infections [85–90]. Although HPV is undeniably transmitted predominantly through sexual contact, it should be managed less as a typical sexually transmitted infection and more as a strong risk factor predisposing to cervical cancer development. Also, because HPV is an almost ubiquitous but transient infection in most sexually active women, direct screening methods such as those employed for other sexually transmitted infections may not be appropriate for HPV. Availability of a highly effective prophylactic vaccine is what holds real promise. If 100% coverage is obtained, theoretically 50% to 70% of invasive cervical cancers and most genital warts could be prevented [76].

On June 8, 2006, the FDA approved a prophylactic, quadrivalent, three-dose HPV vaccine (Gardasil, Merck Research Laboratories, West Point, PA) for use in females 9 to 26 years of age [91]. Because it is a prophylactic vaccine, it is recommended for use before the onset of sexual activity. The vaccine contains types 6, 11, 16, and 18. Although it is designated as a category B drug, it is not recommended for use during pregnancy. The vaccine prevents infection by inducing neutralizing antibodies against HPV capsid proteins L1 and L2. The vaccine contains “virus-like particles” that mimic the viral capsid antigens but contain no viral DNA.

Placebo-controlled studies of 551, 16- to 23-year-old females, given a prophylactic three-dose regimen of a quadrivalent HPV (type 6, 11, 16, and 18) virus-like particles L1 vaccine resulted in excellent anti-HPV–specific neutralizing antibody responses that led to a 90% reduction in the combined incidence of HPV type-specific persistent infection or cervical or external genital disease. In a subsequent study of this vaccine in more than 12,000 women aged 16 to 26 years, similar immune responses were observed, leading to 100% prevention of HPV 16 and 18 related cervical intraepithelial neoplasia grades two and three, and adenocarcinoma in situ and pre- or noninvasive cervical cancer compared with placebo. These findings suggested that in individuals not yet
infected with HPV, immunization with vaccine would substantially reduce the risk for developing cervical cancer and genital warts later in life [92–94].

On June 29, 2006, the ACIP recommended that the three-dose HPV vaccine be routinely administered to all females 11 to 12 years of age as well as 13 to 26 year olds who have not previously received the vaccine. Noninferior immunogenic responses to all four HPV types in the quadrivalent vaccine permit the bridging of efficacy data that were generated in young women to girls [95]. Females 9 to 10 years of age may be vaccinated at the discretion of the provider. Vaccination is recommended regardless of a previous history of HPV vaccination or abnormal Papanicolaou test result. These recommendations have been endorsed by the Society for Adolescent Medicine [96]. Recommendations from the AAP are still awaited.

A second prophylactic HPV vaccine (Cervarix, GlaxoSmithKline Biologicals) underwent two phase-III clinical trials in 90 sites in 15 countries. The vaccine contains virus-like particles of types 16 and 18. Included in the trials were women who already had evidence of prior or ongoing HPV infection but the primary end point will be evaluated against women who were HPV naïve at recruitment. Similar criteria were used in the clinical trials conducted for Gardasil. Although the heterogeneity of the viruses will undoubtedly have different results in different parts of the world, it is expected that Gardasil and Cervarix, once licensed and available for public use, will be able to prevent 70% of cancers worldwide [65]. The two vaccines will be studied in a head-to-head phase III randomized, observer-blind, multicenter study in the US [97].

Several questions remain unanswered, including if and when booster doses of vaccine would be required so as to sustain immunity for an individual’s lifetime. Vaccination of male subjects also remains a controversial issue and trials in males are currently underway. Available data lend support for the implementation of gender-neutral HPV vaccination programs [95].

Another controversy surrounding this vaccine is parent acceptability of vaccinating prepubertal girls. Michigan became the first state in the US to propose legislation calling for compulsory vaccination of all girls entering sixth grade unless their parents choose to “opt-out,” while Texas became the first state in the US to mandate vaccination of 11- to 12-year-old girls [98]. Studies looking at vaccine acceptability show that most parents lack knowledge about HPV, and many are concerned about sexual health issues that may arise out of such a vaccination program. Studies aimed at increasing knowledge did not seem to have a significant impact on the acceptability of HPV vaccines by parents [99,100]. Marketing of the vaccine as a sexually transmitted infection or cancer prevention vaccine may impact the overall acceptance of the vaccine.

In addition to this, it is well established that HIV-infected women have at least double the HPV prevalence of HIV-negative women with similar risk profiles [101]. This is not surprising because we know that resolution of HPV infection requires an effective host immune response. However, to date, this vaccine has not been licensed for use in HIV-infected individuals. The vaccine should be safe in HIV-infected individuals, although
immunogenicity needs to be investigated. A study sponsored by the National Institute of Health looking at immune responsiveness as well as safety amongst HIV-infected preteens is ongoing [102].

NEW VACCINES FOR CHILDREN
Pentavalent (human-bovine) reassortant rotavirus vaccine

Rotavirus is the most common cause of severe diarrhea in infants and young children in the US and worldwide [103]. In the first 5 years of life, 4 out of 5 children in the US will develop rotavirus gastroenteritis, 1 in 7 will need to be seen in the doctor’s office or emergency room, 1 in 70 will be hospitalized, and 1 in 200,000 will die from the disease [104–106]. Rotavirus is also a significant cause of nosocomial diarrhea and acute gastroenteritis in children attending daycare centers [107–109]. Several cases of gram-negative bacteremia following rotavirus gastroenteritis in infants have also been reported [110–112].

Because rotavirus is easily transmissible from person to person primarily by way of the fecal–oral route, the infection is difficult to prevent. Nearly every child has had at least one rotavirus infection by the time they are 5 years of age. Although there is no specific treatment for rotavirus, the diarrhea is manageable, but the disease burden is high in terms of morbidity and economic costs [113,114]. Approximately 4% to 5% of all childhood hospitalizations in the US are associated with rotavirus [115]. This may not represent the true burden of disease because all hospitalizations may not be adequately captured [116]. Globally the disease burden is even higher in terms of economic costs as well as morbidity and mortality accounting for approximately 5% of all deaths among children less than 5 years of age [117,118].

Rotaviruses are classified into seven distinct serogroups A through G. Of these, groups A, B, and C cause disease in humans with group A being the major human pathogen [119–121]. Group A rotavirus is further classified into G and P serotypes; VP4 (correlates to the P serotype) and VP7 proteins (correlates to the G serotype) of the rotavirus outer capsid stimulate the humoral response and thus production of neutralizing antibodies [122]. The strategy of preventing rotavirus through immunization derives from studies demonstrating that wild type rotavirus infection induces immunity against subsequent rotavirus gastroenteritis. It has also been shown that protection against future infections seems to be increased with each rotavirus infection, although natural infection best protects against severe disease and to a lesser extent against less severe or asymptomatic disease [104,117,123–125].

The predominant G serotype varies by region and year [126]. G1 tends to be the predominant pathogenic serotype in the US [127,128]. Worldwide, the predominant serotype is also G1 although to a lesser extent, occurring approximately 53% of the time [129]. Other predominant serotypes are G2 (11%), G3 (14%), and G4 (5%) with other genotypes accounting for 17% [122,129].

The first rotavirus vaccine to be used in the US was rhesus rotavirus tetra-valent vaccine (Rotashield; RRV-TV: Wyeth-Lederle Laboratories). The vaccine was licensed in August 1998 and recommended for routine immunization
in infants by the ACIP and the AAP [130]. From December 18, 1998, through June 2, 1999, 10 cases of intussusception were reported to Vaccine Adverse Event Reporting System, compared with a total of 4 cases reported during the previous 10 years [114]. In response to this, the CDC conducted a large study to investigate the possible association of intussusception with RRV-TV. The study found that there was a strong association between vaccination with RRV-TV and intussusception among healthy infants. The researchers estimated that 1 case of intussusception would occur for every 4670 to 9474 infants vaccinated with RRV-TV [131]. The vaccine was subsequently withdrawn from the market in October 1999, just 15 months after initial licensure. Research looking at the development of a safer vaccine continued because of global consensus that a rotavirus vaccine was desperately needed in resource-rich as well as resource-poor countries [132].

On February 3, 2006, the FDA licensed a second rotavirus vaccine for the routine immunization of infants [133]. Rotateq (Merck and Co. Inc, Whitehouse Station, NJ) is a pentavalent (human-bovine) reassorted rotavirus (PRV) vaccine. Using what has been called a modified "Jennerian approach," the rotavirus parent strains of the reassortants were isolated from human and bovine hosts. Four reassortant rotaviruses express one of the outer capsid proteins (G1, G2, G3, or G4) from the human rotavirus parent strain and the attachment protein (P7[5]) from the bovine rotavirus parent strain. The fifth reassortant virus expresses the attachment protein (P1A) from the human rotavirus parent strain and the outer capsid protein G6 from the bovine rotavirus parent strain. The oral vaccine contains no preservatives or thimerosal [134].

The efficacy and safety of PRV was evaluated in two phase-III trials (REST-Rotavirus Efficacy and Safety Trial) [135]. Active surveillance was used to study healthy infants 6 to 12 weeks of age from 11 countries, including the US, who were randomly assigned to receive three oral doses of PRV or placebo at 4- to 10-week intervals. Excluded from the study were infants who had received oral poliovirus vaccine during the 42-day period preceding the planned first dose or if it was anticipated that they would receive the oral poliovirus vaccine during the study. After completing the three-dose regimen, the efficacy of PRV against rotavirus gastroenteritis of any severity was 74%, and against severe rotavirus gastroenteritis was 98%. Efficacy was observed against all G1 through G4 and G9 serotypes, although few non-G1 rotavirus cases were reported. PRV reduced the incidence of office visits by 86%, emergency department visits by 94%, and hospitalizations for rotavirus gastroenteritis by 96%. Efficacy against all gastroenteritis hospitalizations of any etiology was 59%. Efficacy of PRV in the second postvaccination rotavirus season was 63% against rotavirus gastroenteritis of any severity and 88% against severe rotavirus gastroenteritis. Data on the efficacy of the vaccine in those receiving less than three doses of the vaccine are limited (Table 2).

Safety of the pentavalent vaccine with respect to intussusception was evaluated in 71,725 subjects enrolled in phase III efficacy trials [135]. For the prespecified 42-day postimmunization endpoint, 6 cases of intussusception were
observed in the PRV group versus 5 cases of intussusception in the placebo group. The data did not suggest an increased risk of intussusception relative to placebo. There was no confirmed case of intussusception amongst vaccine recipients within the 42-day period after the first dose, which was the period of highest risk for the previously licensed RRT-TV. In the 1-year follow-up period after administration of the first dose, 13 cases of intussusception were observed in the PRV group versus 15 cases of intussusception in the placebo group. The incidence of other serious adverse events was similar between the PRV group and the placebo group. In the 42-day period after immunization, vaccinees had a small but significantly (*P* < 0.5) greater rate of several symptoms compared with the placebo group. These included vomiting, diarrhea, nasopharyngitis, otitis media, and bronchospasm. The rates of fever were similar between the two groups.

On February 21, 2006, the ACIP recommended universal immunization of US infants against rotavirus with an oral three-dose series at 2, 4, and 6 months of age [136]. Following this, the AAP issued their policy statement in January 2007 recommending addition of rotavirus to the routine vaccination schedule of infants [137]. The first dose of the vaccine must be given between 6 and 12 weeks of age, and dosing must be complete by 32 weeks of age. Immunization must not be initiated for infants older than 12 weeks of age. The minimal interval between doses is 4 weeks.

### Table 2

<table>
<thead>
<tr>
<th>Number of cases&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Disease severity</th>
<th>Vaccine (N = 3484)</th>
<th>Placebo (N = 3499)</th>
<th>% Efficacy</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>First rotavirus season</td>
<td>Any</td>
<td>97</td>
<td>369</td>
<td>73.8</td>
<td>67.2–79.3</td>
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<tr>
<td></td>
<td>Severe</td>
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<td>57</td>
<td>98.2</td>
<td>89.6–100.0</td>
</tr>
<tr>
<td>Second rotavirus season</td>
<td>Any&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>62.6</td>
<td>44.4–75.4</td>
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<tr>
<td></td>
<td>Severe&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2</td>
<td>17</td>
<td>88</td>
<td>49.4–98.7</td>
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<table>
<thead>
<tr>
<th>Type of Contact</th>
<th>% Rate Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalizations&lt;sup&gt;d&lt;/sup&gt;</td>
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</tr>
<tr>
<td>ED Visits&lt;sup&gt;d&lt;/sup&gt;</td>
<td>14</td>
</tr>
<tr>
<td>Office Visits&lt;sup&gt;e&lt;/sup&gt;</td>
<td>13</td>
</tr>
</tbody>
</table>

<sup>a</sup>number of cases for first rotavirus season and type of contact cases include only those that occurred at least 14 days after dose 3.

<sup>b</sup>36 cases of G1-G4 rotavirus cases among 813 vaccine recipients with data that could be evaluated.

<sup>c</sup>occurred in 2 vaccine recipients and 17 placebo recipients.

<sup>d</sup>N = 34,035 vaccine and N = 34,003 placebo recipients.

<sup>e</sup>N = 2834 vaccine and N = 2839 placebo recipients.
The vaccine has also been shown to be safe in phase-III trials in preterm infants (25 to 36 weeks gestational age, median 34 weeks), and the AAP supports the immunization of preterm infants provided the infant is at least 6 weeks of age, is stable clinically, and the first dose of vaccine is given at the time of discharge or after discharge from the nursery. Infants who have a history of rotavirus gastroenteritis before completing the full series should still receive the complete dosage schedule because initial infection confers only partial immunity. For infants who have a previous history of intussusception, the risks and benefits of immunization should be considered because such infants may be at a higher risk of a repeat episode compared with other infants.

Although Rotateq may be coadministered with other childhood vaccines, validation of pertussis assays are still under review, and at present there is still insufficient immunogenicity data to confirm lack of interference of immune responses when PRV is concomitantly administered with other childhood vaccines to prevent pertussis [137].

Monovalent human rotavirus vaccine (Rotarix HRV: GlaxoSmithKline)

Human rotavirus vaccine is a monovalent attenuated human strain vaccine. It was derived from the most common strain of human rotavirus in the US, G1P[8]. It shares neutralizing epitopes with G1, G3, G4, and G9 rotavirus serotypes but not G2. It has been attenuated through serial passage in tissue culture. The vaccine is administered in two oral doses 1 to 2 months apart. The first dose should be initiated at 6 to 14 weeks of age, and the second dose should be given at least 4 weeks apart but before the infant reaches 24 weeks of age. Rotarix provides cross protection against other rotavirus serotypes.

Rotarix was studied in a randomized, double-blind placebo controlled trial conducted in 11 Latin American countries and Finland. Infants studied ranged in age from 2 to 4 months and were to receive two doses of HRV or placebo. In the safety cohort, 31,673 healthy infants received two doses of HRV, and 31,552 infants received two doses of placebo at approximately 2 and 4 months of age [138]. The overall cohort was followed for a median of 100 days after the first dose for assessment of adverse effects including intussusception and a smaller safety and efficacy cohort of 20,169 patients was followed until they reached 1 year of age. The incidence of intussusception was no greater in the vaccine recipients compared with the placebo recipients. Other side effects reported such as fever, vomiting, and diarrhea were also similar between the two groups. Rotarix demonstrated an efficacy of 84.7% against severe rotavirus gastroenteritis. It was also 85% effective in reducing hospitalizations due to rotavirus gastroenteritis [138]. Rotarix is currently not licensed in the US; however it is licensed in 30 countries including the European Union and is part of the national immunization programs in Brazil and Panama. The vaccine is currently pending submission to the FDA.

Given their efficacy and safety profiles, these vaccines show great promise in controlling severe rotavirus disease worldwide. The success of the immunization programs, however, depends not only upon the acceptability of the new
vaccines by the general public but also on the affordability of the vaccines. Studies in the US have shown that most pediatricians would be willing to implement the vaccination series despite concerns about vaccine cost and reimbursement issues as well as parental acceptance of the vaccine [139,140].

The success of a rotavirus implementation program overseas would hinge upon the cost of such a program. In the US, Rotataq is currently priced at $63.25 if purchased in the private sector and $52.00 if purchased by the Vaccines for Children Program, similar to the costs for pneumococcal conjugate vaccine [141]. Worldwide, rotavirus vaccines are offered in the private sectors of several middle-income countries for as much as $50 per dose and for roughly $7 per dose in the public sector. These are unacceptably high prices for many of the poorest countries where the need may potentially be the greatest. Although funding for two major childhood killers (rotavirus and pneumococcal disease) in some of the world’s poorest countries was just announced by the Global Alliance for Vaccines and Immunization Alliance, it remains to be seen if these vaccine programs will be sustainable based on available funding for some of the world’s poorest countries [142].

RECENT CHANGES IN THE CURRENTLY RECOMMENDED IMMUNIZATION SCHEDULE IN THE UNITED STATES

Varicella vaccine

Since the implementation of a routine varicella immunization program in 1995, there has been a dramatic reduction in the morbidity and mortality from varicella in the US [143–145]. Despite this, outbreaks of varicella continue to be reported particularly in communities that have high rates of immunization [146–149]. The incidence of varicella in immunized children may be as high as 20% [150]. Although the disease may be milder in such cases, wild type virus can be transmitted by these individuals to others who may be at higher risk.

There is now enough evidence that a single dose of varicella vaccine is not sufficiently immunogenic when given to some children from 1 to 12 years of age, and a two-dose regimen such as that recommended for adolescents and adults would result in higher seroconversion rates. A study in healthy children comparing one versus two doses of varicella vaccine over a period of 10 years showed that the efficacy for two doses was significantly higher than for one dose of varicella vaccine (98% versus 94%, respectively) [151]. The risk of developing varicella at least 42 days after vaccination in children receiving two doses was 3.3 fold lower than those who received only one dose of the vaccine. Of the children receiving two doses, 99% achieved a glycoprotein-based enzyme-linked immunosorbent assay (gpELISA) level of greater than 5 units, 6 weeks after vaccination compared with 86% of children who received only one dose. The six-week gpELISA level of greater than 5 units has been proposed as a good surrogate marker for protection from natural disease [152,153].

Given the facts, it was obvious that two doses of varicella vaccine should be given to children 1 to 12 years of age for optimal protection from varicella.
Apart from protecting against primary vaccine failure, which is the rationale for two doses of measles vaccine, it is also necessary to protect individuals who may have had a weak primary response thus rendering them susceptible to varicella as they progress into adolescence and adulthood [153].

On June 26, 2006, ACIP voted to recommend a second dose of varicella vaccine for children 4 to 6 years of age in addition to the first dose at 12 to 15 months. A second dose is also recommended for adolescents and adults who previously received only one dose [154]. These provisional recommendations will become official once published in Morbidity and Mortality Weekly Report.

The licensure of measles, mumps, rubella, and varicella vaccine (Proquad: Merck, MMRV) makes the introduction of a second dose of varicella vaccine easier. Proquad has been shown to have similar immunogenicity and safety profiles compared with the MMR and varicella vaccines given by separate injections [155,156].

Quadrivalent mumps, measles, rubella, and varicella vaccine
The National Immunization Survey reported improved immunization rates in the US closer to the Healthy People 2010 objective of increasing immunization coverage by greater than 80% among children aged 19 to 35 months [157]. The only statistically significant decrease in coverage from 2004 to 2005 was for at least 1 dose of MMR. This decrease was modest however, and national MMR coverage has remained consistent, ranging from 91% to 93% since 2001. In addition to this, rubella and congenital rubella syndrome were declared eliminated from the US [158]. Despite these achievements, we cannot become complacent just yet. Rubella still constitutes a significant health problem in many countries of the world [159]. In addition, the recent outbreak of mumps in the United Kingdom in 2005 and the US in 2006 underscores the importance of timely administration of the first dose of MMR and the need for administration of the second dose at age 4 to 6 years. The recent recommendation of a second dose of varicella vaccine also makes the approval of a combination MMRV vaccine timely and appropriate.

In September 2005, the FDA approved a live, attenuated, quadrivalent combination vaccine for use in children in place of the MMR II (Merck & Co.) and varicella vaccines [Varivax], Merck & Co.). MMRV (Proquad, Merck & Co., Inc, West Point, PA) has been evaluated in several clinical trials in healthy children, 12 to 23 months of age as well as 4 to 6 years of age both as one or two doses. MMR II and Varivax were used as controls for most of the studies. Safety and immunogenicity were assessed 6 weeks after each dose. A single dose of Proquad in 12- to 23-month-old children was shown to be as immunogenic as a single dose of MMR II and Varivax and was also found to be well tolerated. Similar observations were made for the 4- to 6-year age group. The most common side effect reported was fever that was greater after the first dose of Proquad compared with MMR II or Varivax. The incidence of fever was lower following a second dose of Proquad [155,160,161].
Use of combination vaccines at a time when the number of immunizations for infants is increasing would not only improve compliance and increase immunization rates but also serve to allay excessive parental anxiety with regard to the number of needle sticks their infant or child may be submitted to.

**Hepatitis A vaccine**

Before the introduction of hepatitis A vaccines in 1995 and 1996 in the US, outbreaks of hepatitis A virus (HAV) infection occurred in cycles, with peaks arising approximately every 10 to 15 years [162]. Although the actual number of cases reported was between 22,000 and 36,000, it is estimated that there were an average of 271,000 infections per year between 1980 and 1995. This number is taking into account anicteric disease, as well as asymptomatic infections [163]. The costs associated with HAV infection are substantial. A recent analysis estimated economic costs of $133.5 million during the lifetime of a single age cohort of children born in 2005, in the absence of vaccination [162].

In 1996, the ACIP made recommendations to prevent HAV infection through immunization of certain groups known to be at high risk for infection or living in communities that have high rates of disease [164]. As part of the plan for incremental implementation, in 1999, the ACIP expanded its recommendations to include vaccination of children living in states, counties, and communities where HAV infection rates were consistently above the national average [165]. As a result of these recommendations, HAV infection rates have declined to the lowest level ever recorded [166]. The decline was larger in areas of the country where routine vaccination of children was in effect. These results are not surprising. It is well known that children play a key role in the transmission of HAV and serve as a source of infection for others [167,168].

The most current recommendations aim to make possible the elimination of hepatitis A from the US. The CDC as well as the AAP recommends that all children should receive hepatitis A vaccine at 1 year of age [162,169]. There are currently two inactivated vaccines licensed in the US for use against hepatitis A. Vaqta is manufactured by Merck and Co. Inc., and Havrix is manufactured by GlaxoSmithKline Biologicals. There is also another vaccine manufactured by GlaxoSmithKline Biologicals, Twinrix, for use against hepatitis A and hepatitis B in individuals above the age of 18 years. The recommended doses and schedules for these vaccines are shown (Table 3).

Hepatitis A vaccine is also recommended for use in certain high-risk conditions, for those traveling to areas where infection is endemic and may also be used in outbreak situations during which an accelerated vaccination schedule may be considered as an additional control measure. Hepatitis A vaccine is not licensed for use as postexposure prophylaxis [162].

There has also been some interest in developing combined vaccines that would protect against hepatitis A and E. This would be of particular interest in areas of the world where both hepatitis A and E are prevalent and for individuals traveling to those areas [170].
Influenza vaccine

In the US, the annual number of deaths attributed to influenza far exceeds the total number of deaths due to all vaccine-preventable diseases combined. Annual attack rates due to influenza range from 15% to 40% among children and from 10% to 20% among adults [171]. Children under 24 months of age have the highest rates of hospitalizations comparable to those among adults over 65 years of age [172]. Results from a population-based surveillance survey reported an average annual rate of hospitalization attributable to influenza of 450 in 100,000 for infants aged 0 to 59 months of age, 90 in 100,000 for children 6 to 23 months, and 70 in 100,000 for children between 24 and 59 months [173]. Hospitalization and mortality rates are also high in children under 6 months of age [174].

Influenza immunization has long been recommended for children who have chronic medical conditions greater than 6 months of age. Recommendations for immunization against influenza for healthy children were limited to those from 6 months to 23 months of age. On June 28, 2006, the ACIP issued recommendations for immunization of all healthy children from 6 to 59 months of age [171]. These recommendations have been endorsed by the AAP [175].

The rationale for immunizing all healthy children from the age of 6 to 59 months is to reduce the overall burden of disease. Children are important vectors for the spread of influenza within households and communities. Immunizing young children and particularly school-aged children has been shown to induce herd immunity and reduce the overall burden of disease [176].

The overall rates of influenza immunization amongst children including those who have high-risk conditions are low. Estimates for influenza immunization in children aged 6 to 23 months of age, for the 2004 to 2005 season show that 33.4% of children between the ages of 6 and 23 months had received one or more than one dose of influenza vaccine, and 17.5% of children in this age group were fully immunized [177]. These numbers are better than those reported for 2003 and 2004 influenza seasons. One of the reasons for this may be the change from encouragement to full recommendation by the ACIP. Other strategies have been proposed to improve influenza immunization coverage. Universal influenza immunization as well as school-based influenza

### Table 3

<table>
<thead>
<tr>
<th>Age (in years)</th>
<th>Vaccine</th>
<th>Hepatitis A antigen dose</th>
<th>Number of doses</th>
<th>Immunization schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–18</td>
<td>Havrix</td>
<td>720 ELU(^a)</td>
<td>2</td>
<td>Initial and then 6–12 mths later</td>
</tr>
<tr>
<td>1–18</td>
<td>Vaqta</td>
<td>25 U(^b)</td>
<td>2</td>
<td>Initial and 6–18 mths later</td>
</tr>
<tr>
<td>&gt;19</td>
<td>Havrix</td>
<td>1440 ELU</td>
<td>2</td>
<td>Initial and 6–12 mths later</td>
</tr>
<tr>
<td>&gt;19</td>
<td>Vaqta</td>
<td>50 U</td>
<td>2</td>
<td>Initial and 6–18 mths later</td>
</tr>
<tr>
<td>&gt;18</td>
<td>Twinrix</td>
<td>720 ELU</td>
<td>3</td>
<td>Initial and 1 and 6 mths later</td>
</tr>
</tbody>
</table>

\(^a\)ELU indicates enzyme-linked immunosorbent assay units.

\(^b\)Antigen units (each unit is equivalent to approximately 1µg of viral protein).
immunization programs have been proposed as strategies to reduce the overall burden of disease [178,179].

Currently available influenza vaccines include both inactivated vaccines (TIV) and live attenuated vaccines (Table 4). Each year viral strains are selected for inclusion based on projections of strains that would potentially circulate during the following respiratory seasons and strains that have favorable growth characteristics in embryonated hens’ eggs. Both live, attenuated, and killed, inactivated vaccines consist of antigenically similar two type A, and one type B influenza strains.

Vaccination should be started as soon as the vaccines are available and continue for as long as influenza activity is present and as long as the vaccine is available. Children under 9 years of age who have not been vaccinated previously with influenza vaccine should receive two doses 1 month apart. It has been shown that children receiving complete immunization against influenza derive significant benefit from the vaccine as opposed to those who have been partially immunized [180].

Live attenuated vaccines is recommended for those in close contact with high-risk patients and for healthy, nonpregnant persons from 5 to 49 years of age. It is also recommended for health care workers who will not be in contact with a severely immunocompromised person. Advantages of live attenuated vaccines over inactivated vaccines are its ability to stimulate both mucosal and circulating antibody responses that simulate natural infection and may provide increased protection as well as permit avoidance of intramuscular injection. A 4-week interval is recommended before administration of other live vaccines. The vaccine is well tolerated with few side effects. Individuals who have been vaccinated with live attenuated vaccines may shed vaccine virus less than 10 days postimmunization, but the virus is shed at lower titers than those following natural infection.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Age group</th>
<th>Dose (mL)</th>
<th>Number of doses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inactivated Vaccines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluzone (SanofiPasteur)</td>
<td>6–35 months</td>
<td>0.25</td>
<td>1 or 2</td>
</tr>
<tr>
<td>Fluvirin (Novartis)</td>
<td>3–8 years</td>
<td>0.5</td>
<td>1 or 2</td>
</tr>
<tr>
<td></td>
<td>9 years and older</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td><strong>Live, Attenuated Vaccines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flumist (MedImmune)</td>
<td>5–8 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-no previous vaccine</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>-previous vaccine</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>9–49 years</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Flumist ® (MedImmune)</td>
<td>5–8 years</td>
<td></td>
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<tr>
<td></td>
<td>-no previous vaccine</td>
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<td>-previous vaccine</td>
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<td>1</td>
</tr>
<tr>
<td></td>
<td>9–49 years</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>
The live attenuated vaccine was initially not licensed for use in children less than 60 months of age following a statistically significant increase in the incidence of reactive airways disease in children 12 to 59 months of age following one dose of the vaccine [181]. Following this, there is now data to suggest that this may not be the case, perhaps leading to a change in the current age recommendation for use of this vaccine [182]. Studies of inactivated vaccines in children suggest that they are also well tolerated [183].

The FDA approved an application from the manufacturers (MedImmune Inc.) to change the formulation of the live attenuated vaccines (FluMist) to cold-adapted trivalent influenza vaccine (CAIV-T [Flumist(R)]) on January 8, 2007 [184]. This is an intranasal, cold-adapted trivalent influenza vaccine, which differs from FluMist in that it is a refrigerator-stable formulation compared with FluMist, which is a frozen, cold-adapted, trivalent live attenuated vaccine. In clinical studies, it has been shown to elicit greater antibody responses compared with inactivated vaccines. Cold-adapted trivalent influenza vaccine has also been shown to demonstrate efficacy against mismatched strains, especially in children under the age of 5 years [185]. Cold-adapted trivalent influenza vaccine will be available for use in healthy individuals from 5 to 49 years of age for the 2007 and 2008 influenza season. The company is also seeking to expand the age indication for Flumist to include children from the 12- to 59-month age group for those who do not have a history of asthma or wheezing. This is currently under consideration by the FDA.

Influenza immunization rates in the general population as well as in high-risk groups particularly in children have traditionally been low partly because of the issues related to supply and demand as well as misconceptions amongst the general public regarding influenza vaccine and its ability to cause the disease in vaccinated individuals. Several studies have shown that physician recommendation as well as patient education, recall, and reminder strategies work well to increase immunization rates in the community [186–188]. Recommendations for universal immunization will probably also go a long way in helping to increase public awareness and improve compliance with vaccination.

**OTHER VACCINE UPDATES**

Pentavalent combination vaccine (diphtheria, tetanus, acellular pertussis, polio, and Haemophilus influenza type b conjugate)

The Advisory Committee of the FDA on January 25, 2007, voted almost unanimously on the safety and efficacy of a combination DTaP-inactivated poliomyelitis vaccine (IPV)-Haemophilus influenza type b (Hib) vaccine (Pentacel; SanofiPasteur, Swiftwater, PA) (press release, SanofiPasteur, 2007). This vaccine has been licensed for use in nine countries including Canada where it was licensed for use in 1997. Pentacel is the first DTaP-based combination candidate vaccine for use in infants that has both polio- and Hib-vaccine components.

The first safety and immunogenicity trial of pentavalent DTaP-IPV-Hib was undertaken in 560 infants who were randomly allocated to receive either whole-cell DTP-IPV-Hib, the acellular DTaP-IPV as a separate injection, or
one of three lots of the combined DTaP-IPV-Hib [189]. Significant increases in antibody responses were demonstrated for all groups and though there was lot-to-lot variability, no consistent pattern was observed. Adverse events were significantly lower in the separate and combined acellular pertussis vaccine groups compared with the group receiving whole cell vaccine. Further studies were then undertaken and the safety and immunogenicity of DTaP-IPV-Hib were compared with separate administration of Daptacel in 849 toddlers 15 to 16 months of age [190,191].

The diphtheria, tetanus, and pertussis components in Pentacel are based on the formulation in Daptacel. No difference in local or systemic reactions was observed. No difference in responses to the different pertussis antigens was reported either. Following this, other studies evaluating the safety and immunogenicity of DTaP-IPV-Hib for the first four doses at 2, 4, 6, and 15 to 18 months of age were conducted. Findings similar to those of the previous studies were reported [190,192].

Additional studies have examined the safety and immunogenicity of the pentavalent vaccine when given concurrently with other vaccines given at this age [193,194]. No efficacy studies have been conducted for Pentacel. Data that bridge the extended combination vaccines to the data from the DTaP efficacy study completed in Sweden, demonstrating that the antibody response to the antigens contained in the extended vaccines are noninferior to those obtained in the Swedish efficacy study, have been used [33]. Postmarketing surveillance in Canada where Pentacel has been used since 1997/1998, have documented continued safety and effectiveness of this vaccine as well as success of combination vaccine programs for the control of pertussis as well as other diseases for which the vaccine is recommended [195].

There is no question that combination vaccines protect against several infections for which immunizations are recommended, are more convenient for and preferred by parents and health care providers, simplify record keeping, and decrease medication errors. In addition they reduce the number of injections for the infant and toddler, are less painful, and lead to better vaccine uptake. Potential concerns do exist, however, the most being diminished immunogenicity to one or more of the vaccine antigens when given in combination compared with separate injections. This will need to be monitored as more combination vaccines become available and the immunization schedule for infants and children becomes more complicated.

Heptavalent pneumococcal conjugate vaccines
Heptavalent pneumococcal conjugate vaccine (PNCV7; Prevnar, Wyeth) was approved for use in infants in February 2000. The development of this vaccine was prompted by the fact that young children particularly those under the age of 2 years were disproportionately affected by invasive pneumococcal disease (IPD). This became even more evident following the universal immunization of infants who had Haemophilus influenzae type b conjugate vaccine in the early 1990s, leading to virtual elimination of this pathogen as a cause of serious
bacterial infections in young children in the US. Before the heptavalent vaccine, the only other vaccine for use against IPD in children was the 23-valent polysaccharide vaccine. This was not particularly useful for children under the age of 2 years because it is not very immunogenic in this population.

The heptavalent pneumococcal conjugate vaccine contains polysaccharide conjugates of serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. These serotypes were known to cause 80% of IPD and the majority of noninvasive disease, particularly otitis media in the target population [196,197]. It was also hoped that immunization would elicit cross protective immunity to related serotypes, particularly 6A, 9A, and 19A. Both the ACIP and the AAP recommended universal immunization of infants with a three-dose immunization series, given 2 months apart, beginning at 2 months of age [197,198].

Following universal immunization with the heptavalent conjugate vaccine, now approaching its 7th year, several studies have been performed evaluating the long-term direct and indirect effects of the vaccine [199–202]. From 1998/1999 to 2003, the incidence of vaccine type (serotypes included in the vaccine) IPD among children aged under 5 years decreased from 80 cases per 100,000 to 4.6 per 100,000, a decline of 94% (95% confidence interval [CI] 92%–96%). The overall incidence of IPD, which includes vaccine and nonvaccine serotypes, declined by 75% (95% CI 72%–78%) [199]. In addition to this, the disparity between different ethnic groups in terms of the incidence of IPD seems to have disappeared as well.

Before the introduction of the pneumococcal vaccine in 1998, 24% of invasive pneumococcal isolates in the US were nonsusceptible to penicillin. Five of the serotypes in the vaccine comprised 78% of these strains. Modeling predicted that in the absence of a pneumococcal conjugate vaccine, the proportion of pneumococcal strains that were nonsusceptible to penicillin and erythromycin could potentially reach 41% by 2004. The association between the serotype and resistance, however, would be expected to reduce the incidence of disease caused by these resistant strains [203,204].

Following immunization, the incidence of IPD caused by penicillin-nonsusceptible strains peaked in 1999 and decreased by 2004, from 6.3 to 2.7 cases per 100,000 (a decline of 57%, 95% CI 55%–58%). Similarly, disease caused by strains resistant to multiple antibiotics declined from 4.1 to 1.7% per 100,000 (a decline of 59%, 95% CI 58%–60%). Amongst children under the age of 2 years, disease caused by penicillin nonsusceptible strains fell by 81% (from 70.3 to 13.1 cases per 100,000). For persons aged 65 years and older, disease caused by penicillin nonsusceptible strains decreased from 16.4 to 8.4 cases per 100,000 (a decline of 49%). Rates of resistant disease caused by vaccine serotypes, fell by 87%. Rates for children 2 to 4 years of age were 60% lower in 2004 compared with 1999. This reduction in the number of resistant isolates has been observed in older children and adults who have not been vaccinated with the conjugate vaccine [205]. It is relevant to keep in mind when reviewing these numbers that only 73% of children 19 to 35 months old in 2004 had received at least three of the recommended
four doses of conjugate pneumococcal vaccine. This may have been due to the fact that the vaccine was in short supply from August 2001 through May 2003.

The incidence of serious pneumococcal bacterial infections in HIV-infected children who are particularly susceptible to this organism has gone down as well. This is interesting because similar protective effects were not observed with the 23-valent polysaccharide pneumococcal vaccine trials in HIV-infected adults in Africa [206,207].

The decrease in nasopharyngeal colonization by vaccine serotypes has resulted in an overall decline in the incidence of IPD in adults as well [201,202]. This is not surprising because it is known that pneumococcal-colonized children serve as reservoirs for transmission to other children and adults. Reduction in the overall incidence of disease (ie, induction of herd immunity) has important implications for the future.

Despite the tremendous success of the vaccine and the overall decline in invasive disease, however, a note of caution must be added. Disease caused by vaccine serotypes has to some extent been offset by disease caused by nonvaccine serotypes. In particular, serotype 19A has been shown to increase, and it is reported that the frequency of serotype 19A among multiple antibiotic strains has risen from 1 in 100 in 2000 to more than 1 in 5 by 2005 [208]. Results from a recent surveillance study show resistance to penicillin, macrolides, cotrimoxazole, and amoxicillin-clavulanate, as well as multidrug resistance in nonvaccine serotypes, have all increased between 2000 and 2005. Selective pressure of the vaccine as well as inappropriate or indiscriminate antibiotic prescribing may be responsible for this change [209]. Surveillance for such epidemiologic changes is something that will need to be carefully monitored over the next several years.

Other pneumococcal conjugate vaccines, 9-valent and 11-valent, have been developed; however they are not licensed for use in the US.

**SUMMARY**

Although the development and licensure of new vaccines over the last 2 years has generated a lot of excitement as well as debate, there is a lot more to come. Not discussed in this article, licensure of another long-awaited vaccine albeit for use in adults was that for herpes zoster. The second HPV and rotavirus vaccines are awaiting approval in the US. Next in line are the vaccines both prophylactic as well as therapeutic against HIV. Topics of debate over the new vaccines include discussions amongst practices as to the affordability and cost of the new vaccines as well as the ethical debate amongst lawmakers and the general public regarding the rights and wrongs of compulsory vaccination against HPV.

Another ongoing discussion is regarding the availability of approved vaccines. Shortages have been seen with several of the childhood vaccines including heptavalent pneumococcal conjugate vaccine, tetravalent meningococcal conjugate vaccine, hepatitis A vaccine, as well as the ongoing saga with influenza vaccines. Across the globe while the struggle against polio continues, there
is encouraging news regarding the reduction in measles-related deaths, particularly in Africa. The last few years have indeed been landmark years in infectious disease research as the search continues for better and safer vaccines globally.

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The Health of Homeless Children Revisited

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FAMILY HOMELESSNESS IN PERSPECTIVE

Homelessness in America steadily declined through the 1950s and 1960s and ceased to be viewed as a problem during the 1970s [1]. It then began to re-emerge and, based on a finding that homelessness could no longer be ignored, the McKinney-Vento Homeless Assistance Act was passed by Congress and signed into law in July 1987 [2]. This legislation protects access to health care and a free, appropriate public education for the homeless.

McKinney-Vento defines the term homeless as applying to individuals who lack a fixed, regular, and adequate nighttime residence and have a primary nighttime residence in a supervised shelter or other transitional housing situation or a public place not designed as sleeping accommodations [3]. This definition excludes as homeless individuals or families who have children who do not have a fixed residence, ie, a home, but who are able to find accommodations in someone else’s home. As such, this definition severely undercounts the extent of family homelessness and contributes to confusion about the actual number of homeless people in the United States [4].

In New York City, for example, there were 1134 sheltered homeless families in 1982, increasing to more than 4600 homeless families in 1987 [5]. An estimated 17,000 families, however, were doubled-up in New York City in 1983, growing to more than 100,000 families with more than 300,000 people by the end of 1986 [6]. Nationally nearly 3 million households were living in overcrowded conditions in 1983, according to the US Census Bureau [7]. In 1988 the US General Accounting Office estimated that 73% of the nation’s
homeless children and youth were living in doubled-up situations, with only 10% in shelters and welfare hotels [8].

In 1998 it was estimated that 2 million single parent households in the United States were living in doubled-up housing. In New York City the number of doubled-up households in public housing alone was 20 times the number of homeless families in shelters. Doubled-up housing is associated with homelessness, because families whose overcrowded conditions become untenable often seek emergency shelter. In a national household telephone survey, 59% of those who had been doubled-up also reported periods of homelessness [9]. Families who find themselves in doubled-up situations after exiting the homeless shelter system are more likely to become homeless again, whereas families who are able to obtain rent subsidies when they exit shelters are more likely to remain housed [10].

Policy analysts generally attribute the growth of child and family homelessness to economic conditions, specifically consistent reductions in federal support for new or subsidized housing and stagnation of public assistance benefits and the minimum wage. US Department of Housing and Urban Development (HUD) funding declined from $32 billion in 1980 to $7 billion in 1987 [6]. The US Conference of Mayors reported that the demand for emergency shelter increased in 92% of the large cities surveyed during 1986. There was an 88% increase in demand for low-income housing, with only 30% of eligible households (10% in New York City) having their housing needs met. The population whose shelter needs grew most during this period was families with children [2,11]. These economic factors especially impacted families with psychosocial vulnerabilities, including domestic violence, substance abuse, and mental illness [12].

Throughout the 1990s the disparity between income and market-based rental costs, together with limited housing assistance, continued to place low-income families at risk for homelessness or overcrowded, doubled-up housing conditions [13]. The percentage of rental households with a heavy rent burden (more than 35% of monthly income spent on rent) peaked in 1995 at 35.6% and remained at greater than 30% at least through 2001. Recent US Census Bureau, American Housing Survey data show that more than 14 million American households pay 50% or more of their income for rent [14].

The typical homeless family in the 1980s was headed by a single mother who had been receiving public assistance benefits for 2 or more years and did not have a job or work history. Social isolation was common [15]. Socially isolated families are by definition less likely to have a support network that would make doubled-up housing an alternative to the homeless shelter system. Other factors associated with family homelessness include family violence (intimate partner violence or a history of having been abused as a child) that may have contributed to social isolation. Serious mental illness only affected a small minority of homeless mothers [16].

This general profile has remained consistent. A 1999 national survey found the following demographic characteristics for homeless families: female head of household (95%); race-ethnic minority: African American (58%), Latino (13%), white (22%); unemployed (79%); median earned income, current or previous,
$11,400; children younger than 5 years of age (47%), 5 to 17 years (53%) [17]. More generally the demographics of homeless families mirror those of poverty in each community [18].

A 2004 study by the Vera Institute describing New York City’s homeless families found that for most their last address was in 1 of 10 low-income communities, all predominantly African American and Latino. The two most common reasons for entering the shelter system were overcrowded housing and eviction, followed by domestic violence, unsafe housing conditions, and economic strain [19].

As family homelessness increased, so did hunger and food insecurity. These trends are tracked annually by the US Conference of Mayors. Food emergencies and need for food assistance increased in 76% of the large cities surveyed during 2004, with an average 7% increase among families who had children. Nearly one out of five (18%) of requests for food assistance could not be met [11].

In New York City from 2003 to 2005, one in six residents (1.25 million) could not afford enough food, and 15.4% lived in a food-insecure household, an increase of 112,000 people over 2000 to 2003. Nearly half (46%) of the city’s emergency food pantries did not have sufficient food to meet demand, turning people away, rationing, or limiting hours of operation [20].

**HOMELESSNESS AND CHILD HEALTH**

As family homelessness grew, many studies were published describing the health status of homeless children. A 1988 study of children younger than 5 years of age in the New York City shelter system found that, based on retrospective review of medical charts, homeless children had more serious medical problems than low-income housed children, including immunization delay, high lead levels, and hospital admissions [21]. Also in 1988, survey data from Seattle found a high obesity rate (35%) based on weight-for-height. Homeless children were much more likely to be rated as being in fair or poor health than typical, and emergency department use was two to three times greater than for the general pediatric population. Combined with a high rate of under-immunization, the data strongly suggested that homeless children did not have access to preventive healthcare [22].

A 1991 survey of homeless children in Philadelphia found high rates of accidents and injuries, elevated lead levels, and speech-language delay [23]. A 1990 Los Angeles study found homeless children frequently had poorly balanced diets. Compared with housed low-income children, homeless children had a higher rate of obesity and higher rates of developmental delay, school failure, and behavior problems [12]. These health problems have persisted for homeless children. In a 1998 Boston study, homeless children had higher rates of acute illnesses, including ear infections and chronic conditions including asthma, and of emergency department use, than did low-income housed children [24].

Nutritional problems were emphasized in a 1991 study that found a high rate of growth delay, specifically stunting without wasting, suggestive of chronic
nutritional stress, among New York City homeless children [25]. Homeless shelters are especially challenging environments in which to maintain adequate nutritional intake. Most do not have cooking facilities, and some do not allow food, even infant formula, to be stored in shelter rooms. These problems are often compounded by extreme poverty and geographic isolation from adequate food shopping options [26,27].

School attendance for homeless children is frequently disrupted because of moves among unstable housing situations and shelters and logistic problems of transportation, obtaining school books and clothes, space to do homework, and so on. Too often the legal rights to an appropriate education are not honored for homeless children despite the protections of the McKinney-Vento Act [28].

By 1987 studies done in Massachusetts established high rates of developmental delay, depression, anxiety, and academic problems among homeless children. Approximately half required psychiatric referral [29]. A 1990 Boston study found a higher rate of developmental delay among preschool homeless children compared with poor housed children [16]. More recent data show that more than half (57%) of school-age homeless children had depressive symptoms based on the Children’s Depression Inventory (CDI), and one fourth (26%) required psychiatric evaluation based on CDI and Child Behavior Checklist (CBCL) scores [30].

Studies of homeless children in Los Angeles found that approximately three fourths (78%) showed signs of depression, anxiety, or academic delay based on results of standardized measures, with only 15% having received mental health or special education services. Fewer than half of the 45% of homeless children who met criteria for special education evaluation received any intervention [31,32].

In a 1991 descriptive study at the once-notorious Hotel Martinique in New York City, three fourths of 3- and 4-year-old children presented with speech-language delay and/or behavioral problems characterized by impulsivity on entry to an on-site comprehensive day care center. Delivery of preschool education in a normalizing setting was sufficient to restore age-appropriate functioning for most of these young children [33]. These findings were consistent with earlier studies [34,35]. Environmental factors negatively impacting the development of young homeless children in the late 1980s included extremely harsh shelter conditions marked by small, overcrowded hotel rooms fraught with potential sources of accidental injury [36].

Recent studies of the health impact of homelessness have focused on asthma. Shelter-based surveillance in New York City found a lifetime asthma rate (using a screening instrument consistent with National Heart, Lung and Blood Institute guidelines) of 40% among homeless children in 1999, the highest documented pediatric asthma prevalence rate in the United States [37]. Continued screening with this protocol in subsequent years (1999–2002) showed the asthma prevalence rate leveling off at 32% [38]. These findings are consistent with data from a school-based health center in East Harlem, a New York
City community with a high pediatric asthma prevalence rate [39]. Homeless patients were 2.5 times as likely to have a health problem and 3 times as likely to have a severe health problem as were housed children using the school health center. The asthma rate among the homeless patients was 33% [40].

**SETTING FOR THE STUDY**

The New York Children’s Health Project (NYCHP), a program of The Children’s Health Fund (CHF), has provided comprehensive health care to homeless children and families in a medical home model continuously since 1987. Health care is delivered through mobile medical units parked in front of shelters or in clinics established on-site at shelters. Typically children have their first pediatric visit within weeks of their entry to the shelter system. As the number of homeless children in New York City grew (reaching 9090 families with 16,594 children in December 2003) [41] and attention to the health of homeless children diminished, investigators at NYCHP and CHF conducted a comparison study of health status of homeless children in 1988 and 1998.

Results showed statistically significant improvement in immunization status and prevalence of iron-deficiency anemia and significantly higher rates of asthma and otitis media based on retrospective electronic health record review of representative samples of pediatric patients for those years. There was a trend toward increased obesity, defined within the limitations of anthropometrics taken at the time, as weight at or greater than the ninety-fifth percentile [42]. The present study was designed to expand on that study, comprehensively describing the health status of homeless children in 2004.

**METHODOLOGY**

A representative random sample of homeless pediatric patients age 3 months to 19 years (n = 520) was derived from a list of all pediatric patients of the NYCHP seen during 2004 (n = 3380). The age distribution mirrored that of the general patient population: 3 to 23 months, n = 180 (35%); 24 months to 5 years, n = 140 (27%); 6 to 19 years, n = 200 (38%). Data were extracted from electronic health records, and key health conditions were recorded as yes/no for each patient. An additional random sample of 100 patients aged 19 to 35 months was assessed for immunization status.

Immunization status was assessed relative to American Academy of Pediatrics and Centers for Disease Control (CDC) Advisory Committee on Immunization Practices (ACIP) guidelines in effect during the service year. For the 2004 sample, obesity was determined by body mass index (BMI) and percentile. Obesity was defined as BMI at or greater than the ninety-fifth percentile on CDC 2000 growth charts. Iron-deficiency anemia was determined by hemoglobin values relative to CDC criteria [43]. Asthma data were based on lifetime diagnosis and included diagnosis of reactive airways disease. Otitis media data were based on primary care providers’ recorded ICD-9 code for visit and included diagnoses of acute otitis media, chronic otitis media, serous otitis media, and, least frequently, otitis media with effusion (OME).
By 2004 NYCHP behavioral health services had expanded, and data were recorded for developmental and mental health conditions. Diagnoses were made using ICD-9 and DSM-IV criteria by a clinical psychologist following referral by the primary care provider or parent. Formal testing was not done. Children who had developmental or behavioral problems were referred to the age-appropriate service system (Early Intervention Program, Preschool or School-Age Special Education), and the authors were concerned that a practice effect from repetition of formal testing might influence eligibility determination for these Individuals With Disabilities Education Act (IDEA) programs.

All diagnosed children were referred for services, and all who followed through with an IDEA program evaluation met eligibility criteria. In New York State, IDEA eligibility criteria are developmental delay of at least 33% relative to chronologic age in one developmental domain or at least 25% in two developmental domains, or test scores of at least 1.5 standard deviations below the mean on a norm-referenced test.

Where possible, comparisons were made between prevalence in this homeless population and available data for typical and at-risk pediatric populations.

**STUDY RESULTS**

**Demographic characteristics**

The mean age of the sample was 5.4 years; the mean age of all pediatric users for 2004 was 5.6 years. Race-ethnicity of the patients was 56% African American, 42% Latino, and 2% other or unknown. Forty-nine percent were male. All were eligible for Medicaid. Virtually all lived in single parent, female-headed households.

**Immunization status**

In 2004 78% of homeless children were up-to-date for mandatory immunizations. These data exclude patients who did not have an immunization record available for inspection. This up-to-date rate is comparable to immunization data from a 2004 national study of children 19 to 35 months of age participating in the Women, Infants, and Children (WIC) supplemental nutrition program. Investigators found 77% up-to-date for WIC participants and 71% up-to-date for WIC-eligible children who had never participated [44].

The immunization rate in this homeless population is consistent with 2005 data from the New York City Department of Health and Mental Hygiene for many of the city’s low-income communities [45]. This rate for homeless children meets the CDC Healthy People 2010 target of 80% up-to-date for DTP, polio, HiB, MMR, and HepB immunizations [46]. This 2004 up-to-date rate is a statistically significant improvement ($P < .01$) over the 54% rate found for 1998.

By 2004 the WIC program required that participating infants and toddlers have mandated immunizations to receive nutrition benefits. The authors attribute the improved immunization rate to the fact most young homeless patients participate in WIC and have their immunization status monitored there. Also
most New York City medical providers participated in New York’s Citywide Immunization Registry. This computerized repository of immunization records allows providers to verify immunization status, minimizing or eliminating unnecessary duplication of vaccinations. The impact of the Registry on lost immunization records is notable. In 2004 only 7% of patients did not have a record ready for review, compared with 13% in 1998 (and 17% in 1988).

Otitis media
For children 3 to 23 months of age, 37% were diagnosed with otitis media. Among patients 24 to 71 months of age, the prevalence rate was 24%. Because of the transient nature of a homeless population, not all patients were seen over time. For patients who did not remain in the care of the NYCHP, prior history of otitis media was obtained by parent report. Patients who had otitis media who remained in NYCHP care were seen for multiple otitis media visits over time.

Otitis media is an extremely common childhood illness, the incidence of which has been increasing. The rate and frequency of recurrence of otitis media in this homeless population exceed those documented for other pediatric populations. Epidemiologic studies have shown that 71% of children have had at least one acute episode by 36 months of age, with one third having had three or more acute episodes. Highest incidence is generally between 6 and 11 months of age. Three or more episodes of otitis media affects up to 20% of infants by 12 months of age [47,48]. In this homeless population, highest incidence was for toddlers older than 12 months of age, and frequency of recurrence was such that some had eight or more episodes during the course of a year.

Risk factors associated with recurrent otitis media include African American or Latino race-ethnicity, day care or other congregate care, early termination of breast feeding, and poor access to health care [49,50], all of which affect homeless children. An additional risk factor for otitis media is exposure to environmental tobacco smoke [51]. Most NYCHP pediatric patients spend time each day cared for by adults who smoke in their presence.

Although there are controversies about whether or not to treat otitis media with antibiotics [52], in this population pediatricians found that failure to complete the prescribed course of antibiotics was associated with recurrence. Issues in failing to comply with medication instructions included hoarding antibiotics for possible later use when access to health care may be more difficult and misunderstanding directions, with antibiotic administration stopped as soon as the child was no longer symptomatic.

Asthma
The asthma prevalence rate for this homeless pediatric population was 31.5%. Because of controversies about early diagnosis of asthma [53], the authors also determined the rate for children less than 36 months of age. This rate (32.2%) does not differ significantly from the overall rate for this homeless population. These data are consistent with the 32% asthma prevalence rate from CHF’s homeless shelter surveillance data (reflecting health status while still housed)
and the 33% rate among homeless school-based health center patients in East Harlem referenced previously.

The CDC (National Health Interview Survey, National Center for Health Statistics) report a lifetime child asthma prevalence of 12% for 2004, with a current asthma prevalence rate for children in poverty (household income below the federal poverty level) of 10%\[54\]. The asthma rate among homeless children far exceeds these figures.

Comparable community data are found in a study by the Harlem Children’s Zone (HCZ) using methodology similar to that used in the CHF homeless shelter surveillance study. The community surveyed, Central Harlem, is one that has been identified as a main community of origin for families entering the city shelter system. HCZ investigators found a diagnosed asthma prevalence rate of 28.5%. Including children who had pulmonary findings consistent with asthma and who had not yet been diagnosed, the Central Harlem child asthma prevalence rate increased to 30.3%\[55\].

The issue of under-diagnosis of children in high-risk communities may contribute to variations in asthma prevalence data. In the CHF homeless shelter screening data cumulative for 1998 to 2002 (n = 2376), 16% of children who had moderate to severe asthma symptoms had not been previously diagnosed \[38\].

Iron-deficiency anemia
For homeless children younger than 3 years of age, the iron-deficiency anemia prevalence rate was 19%. For comparison, the CDC rate (2000) was 7%\[56\], and the National Health and Nutrition Examination Survey (NHANES) III rate was 9%\[57\]. There are significant racial-ethnic disparities in iron-deficiency anemia prevalence, with the rate for white children younger than age 36 months being 6%, for African American children, 8%, and for Mexican American children, 17%\[58\]. The rate for homeless children exceeds the highest of these rates.

Prevalence of iron-deficiency anemia in 2004 was significantly higher than in 1998 (P < .05). The 9% rate in 1998 and significant improvement over 1988 was consistent with a trend toward reduced prevalence of iron-deficiency anemia among low-income young children through the 1990s\[59\]. The increase in 2004 is consistent with the more recent increase in hunger and food insecurity as tracked and reported by the US Conference of Mayors over the past years\[11\].

Among the factors associated with iron depletion and anemia are bottle feeding during the second and third year of life\[60\], which often affects homeless children. Iron-deficiency anemia is also associated with food insecurity, including food insufficiency, poor nutrition, and hunger\[61\]. Many homeless families regularly experience food insecurity, and young children in food-insecure families are more likely to be in fair or poor health, to be hospitalized, and to experience psychologic stress and anxiety\[62\].

Iron-deficiency anemia may also be associated over time with compromised cognitive outcomes. Longitudinal studies, however, have been limited by confounding variables associated with poverty also impacting children
who have a history of early iron-deficiency anemia [63,64]. Iron-deficiency anemia was not associated with developmental delay in this homeless population.

**Overweight and obesity**

Overweight and obesity prevalence for children 6 to 19 years old were 12% overweight (BMI between eighty-fifth and ninety-fourth percentile) and 31% obese. An additional 3% were underweight (BMI, ≤ fifth percentile). Only 54% had a BMI percentile within normal range.

For children 6 to 11 years of age (n = 129), 32% were obese; for children 12 to 19 years of age (n = 71), 28% were obese. These far exceed typical rates. CDC reports a steady increase in child and adolescent obesity, with rates in 2004 of 19% for children 6 to 11 years of age and 17% for adolescents 12 to 19 years of age [65].

Pediatric obesity is a condition with marked racial-ethnic disparities in prevalence and sequelae that may include type 2 diabetes and cardiovascular disease. African American and Latino children are most impacted. Nationally among African Americans, the overweight and obesity rates are 40% (6–11 years of age) and 36% (12–19 years of age). Data for Mexican American children and youth are 43% overweight (6–11 years of age) and 34% obese (12–19 years of age) [66]. The combined prevalence of overweight and obesity in the homeless population was consistent with these race-ethnic disparity data. A higher percentage of homeless children were obese, however, and therefore at higher risk for associated health problems.

This comparison is similar for data from a 2004 New York City Department of Health and Mental Hygiene study of overweight and obesity in public elementary school children (corresponding to the 6–11-year age group). The city public school data showed a 43% rate of overweight and obesity, comparable to the homeless population. Obesity prevalence was 24% [67], however, compared with 32% in the homeless population.

Obese children may show other signs of poor nutrition, including iron-deficiency anemia [68]. For low-income children, obesity may be associated with household food insecurity [69]. Taken together, the rates of iron-deficiency anemia in young homeless children and obesity in school-age homeless children indicate a high degree of health risk associated with poor nutrition.

**Mental health and child development**

For the homeless population 12 months to 19 years of age, 30% had a developmental or psychiatric diagnosis. For infants younger than 12 months of age (n = 82), 15% had a developmental problem. One third of these infants were diagnosed with psychosocial failure to thrive, the others with developmental delay. Overall for the birth to 35-month-old population age-eligible for the Early Intervention Program, 19% met eligibility criteria based on developmental delay. For comparison, data from the New York City Early Intervention Program show that 8% of live births from an annual birth cohort were referred to the program, with virtually all who were evaluated meeting eligibility criteria.
Among 3- and 4-year-old children (n = 81) age-eligible for preschool special education, 41% had developmental delays or behavior problems. Of these children, 52% were diagnosed with developmental delays, 27% with adjustment reactions, 15% with attention deficit hyperactivity disorder (ADHD), and 6% with post-traumatic stress disorder (PTSD). In this homeless population, recurrent otitis media is associated with diagnosed early developmental conditions and is likely to be a contributing factor to developmental delays [70].

Among elementary school-age children (5–11 years of age; n = 157), 34% were diagnosed with a developmental or psychiatric problem. Of these children, 17% were diagnosed with a developmental or learning problem, 47% with an adjustment reaction, 25% with ADHD, and 11% with PTSD.

Among adolescents 12 to 19 years of age (n = 71), 24% were diagnosed with a psychiatric disorder, of whom 29% were diagnosed with an adjustment reaction, 29% with depression, 24% with PTSD, and 18% with ADHD.

Exposure to domestic violence (DV) is associated with having a behavioral health diagnosis. The overall prevalence of DV exposure for this homeless population was 34%; for children who had a developmental or psychiatric diagnosis, prevalence was 44% (P < .01).

Prevalence data for developmental and psychiatric disorders of childhood are inconsistent. For example, a comprehensive review of the literature on behavior problems among low-income preschool children found ranges of 16% to 30% for externalizing problems and 7% to 31% for internalizing problems [71]. One study concluded that approximately 50% of Americans meet criteria for a psychiatric diagnosis at some point in their lifetime, and approximately half of them (25%) meet criteria during childhood or adolescence [72].

The US Surgeon General’s 1999 Report on Childhood Mental Health found 20.9% of children have a current mental disorder causing at least minimal impairment [73]. This is a lower threshold than was applied to the homeless population. The Urban Institute, citing its 2002 National Survey of American Families, found a 13% rate of emotional or behavioral problems among Medicaid-eligible children aged 6 to 11 years, and 14% for children aged 12 to 17 years [74]. The rates in this homeless population were 33% and 24%, respectively.

A limitation of the authors’ chart review methodology is that the authors could not include teacher reports of academic failure, grade retention, special education, and school problem behavior independent of a clinical diagnosis [75,76]. Even with this limitation, the prevalence of behavioral health problems in this homeless population exceeds rates generally considered typical for children and adolescents, including the higher rates for children and adolescents in poverty.

The authors’ data suggest that the most serious impact of homelessness and its antecedent conditions is on younger children, which is to be expected given patterns of typical development. This finding is consistent with a 1998 study (unpublished data from the New York City Local Early Intervention Coordinating Council, 2003).
comparing developmental status of homeless and housed low-income infants and young children, which concluded that the impact of homelessness and poverty is cumulative and emerges over time [77].

**SUMMARY**

To the extent that representative data are available for specific health conditions (e.g., under-immunization, asthma prevalence), the authors’ data suggest that the gap between the health status of homeless children and housed children in minority, low-income families is narrowing. Studies of the health status of homeless children allow a window into the health status of medically underserved children whose needs may not be readily documented because of their lack of access to the health care system.

Although prevalence rates of most of the health conditions discussed in this article exceeded national norms, they were generally consistent with rates characteristic of health disparities based on race-ethnicity and income. It must be emphasized that in most instances, children were seen for their first pediatric visit within weeks of entering the homeless shelter system. The health conditions identified were often present before the child and family became homeless. The high prevalence of asthma among homeless children should therefore be a matter of concern to health providers and payors, because the authors’ data strongly suggest that this is not confined to children in homeless shelters as a special population. Similarly, childhood obesity predates homelessness (or at least the episode of homelessness during which health care was provided) and as such the authors’ data may indicate the extent of this problem more generally among medically underserved children in the communities of origin.

These conditions seem to be exacerbated by the specific conditions associated with homeless shelter life. Asthma care, assuming it was previously available, is disrupted when housing is lost, and shelter conditions may have multiple asthma triggers. Nutrition often suffers as a result of inadequate access to nutritious food and cooking facilities in shelters, as indicated by the high rate of iron-deficiency anemia among very young children.

It is clear that homeless children in shelters require enhanced access to primary and specialist care. Shelter placement necessarily disrupts prior health care relationships (if any), while simultaneously placing additional stress on the child’s physical and emotional well being. A medical home model is strongly recommended to allow for continuous, culturally competent care.

Developmental and mental health problems are also more prevalent among homeless children. These conditions may jeopardize life successes. The overcrowding associated with homeless shelters and the housing conditions that frequently precede episodes of homelessness are associated with the higher prevalence of otitis media found among young children. This in turn is associated with developmental delay. Also contributing to the developmental risk associated with homelessness is exposure to DV, which is also frequently an antecedent of homelessness.
Developmental surveillance for young homeless children, monitoring of school attendance and academic performance, and assessment of mental status for homeless adolescents are recommended to facilitate early identification of problems and delivery of necessary interventions. For young children, providers of health care to the homeless should be well networked into the Early Intervention and Preschool Special Education programs in their locality.

Given the multiplicity of needs for homeless families, which of course includes help finding affordable housing, health care providers serving this population should also develop linkages with community agencies, including those that can help parents develop the skills necessary for economic self-sufficiency and long-term ability to sustain independent housing.

References


[3] US Title Code 42 (the public health and welfare), Chapter 19 (homeless assistance), Subchapter I (general provisions), Section 11302 (general definition of homelessness) [42USC11302].


The term megadisaster has worked its way into the mainstream since the start of the new millennium. The expression once reserved for the technical meaning of the word—a “one in a million” disaster—has recently been brought to the forefront by several large natural events that have occurred in the past 5 years, namely Hurricane Katrina in the United States and the Indian Ocean tsunami of 2004. These two disasters, as well as the terrorist attacks of September 2001 in the United States have directed a persistent spotlight on the systems by which the public and its government plan for, respond to, and recover from high-impact catastrophes.

From the beginnings of human society, both nature and our own species have found ways to traumatically disrupt the status quo. Despite the many catastrophes in our history, the term disaster has been difficult to define. Most definitions include some reference to the event’s impact on people, the economy, or the environment. More theoretically, a disaster can be seen as a complex function of risk and vulnerability. As an example, the magnitude of a hurricane disaster is not as simple as the force of the hurricane itself upon a community but rather a sum of those forces (eg, storm-force winds) plus the special vulnerabilities faced by the community (eg, levee failure) plus the community’s capacity to reduce the actual or potential negative consequences of risk (eg, an inability to evacuate citizens). It is complicated interplay among the forces of destruction and the broad ability (or inability) of a community, for myriad reasons, to withstand them and mitigate their impact.

There is ranging opinion and there has been much discussion about the practical definition of disaster, much of it dependent upon the context in which the term is being analyzed. Many academics feel that for an incident to be technically classified as a disaster, it must overwhelm the day-to-day routine enough...
so much that those who are affected must alter their behavior and reach outside of their normal support structure for assistance that would normally come from within their own community. The layperson, however, has a less restrictive definition and typically describes a disaster as any incident that causes a significant loss of life or property damage. Although there is clearly a continuum between a crisis, a disaster, and a megadisaster, experts disagree as to where the demarcations lie, and the basis for making these distinctions. The situations discussed in this article are clearly at the megadisaster end of this spectrum and, for our purposes, they meet the criteria discussed in Redlener’s book on the subject: an emergency that overwhelms local and regional response capacity and includes such factors as an inability to manage rescue and medical needs, a failure to protect vital infrastructure, and a degree of uncontrolled societal breakdown [1].

Hurricane Katrina is America’s most recent encounter with a megadisaster. But what made it a megadisaster instead of just another category 3 hurricane of the type that seasonally exists in the Gulf of Mexico? Katrina was not the largest or strongest hurricane to strike the United States mainland in the recent past, but its effects were devastating and wide reaching beyond our wildest nightmares, far beyond those of Hurricane Andrew (1992), a category 5 hurricane that scoured much of Florida and the Gulf Coast. Hurricane Katrina’s track directly targeted gaping vulnerabilities in infrastructure and society, and set in motion a series of events that culminated in the deaths of nearly 2000 people, resulted in hundreds of missing individuals, and caused a potential economic impact of up to $150 billion. The disruption of people’s lives was immeasurable, as was the impact on the long-term physical and mental health of the victims, which continues today. Katrina also led to a substantial decline in the confidence that the public has in its government to provide essential services during a disaster.

The year 2001 was a terrible beginning to a millennium that had transitioned uneventfully. Having just dodged the “Y2K” bullet, which many feared would unravel the fabric of society, most Americans went about their lives completely unaware of their susceptibility to terrorism. The nation suddenly entered a new era of vulnerability and fear as thousands died in New York City, Washington, D.C., and Shanksville, Pennsylvania, at the hands of extreme jihadists. Shortly thereafter, a handful of letters tainted with anthrax ushered in the first widespread biological attack that the nation had experienced. Despite the low casualty count, the letters led to a massive disruption of the US Postal Service infrastructure and cost hundreds of millions of dollars to remediate. After extensive investigation, the crime remains unsolved, leaving many to wonder if it could happen again. These events had wide-reaching aftershocks as the nation returned to war and scrambled to improve the nation’s disaster and terrorism detection, response, and recovery infrastructure at an unprecedented cost to the public. The megadisaster of the 2001 terrorist attacks on the United States continues to claim casualties and astronomical costs 6 years later and has affected every person in the United States in one way or another.
Children are among the most susceptible members of a community when catastrophes such as these strike because of their dependent nature as well as their physiologic and psychological vulnerability. Children affected by Katrina were no exception. Persistent critical gaps exist in the ability to prepare for and respond to the needs of the youngest victims. These were clearly exposed as children endured an at times ineffectual disaster response followed by a stressful recovery that is still ongoing. An analysis of the issues that faced children during this event and some others from the recent past may help society reduce the impact of such disasters on children in the future. This article focuses on a few of the major shortfalls in the care of children that have become especially apparent in the last few years:

- Facilitating evacuation
- Providing shelter
- Caring for those with special medical needs
- Addressing mental health needs

These scenarios are not new. Historical accounts of the aftermath of the 1906 San Francisco Earthquake depict a scene that mirrors that following Hurricane Katrina—with widespread suffering; overworked and overwhelmed public services, such as law enforcement and hospital care; and inadequate public relief in the form of food, water, and shelter. As some who have studied this megadisaster observed, “society’s ability to respond to major disasters seems to have progressed little in the century” [2].

Future disasters will predictably overwhelm the public and those who work to maintain health, safety, and lawfulness in society. No amount of prevention and mitigation will ever fully eliminate the burden of large-scale disasters. That said, it is entirely realistic to set achievable goals that may significantly reduce preventable suffering and ensure equity for all affected individuals preparing for, responding to, and recovering from a disaster. These goals are best accomplished by learning from past experiences, both distant and recent, studying new preparedness and response strategies, and taking purposeful action when indicated.

**CRITICAL RESPONSE AND RECOVERY ISSUES**

**Evacuation**

During and after Hurricane Katrina, children were especially vulnerable to harm from the disorderly evacuation and chaos that followed in New Orleans after the levees broke and the city flooded. Estimates are that 80% of the population of the city relocated ahead of the storm, with approximately 25,000 using a “refuge of last resort,” the city’s Louisiana Superdome [3]. Many rode the storm out in their homes. With an immense population on the move and the remainder in areas with conditions that would quickly deteriorate, many of the children involved in the evacuation soon faced struggles that would range from a shortage of shelter, food, water, and chronic medical care to an imminent threat to their lives as their homes were overtaken by floodwaters. Heroic efforts by the military, the US Coast Guard, authorities,
and the public resulted in the rescue of tens of thousands who would likely have perished. Local, state, and federal officials, as well as volunteers, worked tirelessly but haphazardly to provide rescue and relief under oppressive conditions. Many children were removed from harm’s way and delivered to shelters or evacuation waystations, such as the city’s Louis Armstrong Airport, with few initial physical casualties. During the first days of the storm and the subsequent evacuations, nearly 5000 children were reported missing. Eventually, nearly all of the children were reunited with their caregivers. In some cases, however, this process took up to 2 months. Many children endured frightening experiences. One third of surveyed fourth to twelfth graders in the region reported that they were separated from their caregivers during or after the storm. An additional one third reported being separated from a family pet. One in five reported an injury to a family member, and 15% said that a family member had died [4].

Just a few weeks after Hurricane Katrina struck New Orleans, Hurricane Rita threatened the Gulf Coast. The hurricane’s path would likely bring the storm through Houston. Motivated by fears of another Katrina-like catastrophe, 2.5 million people evacuated the region. Ninety of the 111 storm-related deaths in this instance were due to the evacuation process itself as gridlock on the highway and oppressive heat took its toll on the chronically ill and elderly. Several complicated issues emerged as factors affecting the process of evacuation.

**Barriers to preparedness**

A national survey conducted in 2006 by the National Center for Disaster Preparedness demonstrated that only a minority of the American public is personally prepared for a disaster [5]. Less than one third (31%) have made basic family emergency preparations, which means planning on a meeting place and having at hand at least a 2-day supply of food and water, a flashlight, a portable radio, spare batteries, and emergency phone numbers. In terms of attitude, two-thirds (66%) feel personally unprepared. These figures are virtually unchanged from 2005 (31% and 64%, respectively).

During and after Hurricane Katrina, some children were unavoidably separated from families during the rescue process, and others may not have been with their families when the storm made further travel impossible. Still, a general lack of disaster preparedness by individuals and families likely contributed to the large initial number of missing children. Without a mechanism for all members of a family to reconnect, such as via an out-of-area contact, it can take days, weeks, or longer for such agencies as the American Red Cross and the National Center for Missing and Exploited Children to reconnect separated people. Asked why they do not have a family emergency preparedness plan, a quarter of those surveyed (26%) say they have not had enough time to assemble these items with nearly another quarter (22%) saying they do not know what to do to achieve basic preparedness. Only 3% report that they already feel prepared. The percentages for these reasons are virtually unchanged
since 2005. These findings strongly suggest that despite recent well-funded and well-intended efforts by government emergency officials and employers, risk communication has failed to convince the American public that family disaster preparedness is essential.

A community evacuation plan that engages all citizens and accounts for their needs is an essential element of community preparedness. As was made apparent in New Orleans, the government must direct and facilitate the movement of individuals out of harm’s way to the extent possible. However, the cooperation of those citizens who would be required to evacuate is also crucial. Moving people to safety in an orderly fashion during an emergency has been and can be expected to continue to be problematic. Lack of personal or public transportation and concerns about the welfare of dependents are daunting barriers to effective community evacuation, as was demonstrated in New Orleans. Surveys reveal that 29% of respondents cite lack of access to transportation as a reason that they would be unable to evacuate when ordered to by authorities, a figure virtually identical to responses in 2005 (30%). An overwhelming 92% of Americans have at least one reason why they would not evacuate immediately if ordered to do so. This is unchanged since 2005. The most common reasons cited are the need to ensure the safety of dependent family members—children (48%), elderly (47%), disabled (45%), and pets (34%) [5].

The same study also indicates a low level of confidence in the government to be able to provide essential disaster services to the community. After Hurricane Katrina, fewer than half of the residents in the Gulf Region are confident in the ability of government to respond appropriately to a natural disaster (47%). In 2006, only half of those questioned in a national poll felt that their government had adequate plans in place to respond to a natural disaster. This was unchanged from 2005, pre-Katrina. The number of those who said they would resist a mandatory evacuation order increased in 2006 to 42%, up from 36% the year before [5]. These data suggest that there is a critical shortfall in the engagement of individuals and families to become partners with government agencies that are supposed to protect them, and vice versa. As seen in New Orleans during Hurricane Katrina, a disconnect between emergency messaging by authorities and public response likely contributed to poor decision-making by many in the community as the threat from the storm increased and time ran out to evacuate. This led to a drastically unstable scenario that risked the lives of tens of thousands of victims, and generated an immense demand on the government to conduct dangerous, costly, and labor-intensive rescue and relief operations. The challenging logistics of evacuating a family with children, elderly family members, and pets during a disaster suggest that planning has an important role, as does ensuring that all members of the community have access to a means to evacuate when ordered to do so.

An unengaged and unprepared population is at a disadvantage when disaster strikes. It is valuable to explore the different experience that the island nation of Cuba has had with respect to risk communications, public preparedness, and disaster-related morbidity and mortality, for there are likely practices and
behaviors that would serve us well in the United States. The size, intensity, and frequency of hurricanes that seasonally threaten Cuba are similar to those that affect the southeastern United States. What are very different are the outcomes that Cuba has been able to attain. For Hurricane Ivan, nearly 2 million were evacuated with no fatalities compared with 39 in Grenada, 25 in the United States, 17 in Jamaica, 4 in the Dominican Republic, 3 in Venezuela, 2 in the Cayman Islands, and 1 each in Tobago and Barbados [6,7]. Cuba has drastically reduced the number of storm-related deaths and injuries over the last few decades by promoting a system of citizen preparedness and involvement that starts in elementary school and includes mandatory civil defense training for adults. Furthermore, it has been done without a vast expenditure of funds. Children understand the basic concept of risk from hurricanes at an early age, and use this as a foundation for learning such skills as first aid and storm preparedness. Annual government-sponsored nationwide hurricane drills providestandard[8,9] all citizens with the opportunity to test their family and community emergency plans before there is a crisis, and there is near complete buy-in to the benefits of this preparation.

There is also widespread cooperation among the population, the Cuban Red Cross, the civil defense authorities, the military, the government, and the broadcast media. When a hurricane does threaten, the citizens become extremely engaged in the potential threat and follow the storm’s progress closely by television and radio. When authorities order an evacuation, it is undertaken promptly, efficiently, and decisively, with communities ensuring that those who need special assistance receive it. Because the actions of the community are rehearsed annually and are familiar, it is possible to efficiently evacuate and shelter many hundreds of thousands of citizens in short order when necessary. Although it would be naïve to think that the practices of a socialist society could be directly translated into a system that could operate well in the United States, the concept of engaging the public and practicing emergency procedures is an effective, but hardly a foreign, one. Indeed it is a system that has worked well for fire safety for generations in the United States. The ubiquitous fire drill at school, work, and home emphasizes that a behavior that is practiced is a behavior more likely to be used in a crisis. Box 1 lists guidelines in planning for a disaster and evacuation.

**Decision-making**

The issue of communicating risk and influencing public action is complex. Many who stayed behind in New Orleans during Hurricane Katrina may have felt that their lives, pets, and property would be better served by remaining at home rather than evacuating. Others certainly felt that the threat was not severe enough to merit the inconvenience, expense, and inherent risk of taking part in a mass evacuation. Still others may have felt that they had no place to go, and did not feel safe moving into a shelter. The track of a hurricane is difficult to predict at the time when the evacuation of a region needs to begin, typically 30 to 50 hours or more before the onset of a hurricane.
of predicted damaging winds. As a result, many inhabitants of the Gulf Coast had years or decades of experience with “false alarm” warnings and evacuations, and a subsequent perception of low individual vulnerability to the effects of a storm. Despite unprecedented warnings from the National Weather Service and the mayor prior to Hurricane Katrina, many still chose or were forced to stay behind when an evacuation order was issued for the city of New Orleans. There was overdependence by the city on an outdated emergency plan and an overreliance on the anticipated use of personal vehicles for evacuation when nearly 1 in 10 citizens did not have access to one. As a result, some individuals were not physically capable of evacuating in their own vehicles and the city could not make up for this incapacity with public transportation. Similarly, during Hurricane Rita, authorities underestimated the volume of vehicle traffic during the evacuation of the Houston area, resulting in massive congestion and fuel shortages. In Katrina, some state and federal assets were not called upon in a timely manner, and persistent bureaucracy was a steep barrier to many of the out-of-state personnel who wanted to assist. Box 2 lists guidelines related to disaster preparations and decision-making.

Box 1: Lessons learned: planning for disaster and evacuation

Ensure that all family members know of an out-of-area contact they can call.
Teach children their phone numbers and address as early as possible.
Provide children with an emergency contact information card and have them keep it with them at all times.
Put together a supply kit of practical emergency equipment that may be needed in a disaster, and remember that it may need to be portable. Essentials include water, food, shelter, and essential medications. Include a recent photo of your children.
Discuss an emergency plan with all members of the family before there is an emergency. This plan should include actions for family members if they not at home when an emergency occurs.
Practice your emergency plan regularly. How will your family stay warm, find water, stay safe, and obtain emergency information during a variety of emergencies?
Promote and enable a culture of preparedness. Countries with mandatory, routine community disaster drills are capable of responding to disasters with fewer injuries and fatalities because people are familiar what they are supposed to do.
Remember that routine emergency services, such as 911, likely will not be available during a disaster.
If an evacuation becomes necessary, consider writing essential information about your child on his or her arm with a permanent marker in case you become separated.
Include family pets in emergency planning. They may not be able to accompany the family during evacuation or be allowed in shelters.
Obtaining shelter

The mass movement of hundreds of thousands of hurricane victims before, during, and after Katrina placed an enormous burden upon the survivors as well as the agencies and private individuals who assisted with sheltering. The Federal Emergency Management Agency (FEMA) reported nearly 200,000 adults and children were in public shelters, with an unknown number staying in motels, camping, or living with others. The quantity of storm-related “internally displaced persons” who are still living away from their previous home on the Gulf Coast has been cited at 1 million or more [8,9]. As mentioned above, an estimated 25,000 persons sheltered initially at the Louisiana Superdome, with up to 20,000 at the nearby New Orleans Convention Center. This situation was partially a result of the inability of the city to coordinate public transportation out of the area for those who did not have a vehicle. While there is no information about the number of children who sheltered in both the Superdome and the Convention Center, the number can be estimated from a survey of those survivors who were in the Houston Astrodome. Many were initially sheltered at the Superdome or the Convention Center. One third of the adults surveyed report having a child with them, which would suggest a minimum of approximately 15,000 children between the two refuges of last resort in New Orleans [10].

Children in the shelter environment pose special challenges because of their typically curious and active behavior. These challenges can include those related to safety and security, hygiene, health maintenance, and disease prevention.

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**Box 2: Lessons learned: guidelines for being well prepared and making good decisions**

Individuals and their families have a duty to make responsible decisions, using the best information available. Children are dependent upon the good decision-making of their caregivers and should be subjected to the lowest amount of risk possible.

Consistently honest communication with the public regarding projected risk is likely a useful approach in the long term.

Risk assessment is a vital part of emergency preparedness at the personal and governmental level, and it should guide the development of response and recovery plans.

Families and communities should engage their local governments to share important disaster preparedness information.

Communities can play an active role in promoting their own readiness for emergencies through volunteerism, role modeling, and activism.

Children should be encouraged to be active participants in their family disaster planning and know their roles during an emergency. Practice with children essential basic lifesaving skills, such as home fire safety, first aid, and water safety, and review specifics of the family disaster plan.
Disaster survivors frequently arrive at a shelter with few belongings. Frequently, items such as personal medications, personal hygiene supplies, and adequate food, water, and clothing are left behind. Hurricane Katrina was no exception, and many children arriving at shelters found themselves in an environment that could not support them with adequate water, nutrition, diapers, formula, or prescription medications, especially at first. As a result, it was not uncommon for hygiene conditions to rapidly deteriorate—a situation made worse by ineffective or nonexistent hand-washing facilities. Children are an important variable with regards to the spread of disease in a large communal living environment, such as a shelter. Because of their hand-to-mouth activity and close contact with other people and objects, it is thought that children are at a higher risk of acquiring respiratory and gastrointestinal diseases under these conditions. Additionally, because of their mobile and social nature, children are probably more efficient than adults at spreading certain diseases in this environment, which is similar to that of a shelter, such as a school or daycare center, where children will naturally congregate. Several shelters, including the massive Houston Astrodome, were affected by outbreaks of gastrointestinal disease, including *Norovirus* and presumed dysentery, although it is yet unclear the specific role that children played in these particular outbreaks, if any.

For a number of reasons, many emergency shelters are inherently unsafe or poor environments for children. For instance, there is no assurance of childproofing of medications and dangerous items that may be accessible. The supervision of children in this situation can be difficult at best. At the Louisiana Superdome, widespread rumors of child assault and rape contributed to a climate of fear, vulnerability, and stress. In some cases, pets were admitted to shelters because they accompanied the owners during evacuation, posing an additional risk. The stress of sudden dislocation, danger, and disorientation can be extremely challenging for children and their families.

Infants and children are more vulnerable to an interruption in the availability of essential supplies, such as water and nutrition. Problems facing those who were evacuated from New Orleans included a shortage of infant formula and bottles to deliver it. There was great concern about the need to maintain health prevention in the pediatric shelter population after the storm. Shelter managers and medical personnel were concerned about an inability to deliver important treatments, such as tetanus prophylaxis and antibiotics for those injured or exposed to floodwater. There were also concerns about potential epidemics of childhood diseases, such as measles, pertussis, and chicken pox, as well as hepatitis A for those exposed to floodwaters.

As with planning for evacuation, planning for shelter is an essential component in the continuum of disaster preparedness. As discussed above, an over-reliance on authorities or the American Red Cross (a nongovernmental agency responsible for coordinating mass care services) to completely provide for the essentials of food, water, shelter, and family emergency needs, such as
medications, can be problematic. Much of the work of operating a shelter involves assisting those who have not prepared adequately to evacuate. If and when first aid stations are set up at a shelter, the top complaint is typically forgotten medications, an issue that can be time-consuming, if not impossible, to resolve. Forgotten or lost eyeglasses or contacts is the fourth most common chief medical complaint of evacuees, after physical complaints for gastrointestinal or respiratory symptoms.

From the provider standpoint, the experience with Hurricane Katrina revealed a gross underestimate of the basic needs of the sheltered population, especially in the initial stages of the response. In some cases, there were extensive specialized emergency supplies but a drastic shortage of the basics that are important for caring for children, such as formula, diapers, baby wipes, soap, and hand sanitizer. Compounding this situation, the resupply of these consumable items was at times impossible because of a host of logistical barriers. Another issue was the custody and care of children who were lost or unattended. Box 3 lists issues to keep in mind regarding shelter during a disaster.

Children with chronic and special health care needs
The care of children with special health care needs (CSHCN) during disasters is a topic that has come to the forefront after Katrina. Inasmuch as children are an underrepresented minority when it comes to disaster preparedness, CSHCN suffered even more disproportionately during the mass evacuations in the Gulf Coast. Because they depend on dedicated medical equipment, specialized medications, or their “medical home” of providers and specialists, children and adults with chronic health care needs can be especially vulnerable if preparations for disaster are inadequate.

**Box 3: Lessons learned: issues to keep in mind regarding shelter**

Do not assume that an emergency shelter will provide food, water, medication or eyeglass replacement, and hygiene items. These should be part of a family’s emergency supplies and brought along during evacuation and sheltering.

Children play a unique role in the shelter environment with their ability to both spread and contract diseases, and proper hand-washing may not be possible. Waterless hand sanitizer may be a valuable item to bring along.

The shelter environment can be a dangerous place for children. They need to be closely supervised.

Children may be difficult to supervise in a shelter. Consider bringing something to keep them occupied.

Shelter managers should have a plan to reestablish pediatric health care as soon as possible, with a focus on screening for disease and ensuring that post-disaster immunizations can be delivered if needed.

Shelter managers in their planning should recognize the high demand for infant-care supplies, such as baby formula and diapers.
The prevalence and distribution of CSHCN is larger than one might expect, which recently led to disaster planning oversights that had serious repercussions. Approximately 13% of children are identified as CSHCN. The number of families who self-identify as having a family member who is CSHCN is 20% [11]. There is little variability across socio-economic descriptors. As medical technology and home care becomes more advanced, an increasing number of CSHCN who previously lived at a specialized care facility are now in the home.

The conditions that define a child as a CSHCN include, in the order of prevalence, (1) a need for specialized prescription medications (75%); (2) a need for increased medical care (46%); (3) a need for emotional, behavioral, or developmental services (29%); (4) a limitation of activities (21%); and (5) a requirement for specialized therapies (17%) [11]. More than one of these descriptors may apply to many CSHCN. Each of these categories presents a unique vulnerability to the child required to break routine and undergo evacuation or emergency sheltering.

Separation from specialized equipment
The type of equipment that a CSHCN may depend on ranges from the assistive (motorized wheelchair) to the life-sustaining (home ventilator). In the inevitable crowded rush to evacuate before, during, and after a disaster, it is not uncommon for the decision to be made to separate a patient from his or her equipment due to time or space considerations. As New Orleans was evacuated during Katrina, devices that were not life-sustaining were often left behind under the assumption that a substitute could be acquired at the patient’s ultimate destination. At the Louis Armstrong Airport medical waystation outside of New Orleans, evacuating survivors with nonacute medical needs were categorized as either able to walk to a commercial aircraft, or they were placed on military stretchers or in a wheelchair to await specialized military medical evacuation. Few accommodations were made for durable medical equipment that was not small and portable. There were limited options for those who required specialized medicines that were not in the government stockpile of basic pharmaceuticals, and options quickly ran out for patients who needed dialysis in the short term. In addition to the impact on health and life, this posed an unimaginable inconvenience to the patient, for whom the specialized equipment was a part of their identity as much as a technical means for them to care for themselves once they arrived at a shelter.

Separation from specialized care
Evacuation places a special burden on those who frequently visit clinics, rely on home nursing services, or otherwise depend on outside resources. Such resources are likely unavailable or reduced during a disaster, whether an evacuation occurs or not. Without adequate planning, the conditions of patients who are medically complicated are at an extreme risk of deteriorating if disaster has an impact on daily routine or if there is a loss of essential services, such as
electricity or supply delivery. As discussed above, a basic shelter will probably not have any specialized medical supplies or staffing with the knowledge to properly care for a complicated CSHCN. There will likely be limited accommodations for those with sensory impairment.

As a result, specialized medical shelters have been developed in some areas to address the care needs of both children and adults with special health care requirements. These may be separate facilities or they may exist within a large general shelter for the public. With adequate planning and enough lead time, it may also be possible to relocate a CSHCN directly to a medical facility outside the affected region. Proper identification of the systems that will be expected to relocate and care for a CSHCN is a vital part of preparedness that must be done ahead of time. The child’s “medical home” caregiver has a special responsibility to incorporate disaster planning into the overall care plan for the CSHCN.

When a CSHCN is relocated away from his or her medical home, the child may pose an extreme diagnostic challenge to medical providers, who may well be overwhelmed with medical responsibilities and who may not be pediatric specialists. Regardless of the diagnosis, it is helpful for a family emergency kit to contain an updated copy of an emergency information form for a patient with special health care needs (Appendix A). This document is created by the caregiver who knows the patient best, and it will provide invaluable guidance to reestablishing routine or emergency medical care in another location. If special medications are an important part of the child’s routine, this must be accounted for during disaster planning. Medications that require refrigeration and frequent resupply will pose a special, but not insurmountable, challenge.

In some cases, such as Hurricane Katrina, the impact of the storm upon the health care facilities destroyed the permanent medical records of many patients, some of whom were complicated CSHCN. This has the potential to set back the care of the child greatly. In addition to the emergency form, it is important to discuss with the child’s primary care provider how this information is backed up. It may be worthwhile to have a redundant copy stored in a safe location at home. From the perspective of a health care system, it is vital for future operation to be able to re-create any data that is destroyed during a disaster. Having electronic medical records that are backed up at multiple locations is a valuable concept and in all parties’ best interests. Box 4 lists issues and concerns related to accommodating children with special health care needs during a disaster.

Mental health response

The scope of pediatric mental health disorders after disaster

There is extensive literature on the psychological impact of disasters on both children and adults. This literature covers a wide range of events, such as natural and technologic disasters. This section reviews some of the findings describing the psychological impact of disasters, both natural and human-caused on children. With this as background, the authors present new data gathered by the Children’s Health Fund and the National Center for Disaster Preparedness on the mental health consequences of the terrorist attacks of September 11,
2001, and summarize findings from recent survey research following the extensive damage and forced relocation of families in Louisiana and Mississippi after Hurricanes Katrina and Rita, and the flooding in New Orleans subsequent to the breach of the levees there.

Analyses of the responses to past disasters demonstrate that psychological reactions in children do not necessarily follow a routine pattern or match the presentation of a similar condition in an adult. They can be delayed, complex, and long-lasting. For example, focusing on natural disaster in the United States, Shaw and colleagues [12] found that 70% of the school-age children reevaluated 21 months after exposure to Hurricane Andrew continued to exhibit moderate to severe posttraumatic stress symptoms. Two years after a dam break and flood, approximately 37% of the exposed children and adolescents still had a probable diagnosis of posttraumatic stress disorder (PTSD) [13]. Outpatient mental health use increased to a statistically significant degree in the first year after Hurricane Floyd made landfall in North Carolina in 1999 [14]. A failure to provide mental health interventions following exposure to the 1988 Spitak earthquake in Armenia was associated with PTSD and depression in exposed and untreated adolescents [15]. Conversely, school-based mental health screening and targeted psychosocial intervention proved effective in identifying children with posttraumatic stress reactions and reducing their severity and impact following Hurricane Iniki in 1992 [16].

**Box 4: Lessons learned: accommodating children with special health care needs**

The prevalence of children with special health care needs is approximately one in eight.

The prevalence of households who self-define as having a CSHCN is one in five.

A range of conditions may lead to a definition of CSHCN. These include a dependence upon prescription pharmaceuticals, a need for an increased level of care, the need for emotional or behavioral services, a limitation of activities, and a requirement for special therapies.

The separation of medical or adaptive equipment from a dependent patient has significant repercussions and should be avoided wherever possible.

Most shelters will not have the capacity to care for complex CSHCN.

Some specialized medical shelters have been established and may be freestanding or integrated into existing general shelters.

Medical information sharing is essential when a child is removed from his or her medical home. The use of an emergency medical information form should be encouraged to optimize the care of the child by unfamiliar providers.

The loss of medical records in a disaster can have a significant impact upon both patients and the provider. Establishing redundant copies is advisable.

Planning ahead for the disaster-time care of a CSHCN is vital. The child’s primary care provider should be actively involved in developing a preparedness plan for the child and his or her family.
The separation of children from parents as well as parental stress reactions emerged as risk factors for protracted child psychological reactions. McFarlane [17] found that 26 months after exposure to an Australian wildland fire, one third of the children studied continued to present significant posttraumatic stress symptoms. It was reported that separation from parents in the immediate aftermath of the fire, maternal preoccupation with disaster, and the altered family dynamics were more important determinants of continuing symptomatology than the child’s degree of first-hand exposure to the threat. These findings foreshadow some of the risks associated with the mass evacuation and relocation of children and families following Hurricane Katrina.

A substantial body of literature describes the mental health impact on children of the 1995 bombing of the Alfred P. Murrah Federal Building in Oklahoma City. Investigators found that more than 40% of regional middle and high school students knew someone who had been injured and more than one third knew someone who had died in the explosion. Besides the widespread first-degree contact with loss around the event, PTSD symptoms were associated with both direct exposure and with watching television reports of the bombing. Two thirds (67%) reported worrying about their own and their family’s safety [18]. These studies explore the role that mass media likely plays in the development of posttraumatic stress symptoms. Symptoms being manifested in locales geographically distant from the bombing are likely due to this effect [19–22]. Based on the Oklahoma City experience, it was recommended that child and adolescent television viewing of terrorist events be monitored and restricted, but this has proven difficult.

Child reactions to two megadisasters: September 11, 2001, and Hurricane Katrina

Ample experience from prior events could have predicted the widespread and long-standing impact that the terror attacks of 9/11 and the flooding and evacuation following the landfall of Hurricane Katrina had and are continuing to exert upon children.

New York City, September 11, 2001, terrorist attacks. The Children’s Health Fund and National Center for Disaster Preparedness at Columbia University, working with Marist College Institute for Public Opinion, developed and implemented surveys of child and family reactions to the events of 9/11 throughout 2002 and 2003, with representative New York City and national samples consistent with US Census Bureau data. Psychological reactions of New York City children were ascertained by interviewing parents about new concerns and new symptoms. It was immediately appreciated that in the first year after 9/11, reactions were geographically dispersed throughout New York City rather than concentrated or confined to those directly impacted; there was no psychological ground zero. The most pervasive reactions were concern about safety and fear of another attack, at 45% and 42% respectively 1 year after 9/11. The most stable symptomatic reaction was somatic complaints (headache, stomachache), reported by 15% of parents 3 weeks after
9/11. Somatic complaints affected 16% of city children by the end of the first year and the same percentage 2 years post-9/11. This finding has implications for pediatricians and other health care providers, since these “subclinical” physical complaints may be indicative of posttraumatic stress reactions. Detailed results are included Table 1.

As an indicator of the need for mental health assessment and intervention, positive responses on these surveys were aggregated for children reported to have had four or more concerns or symptoms. Three weeks after 9/11, 36% of children reported multiple psychological reactions, declining only to 34% at 6 months and 29% at 1 year. Two years after the attacks, this figure had only declined to 23%, nearly one in four New York City children still exhibiting multiple reactions. These data suggest that posttraumatic stress reactions are likely to be protracted, at least without appropriate intervention. A review of the geographic distribution of children with multiple concerns and symptoms reveals that the highest rates were in the boroughs with the lowest income and highest proportion of racial–ethnic minority diversity with 32% in the Bronx and 31% in Brooklyn affected. This is in contrast to the 26% rate among children residing in Manhattan, which was the wealthiest borough and the location of the World Trade Center, where the attack took place.

In the iteration of the survey 2 years after 9/11, questions regarding parental reactions to the terrorist attacks and prior exposures to trauma within the family were added. Child reactions were analyzed for associations with parent reactions and prior stressors, and a positive correlation was apparent. Children with at least one post-9/11 concern were significantly more likely to have parents with at least one post-9/11 symptom. Fifty-two percent of children with multiple concerns and symptoms had a parent who reported being more impatient and irritable compared with 8% of children with no reactions and 16% with one to three reactions. Sixty-two percent of children with four or more

<table>
<thead>
<tr>
<th>Concern or symptom</th>
<th>3 weeks post-9/11 (October 2001)</th>
<th>6 months post-9/11 (March 2002)</th>
<th>1 year post-9/11 (August 2001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concern about own and family safety</td>
<td>52%</td>
<td>52%</td>
<td>45%</td>
</tr>
<tr>
<td>Fear of another terrorist attack</td>
<td>52%</td>
<td>47%</td>
<td>42%</td>
</tr>
<tr>
<td>Nightmares, sleep disturbance</td>
<td>20%</td>
<td>17%</td>
<td>17%</td>
</tr>
<tr>
<td>Anxiety, distractibility</td>
<td>39%</td>
<td>38%</td>
<td>30%</td>
</tr>
<tr>
<td>Depression, sadness, crying</td>
<td>29%</td>
<td>21%</td>
<td>16%</td>
</tr>
<tr>
<td>Somatic complaints: stomachache, headache</td>
<td>15%</td>
<td>16%</td>
<td>16%</td>
</tr>
</tbody>
</table>
concerns and symptoms had a parent who reported being sad or depressed, compared with 14% with no reactions and 26% with one to three reactions.

The most common child reaction 2 years post-9/11 remained concern about safety, affecting 42% of the city’s children. All (100%) children with one or more complaints reported having this concern as one of the multiple issues. Children with concern about their own and their family’s safety were significantly more likely to be fearful of another terrorist attack than those who did not have this concern.

By the end of the 2003, a profile of children with the greatest need for mental health intervention became apparent, with 67% of these children reported as depressed, sad, or prone to crying, and 87% being distracted, anxious, or nervous. Almost half (48%) showed regressive behavior, which included being clingy and attention-seeking.

In terms of race and ethnicity, the highest rate of posttraumatic distress was among Hispanic children, among whom 32% had multiple concerns and symptoms, compared with 22% of black children and 15% of white children. Poverty was also a factor. Among families with incomes below $50,000, 28% of children displayed multiple concerns and reactions compared with 17% among families with income above $50,000. In New York’s poorest borough, the Bronx, 26% of children had multiple concerns and symptoms and only 27% had no reactions at all. In Manhattan, 15% had multiple concerns and symptoms while nearly half (48%) had no post-9/11 reactions. These results are consistent with findings that low income is a risk factor for posttraumatic stress reactions following a disaster or terrorist attack [23, 24].

Prior exposure to trauma emerged as a factor in post-9/11 reactions. One fourth (25%) of children with multiple concerns and symptoms had experienced some prior trauma, such as being a victim of or a witness to violent crime, or being in a serious accident, compared with 18% of families of children with one to three reactions and 16% of families of children with no reported reactions.

The key child symptom questions asked in New York City were then repeated with a representative national sample. The degree to which the psychological impact of a megadisaster is experienced nationwide is reflected in these results 2 years after the terrorist attacks of 9/11. About one child in five nationally (21%) had increased concern about safety and was fearful of another terrorist attack; 13% were reported to be demonstrating a qualitative increase in regressive behavior; 12% anxiety; 9% somatic symptoms; and 5% depression and sadness. These children were evenly distributed among the regions of the country. However, racial–ethnic and income disparities were marked. Twenty-four percent of Hispanic children had multiple reactions, compared with 12% black and 7% white. The percentage of children with multiple reactions in families with incomes below $50,000 was 50% higher than in families with incomes above $50,000 (12% versus 8% respectively).

Hurricane Katrina and the Gulf Coast. Before the hurricanes, Louisiana and Mississippi vied for the nation’s highest poverty rates, highest percentage of
uninsured children, and worst child health indicators [25,26]. These everyday social and public health challenges suggest that the region was poorly positioned at a baseline to respond to a surge in acute medical and mental health need, which was demonstrated in 2005.

Federal survey data from Katrina evacuees sheltered in San Antonio several weeks after the hurricane found that 42% of evacuee households had at least one member with a chronic health condition, 28% had at least one member with a physical or mental disability, and 20% reported a current need for mental health intervention for at least one member [27]. These high rates of chronic conditions and mental health needs were subsequently corroborated in survey research done by Columbia University’s National Center for Disaster Preparedness with families living in temporary FEMA-subsidized housing, typically mobile-home-style trailers. In common with earlier survey data of adult Katrina evacuees in Houston [10], the families in FEMA housing in both Louisiana and Mississippi were disproportionately low-income and African-American. Abramson and Garfield [28,29] observed that low-income families making <$10,000/y were the hardest hit economically by the hurricane, with 53% losing all source of income (compared with 15% for families with income >$20,000/y).

One year after Katrina, more than half of caregivers at relocation sites in Mississippi reported that at least one of their children had new mental health concerns that emerged after the hurricanes. This is an even higher rate than was reported with similar methodology in FEMA relocation sites in Louisiana 6 months after the disaster, strongly suggesting that mental health issues after a megadisaster continue to emerge over time. In Mississippi, the rate of diagnosed child depression and anxiety disorders nearly quadrupled. Reported behavior problems doubled. It is likely that the pattern of overcrowded, occasionally dangerous, and transient living conditions that evacuees have been subjected to has contributed to the emergence of ongoing psychological problems [28].

In Mississippi, data following screening with a standardized instrument show that adult mental health symptoms are endemic amongst evacuees [30]. Sixty-two percent of parents or caregivers reported symptoms of depression, anxiety, and/or posttraumatic stress disorders. This exceeds the screening results for Louisiana parents in FEMA shelters of >50%, again reinforcing evidence that postdisaster mental health problems emerge over time. Thirteen percent of parents reported that they were not able to cope day to day with the demands of caring for a child, an eightfold increase compared with pre-Katrina levels. Given the established degree to which parental coping mediates child reactions, this finding indicates an additional risk factor for problematic posttraumatic stress reactions in children.

Reports from school-based health centers throughout Louisiana indicate a greatly increased need for mental health services in the schools following Hurricane Katrina. Schools, especially those with a greater number or percentage of relocated students, reported relative increases in quarrels and
fights among students (73% and 67% of schools respectively), truancy (55%), disruptive behavior (43%), and sexual promiscuity (31%). School personnel, including mental health professionals, reported a greatly increased need to provide case management and other concrete support services to parents [31].

Unmet postdisaster mental health needs. FEMA reports that it made available the highest level of funding (more than $150 million) for postdisaster crisis counseling to New York following 9/11. Despite this, numerous sources indicate that there was and continues to be a mismatch between those in need and the services that could help them. A New York City study of the psychological impact and services received by children after the terrorist attacks of September 11 reported that approximately 18% of children had severe or very severe post-traumatic stress reactions, with only 27% of them receiving counseling or intervention services [32].

One year after 9/11, only 13% of children in need had received mental health intervention. It was again observed that those with the most severe post-disaster responses (four or more post-9/11 reactions) were more likely to receive care. However, only 24% of these children received professional intervention, leaving three fourths untreated or potentially receiving inadequate services. Particularly noteworthy was the asymmetric distribution of, and access to, pediatric mental health resources. As noted previously, the need was greatest in the city’s poorest borough, the Bronx, where only 9% of children with multiple postdisaster reactions received mental health services compared with 22% in Manhattan.

The disparity between federal funding and actual receipt of mental health services by those in need is related in part to the narrow definition that the federal government has adopted for the term “crisis counseling.” Restrictions on the allowable use of federal crisis counseling funding have impeded the ability of communities in New York and the Gulf Coast to rapidly ramp up their clinical mental health services after a disaster. Instead, “crisis counseling” has frequently consisted of simple mental health screening with little opportunity for necessary referral or follow-up, peer counseling, or the distribution of public service announcements. These broad and shallow interventions fall short of reacting to the acute need for true mental health services by patients with postdisaster depression, anxiety, and posttraumatic stress reactions. Children can become trapped in this process and, as we have seen, in many cases go un- or under-treated. In New York, data from the State Office of Mental Health show that 687,848 crisis counseling sessions were provided to 465,428 individuals, an average of approximately 1.5 sessions per user, most of whom were adults. These sessions were provided between September 2001 and December 2003 [33,34]. These data suggest that aggressive, longitudinal mental health interventions for children were poorly provided within the context of post-9/11 acute crisis counseling services. Additionally, most of the crisis counseling services funded with FEMA appropriations to New York City were terminated in August 2003. This in part accounts for the
The fact that only $137 million of the $155 million appropriation was spent and that services were terminated abruptly despite a documented ongoing need.

In recent years, evidence has been accumulating about the effectiveness of interventions for children’s mental health disorders. Unfortunately, many knowledge and practice gaps still remain. The literature is limited regarding best-practice models and evidence-based treatments for poor, underserved, or ethnic-minority children impacted by extensive trauma, exactly the demographic that suffered the most during Katrina. More information about pediatric postdisaster symptomatology, as well as comorbidities, such as substance abuse, nonaccidental injury, and suicide, need further exploration. Initial research suggests that all may play a significant role in this environment.

Increasing the ability to recognize pediatric psychological problems should be a priority, as should bolstering the training to pediatricians, family doctors, mental health professionals, and other caregivers. There should be an emphasis on the importance of using traditional support systems, such as clergy, extended family, and community agencies, to supplement acute-care services. First responders should be oriented to the possible mental health issues impacting children postdisasters and become skilled in providing psychological first aid to families during the initial stages of a disaster response. Psychological first aid is a concept of promoting a sense of safety, calmness, connectedness, and self-efficacy during the evolving stages of a disaster, while at the same time offering assistance if it is needed. For those who will be monitoring children for symptoms, it is important to have a better understanding and practice with differential diagnosis in particular of such disorders as PTSD, depression, and those associated with adjustment, anxiety, and mood. The unique needs of children with preexisting mental health conditions also must be taken into account as they are the most vulnerable to subsequent problems and long-term effects.

For the appropriate mental health care of children and families after a disaster, a mechanism should be in place to provide for concrete needs, such as housing, food, and clothing assistance, as well as rapid return to a sense of routine, including school. This must be accompanied by screening for all and prompt aggressive therapy for mental health issues when indicated. Children and adolescents need to feel safe, have significant support, and possess a sense of hope and consistency to give them the best chance at recovering psychologically after a disaster. This has been a major shortfall in the Hurricane Katrina recovery efforts. Many families with children—the estimates are 125,000—continue to live in isolated and crowded FEMA housing or trailer parks. Up to one third of these children are suffering from a chronic illness, such as asthma, and only 50% of those who previously had routine medical care still do. Truancy is epidemic, and the quality of the education children are receiving is significantly affected by overcrowding and a progressively unsafe learning environment [28,29].

Fostering a culture of resilience is an important way to empower individuals and families to recover their own lives after a disruption. In the postdisaster
context, resilience is the ability to summon personal, relational, social, and cultural resources to handle adversity in a way that does not interfere with long-term functioning. Enhanced self-esteem and generalized efficacy, improved communication, better conflict mediation skills, and augmented capabilities in other domains of cognitive problem-solving are related to increased resilience. These can all be encouraged by engaging families and individuals in the disaster planning process at all levels, and by promoting the sense that they cannot depend entirely upon a system that may not have the capacity to care for them in a time of need.

On a policy level, it is essential that all disaster plans include extensive resources for assessing and treating child mental health issues and concerns and those of their caregivers. This should involve the integration and prioritization of psychosocial needs of children in the preparedness planning of federal, state, and regional/local government agencies. Similarly, community-based agencies with a mission to promote wellness, foster resilience, and

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**Box 5: Lessons learned: guidelines for pediatric mental health services**

Immediately after a disaster, pediatric mental health interventions should be practical and responsive to the concrete needs of children.

As soon as possible after a disaster, it is essential to create opportunities for children to express their feelings and concerns, to establish an environment where children feel safe, and to re-establish for children a sense of normalcy.

Providing psycho-education services and intervention where necessary to parents and caregivers is an essential component of early-stage relief that can have a significant impact on children.

Children obtain their sense of safety from adult cues. For children, a predictable routine (e.g., school) and a consistent support system is important.

Direct losses may result in the development of more serious symptomatology, especially for children with previous exposure to loss or tragedy, or for those with preexisting mental illness.

Posttrauma symptoms often develop weeks or months after the “trigger” event.

Psychological problems may be inclusive or exclusive of PTSD. Such problems, which include depression, interpersonal problems, regression, stress, and an inability to trust and to feel safe and secure, may present right away or emerge over time. They may also be long-lasting.

There is no “ground zero” for the psychological effects of a disaster: The distance from the incident may not be directly related to the type or severity of symptoms.

Exposure to repetitive images or reports of a disaster on television or in other media may exacerbate the psychological response of a child and should be limited. The child should have an opportunity to discuss the meaning of those reports or images with an adult.
prepare families for disaster should be developed and funded. These agencies can focus on encouraging self-efficacy, better communication, and effective ways to involve all members of family in age, language, and culturally appropriate preparedness activities. Box 5 provides guidelines for pediatric mental health services during and following a disaster. Box 6 summarizes findings related to pediatric disaster mental health systems.

**Box 6: Lessons learned: pediatric disaster mental health systems**

Failure to provide adequate pediatric postdisaster mental health services when needed may increase the number and severity of symptoms, such as PTSD and depression.

Children in families with a low income as well as members of racial or ethnic minority populations are at a disproportionate risk for experiencing new and multiple psychological symptoms and/or behavior problems after a disaster.

After a disaster, the ability of a family with children to cope with the day-to-day pressures of care may decrease significantly.

Many children in need of services in the postdisaster environment may not be receiving them. A high index of suspicion is prudent to monitor for depression or stress-related symptoms.

After a disaster, there may be increased incidents of substance abuse, child maltreatment, suicidal ideation, and completed suicides.

**SUMMARY**

Many specific lessons were learned from recent megadisasters in the United States at the expense of children who suffered from a government and a citizenry that was desperately unprepared to respond to and recover from the disaster’s short- and long-term effects. During the 9/11 attacks, the nation learned a new sense of vulnerability as the specter of terrorism was delivered repeatedly to our collective consciousness. As this article has emphasized, children experienced significant and widespread psychological effects from this event, and many did not receive adequate treatment. Hurricane Katrina exploited the weaknesses of an already strained child mental health system and vividly demonstrated the liability of poor preparedness and inadequate communication by both families and governments. The impact of Katrina continues to affect many thousands of children over a year later, as the systems that were intended to care for them have largely moved on. Indeed, there was no mention of Hurricane Katrina, the Gulf Coast, or the storm’s survivors in the 2007 State of the Union address by the President.

After 9/11 and the unprecedented federal spending that occurred to increase our nation’s readiness, it is discouraging that the response to Hurricane Katrina fell so short of what had the potential to be the greatest disaster response and recovery story in the history of our nation. It is unlikely that further
Box 7: Lessons learned: national priorities for child disaster care

Encourage a national culture of preparedness that engages the public in taking responsibility for some of its own care during a crisis. Draw from successful examples, such as the Cuban disaster readiness system, which teaches children the fundamentals of preparedness and resilience and how to apply these skills. A national disaster preparedness day to apply and evaluate response and recovery planning at all levels would send a strong message to families, communities, and businesses in the United States that this is time well spent.

Assure that the disaster planning agencies as well as the medical response and sheltering systems in the United States are better informed and empowered to address the special medical and psychological needs of children after a disaster.

Encourage primary care providers for children, especially those with special health care needs, to become involved in advocating for effective family disaster preparedness.

Significant attention needs to be paid to the wide-reaching and long-lasting effects of disasters on the mental health of children. Recent research-based evidence should drive major efforts to increase the availability of direct services after a significant event. A special focus is needed for children identified to be at the highest risk for debilitating psychological effects, such as those who are members of racial or ethnic minority groups and those in poor families.

uncontained expenditures will solve the problems that were exposed in the Gulf Coast. There is not a solution that money can buy. One need only look a few hundred miles south to the Cuban disaster response system to appreciate where some of our shortfalls lie. Cuba has succeeded where the United States has not in part because its citizens are participants in their own preparedness. They engage their children and their families in preparedness planning and they rely upon other members of their community to strengthen their ability to survive as individuals. The American mentality of “dial 911 in an emergency and wait for help” works only as long as there are enough resources to match the need. In a disaster, this approach has proven to be inadequate over and over again. In America, we are well positioned to be leaders in responding to the needs of children affected by disaster. The resources of our government and the resourcefulness of our people should offer much promise for the future. By analyzing our past shortfalls and taking practical steps to mitigate the existing barriers to preparedness, our children, we hope, will fare much better the next time a megadisaster strikes. Box 7 includes suggestions for national priorities for child disaster care.

Acknowledgments
We are grateful to Sarah Overholt at the Children’s Health Fund for her assistance in the preparation of this document.
APPENDIX A. EMERGENCY INFORMATION FORM FOR CSHCN

Form includes statement that document may be released with credit to the American College of Emergency Physicians and the American Academy of Pediatrics.

### Emergency Information Form for Children With Special Needs

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### Diagnoses/Past Procedures/Physical Exam:

1. Baseline physical findings:

2.  

3. Baseline vital signs:

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<td>Baseline neurological status:</td>
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*Consent for release of this form to health care providers*
## References

1. Redlener I. Americans at risk: why we are not prepared for magadisasters and what we can do now. New York: Alfred A. Knopf; 2006.


Oral health is an integral part of overall health [1]. The oral health status of an individual reflects their general health status and, as such, is an important part of their well being. A body of knowledge is rapidly increasing on the association between oral and systemic health [2–4]. This should not be surprising considering that the mouth may serve as a portal of entry for disease, a source of contagion, a primary site for disease that can spread systemically, a frequent site of manifestations of systemic disease, and may contribute to increased morbidity caused by other systemic diseases.

Oral health is an encompassing term that includes more than just the teeth. It includes the whole of the craniofacial complex, which includes the teeth, gums, hard and soft palate, mucosal lining of the mouth and throat, tongue, lips, salivary glands, muscles of mastication, and upper and lower jaws as well as the neurovascular network that innervates and circulates through the complex. Thus dental caries, a disease process primarily affecting the teeth, is just one component of a child’s oral health. Yet, it causes the overwhelming majority of morbidity in children’s oral health status. It is this common, consequential, and truly preventable disease process that is the focus of this article.

TAXONOMY

Before beginning a discussion of dental caries, there must be a definition of terms so there is no confusion. Dental caries is a disease process. For the sake of language, caries can be likened to diabetes in that diabetes is also a disease process, but one does not have a “diabe-te.” Similarly, one does not have a carie. Along those lines, it is important to know the term cavity is not interchangeable with caries. The disease process of dental caries can lead to a cavity (a hole in the tooth), but the cavity is not equivalent to the disease process. A lay term that probably closest approximates, though is not interchangeable for
dental caries, is tooth decay, as it can be understood to mean the process, but can just as well be understood to mean the end result of the process.

Several terms have been used to describe processes of decay that are unique to certain age groups. These terms have been alternately known as “baby bottle tooth decay,” “nursing bottle caries,” and “bottle mouth.” This process and presentation of decay has most recently been termed early childhood caries as it best moves away from placing blame only on bottles and incorporates the disease process aspect of dental caries. This article uses the term caries or dental caries to refer to the disease process, cavity to refer to the hole in the tooth, and early childhood caries to refer specifically to the rapid presentation and advancement of the disease in infants and toddlers.

**Epidemiology**

**General**

On a national scale, dental caries prevalence is measured using the National Health and Nutrition Survey. This survey of a nationally representative sample of approximately 5000 persons per year is conducted by the Centers for Disease Control and Prevention and includes an interview and physical examination. A dental examination is included in the survey.

Data from the National Health and Nutrition Survey 1999–2002 showed that 41% of children ages 2 to 11 had caries experience in their primary teeth (defined as decayed or filled teeth) [5]. Twenty-one percent of children in this age group had untreated decay in their primary teeth. For children and adolescents ages 6 to 19 years, 42.0% had caries experience in their permanent teeth, whereas 14% of children and adolescents in the same age group had untreated tooth decay in their permanent teeth. In addition to caries prevalence, the severity of decay is also measured by counting the number of decayed and filled teeth, and decayed and filled surfaces (dfs) for primary teeth; and decayed, missing, and filled teeth, and decayed, missing, and filled tooth surfaces (DMFS) for permanent teeth. The mean decayed and filled teeth for children ages 2 to 11 years was 1.4. The mean dfs was 3.2. The mean decayed, missing, and filled teeth among children and adolescents ages 6 to 19 years was 1.6. The mean DMFS was 2.7.

These numbers, when compared with National Health and Nutrition Survey from 1988 to 1994, show no change in the prevalence and severity of dental caries in primary teeth, but a decrease in permanent teeth. This is significant because there had been a consistent decline in dental caries in primary teeth until the mid-1980s [6]. The decrease in permanent teeth, however, has continued with a 5.3% drop in 6- to 11-year-olds, 7.7% drop in 12- to 15-year-olds, and 10.2% drop in 16- to 19-year-olds.

**Differences in subpopulations of children**

In spite of the historical trend of decreasing caries experience in primary teeth and the continued trend in permanent teeth, there still exist subpopulations of children who experience higher and lower caries prevalence. These differences
Race and ethnicity
Differences in the prevalence and severity of dental caries exist when looking at children of different races and ethnicities. Native American children have the highest rates of caries experience in the United States. Almost 80% of Native American children ages 2 to 5 years, 91% ages 6 to 8 years, and 96% of 16-year-olds have had caries experience [7].

National Health and Nutrition Survey data show that Mexican–American children ages 2 to 11 years had higher caries experience (54.9%) in their primary teeth, compared with black (43.3%) or non-Hispanic white children (37.9%) [2]. Mexican American children experienced 1.5 times more cavities than black and non-Hispanic white children (4.62 dfs versus 2.98 dfs and 3.06 dfs). In the permanent teeth, Mexican–American children and adolescents had higher caries experience (48.8%), compared with non-Hispanic white (39.9%) or black (38.8%) 6- to 19-year-olds. Similar findings emerge in a study of the children of Hispanic migrant and seasonal farm workers [8]. The overall caries experience of these children was 64%. Cavitated lesions were found in 47% of 6- to 9-year-olds and 34% of 10- to 15-year-olds. In children new to the United States, differences in caries experience have been noted. Children from Eastern Europe, in one study, had a higher prevalence of caries experience (79.7%) than African children (38%) [9]. Although this was similar to the prevalence in United States children, there were significant differences for treatment urgency, untreated caries, extent of dental caries, and presence of oral pain.

Socioeconomic status
Differences also exist in caries prevalence between rich and poor children in the United States. Just over 55% of children ages 2 to 5 years from families with incomes less than 100% of the federal poverty level (FPL) had caries experience (55.3%) [2]. This was more than that of children of families with incomes of at least 200% of the FPL (30.7%) and those from families of at least 100% but less than 200% of the FPL (45.2%). Similarly, children and adolescents ages 6 to 19 years from families incomes less than 100% of the FPL had higher caries experience than children from higher income level families (48.3% versus 46.7% with family incomes ≥100% but <200% of the FPL and 36.1% with incomes ≥200% of the FPL).

The severity of caries also differs by socioeconomic status. Children 2 to 5 years of age in the lowest income category have a higher mean dfs (5.2) than their more affluent peers (3.8 and 1.96, respectively). The same is true, though less dramatic, for children and adolescents ages 6 to 19 years (mean dfs 3.3 versus 3.2 and 2.1).

Numerous studies of children in Head Start, a program focused on economically disadvantaged children, have shown high rates of dental caries ranging from 30% to 62% [10–14]. A study from a single county in Florida found
that 86% of the 5-year-olds had experienced noncavitated or cavitated caries lesions in their primary dentition [15]. A larger study from Ohio found 38% of 3- to 5-year-old Head Start children screened had caries experience. Of those children, 73% had decayed teeth, whereas the remaining 27% had restorations only [16].

**PATHOLOGY**

In the later part of the 19th century, it was proposed that dental caries was a bacterially mediated process [17]. The 20th century expanded the concept into the well-known dental caries model. This model, or Venn diagram, consists of three overlapping circles of host (tooth), bacteria, and nutrients (food), with dental caries being the intersection of all three circles. Later, time was added as the fourth component. This model indicates that all four components coexist for dental caries to be present.

A more contemporary view of dental caries is the model of a fluctuating continuum, or a balance between pathogenic factors (eg, acid-producing bacteria, frequent eating/drinking of fermentable carbohydrates, subnormal salivary flow, and function) and protective factors (eg, saliva flow and components, fluoride-remineralization, antibacterials-chlorhexidine, xylitol) [18,19]. Fig. 1 illustrates the concept of the caries balance [19]. The ideal is for the pathologic factors to be dominated or outweighed by the protective factors (ie, healthy mouth, no caries activity), but the balance could shift such that the pathogenic factors dominate and caries activity begins or progresses. According to this model, the three pathologic factors versus the three protective factors are not exclusive, but seem to be the most significant in assessing the patient’s caries risk [19].

It is clear that dental caries is a multifactorial or complex disease. It must be understood that various factors are involved, and a single treatment modality is not likely to completely eliminate the dental caries process [20,21].

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**Fig. 1.** The caries balance. (Adapted from Featherstone JDB. Caries prevention and reversal based on the caries balance. Pediatr Dent 2006;28:129; with permission.)
caries has also been described as a chronic disease in that even when the balance of the individual intraoral environment is shifted or tipped in favor of the protective factors, the caries risk is never zero [21].

Cariogenic bacteria, *Streptococcus mutans* (and other streptococcus species that are implicated in the caries process termed “mutans streptococci”), and *Lactobacillus* species produce acids (acidogenic) and thrive in an acidic environment (aciduric) are normally found in limited concentrations in healthy plaque [22–24]. With changes in the oral environment, especially high concentrations of refined carbohydrates as nutrient sources, the cariogenic bacteria produce large amounts of acid and become dominant because they have a competitive advantage in the altered acidic oral environment [21,22]. These acids contribute to the dissolution of calcium and phosphate from the hydroxyapatite crystalline structure of the tooth [22]. Initially the dissolution of tooth structure is a reversible process, but if pathologic conditions persist, the balance shifts or tips in favor of the pathologic factors, and caries activity progresses. Dissolution of calcium and phosphate from the tooth continues progressively until the hydroxyapatite crystals are so weak that they collapse and cavitations appear (cavities) [22]. Cavities, therefore, are a late manifestation of a disease process that is biologically a microbial infection [22].

Traditionally the diagnosis of dental caries relied on identifying carious lesions or areas of tooth demineralization. This method of diagnosis is not appropriate for the contemporary practice of dentistry. A more comprehensive approach to the diagnosis of dental caries encompasses assessment of clinical risk factors (eg, socioeconomic status, diet, oral hygiene, tooth morphology, general health), molecular risk factors (eg, detection of cariogenic bacteria, virulence of the microbial flora, plaque pH), and the ability to identify areas of demineralization early and accurately [22]. Conceptually, it is critical to regard dental caries a common, complex, chronic disease process as opposed to focusing on cavities, which are a late manifestation of the disease process [20,22]. The distinction between the caries process and cavities allows the skilled clinician to move beyond the surgical model of treatment that is still prevalent today and is ineffective in eliminating the causative microbial infection [20–22].

**ACQUISITION AND TRANSMISSION**

Previously, it was thought that mutans streptococci could not colonize oral mucosal surfaces, and the presence of a natural or unnatural (eg, prosthetic) non-shedding surface was necessary for colonization [23]. More recently, investigators have demonstrated that mutans streptococci are commonly detected before the eruption of the first tooth; this questions the necessity of a non-shedding surface for mutans streptococci colonization [25,26]. The lateral border and dorsal surface of the tongue and the buccal mucosa have been shown to harbor bacterial populations that are implicated in repopulating supragingival and subgingival sites after a complete dental prophylaxis [23,27]. The timing of mutans streptococci acquisition is significant, because
early acquisition is an important risk factor in the development of early childhood caries [28,29].

Mutans streptococci can be transmitted vertically or horizontally. Vertical transmission is the transfer of bacteria from caregiver to child. The primary source from which infants are infected with mutans streptococci is their mothers [30,31]. Data indicate that mothers who have dense salivary concentrations of mutans streptococci are at high risk of infecting their infants early, and reductions in the salivary level of mutans streptococci in highly infected mothers can postpone the infants’ colonization with mutans streptococci [32,33]. Horizontal transmission is the transfer of bacteria between members of a group. In the daycare environment, horizontal transmission has been shown to take place as evidenced by genotyping *S mutans* isolates and comparing the similarity of the isolates among children [34,35].

Because early acquisition of mutans streptococci is such a significant risk factor for the development of early childhood caries, steps taken to interfere with the early acquisition of mutans streptococci could be helpful in reducing the infant’s caries risk. Current recommendations for providers addressing early acquisition and transmission of mutans streptococci include the following: (1) reduce the mutans streptococci in the mother, siblings, and other caretakers; (2) alter or discontinue saliva-sharing activities; (3) twice daily tooth brushing of the dentate infant with the appropriate amount of American Dental Association–approved fluoridated dentifrice; (4) avoid dental decay–promoting feeding behaviors; and (5) have an oral health evaluation of the infant by a dental professional by the first birthday [23].

**MICROBIOLOGY**

From a microbiologic view, it is important to recognize that dental caries, or the caries process that affects teeth, takes place within a larger ecologic system. The oral soft tissues account for approximately 80% of the total surface area of the oral cavity, whereas the teeth account for only approximately 20% [27]. Our current understanding of the oral environment, with its emphasis on microbiology, has developed from changing paradigms as it relates to dental plaque. The nonspecific plaque hypothesis assumed that dental caries was a result of noxious products produced by the entire plaque flora [36]. If the noxious products were kept below a threshold level, host factors could detoxify the irritants; however, if more noxious products were present, the host’s capacity to neutralize the irritants would be overwhelmed, and dissolution of tooth structure or demineralization would begin. As a result of the nonspecific plaque hypothesis, mechanical plaque control procedures (eg, tooth brushing and flossing) were recommended to maintain the level of noxious products below the threshold level at which disease activity occurs. Unfortunately, mechanical plaque control procedures have failed to decrease the incidence of dental caries in many populations.

The specific plaque hypothesis states that only certain bacteria are pathogenic and cause disease, because of the presence of pathogens or increased
levels of endogenous bacteria [36]. From this, three types of plaque were identified based upon existing clinical conditions: a nondisease-associated plaque, a dental caries–associated plaque, and a periodontal disease–associated plaque. These plaques have been shown not to be distinct entities but rather different proportions of the same basic flora [36].

Recently, dental plaque has been discussed as a component of a more complex biofilm (accumulation of microbes in a matrix using available nutrients) [37]. Most biofilms contain multiple microbial species called “microbial communities,” that are involved in various physical, metabolic, and molecular interactions that provide advantages to the participating microbial communities. The dental plaque has all the components of a biofilm and can have more than 700 contributing oral microbial species. Dental biofilms have two characteristics that increase their pathogenicity: (1) increased antibacterial resistance and (2) decreased phagocytosis by host inflammatory cells [37].

Oral mucosal surfaces are a significant component of the oral biofilm. They account for approximately 80% of the surface area of the oral cavity. These mucosal surfaces are a source of bacteria. Bacteria are constantly shed from the teeth and mucosal surfaces (sessile bacteria) into saliva (planktonic bacteria) and carried to other sites of the oral cavity [35,37].

Clearly, prevention of dental disease, and more specifically dental caries, should not solely focus on elimination of pathogenic bacteria, but also on altering the complex oral ecologic environment (hard and soft tissues) such that pathogenic bacteria do not have a competitive advantage [37]. It is unrealistic to think that dental plaque and mucosal biofilms can be eliminated, but the nature of the biofilm can be altered or shifted so it is less pathogenic. This is accomplished by decreasing the microbial burden (total microbial numbers and pathogenic isolates) and maintaining a normal nonpathogenic oral environment with good oral (hard and soft tissue) hygiene behaviors [22,37].

**PREVENTION**

A widely used taxonomy of prevention describes primary, secondary, and tertiary prevention. These terms can be applied to the disease process of dental caries and can help providers to understand where in the process they can intervene and how they can do so. Primary prevention is the prevention of the disease process before it begins. For dental caries, primary prevention would encompass assessing the risk of children for dental caries and instituting efforts to decrease or remove that risk. Secondary prevention refers to detecting the presence of disease early in the disease process and intervening to prevent further development of the disease. For the clinician, this would involve recognizing the signs and symptoms of the early stages of dental caries, intervening, and referring for intervention. Tertiary prevention, alleviating the effects of the disease, lies primarily within the surgical realm of the dental professional in rehabilitating the damaged tooth.

Now, more than ever, providers should recognize that no single treatment or preventive strategy can be expected to eliminate caries as a disease [20], but the
caries process may be controlled through judicious use of multiple interventions [38]. Primary and secondary preventive therapeutic approaches to dental caries target the tooth enamel to enhance host defenses or target the cariogenic bacteria to control plaque formation or composition (Tables 1 and 2) [38]. A preventive regimen designed to decrease the pathologic factors and enhance the protective factors should include the following: (1) the ability to detect carious lesions early enough to reverse or prevent progression, (2) a preventive plan based on caries risk assessment, (3) daily use of a fluoride dentifrice, (4) use of antimicrobial therapy in patients who have high risk with baseline bacterial cultures to measure treatment effectiveness and patient compliance, (5) additional fluoride therapy such as varnish or high-concentration dentifrice or gel, and (6) xylitol gum or mints to enhance remineralization and supplement antibacterial therapy [38].

Risk assessment
At its most simplistic, the key components required for the dental caries process are teeth, bacteria, and sugar. At its most complex, dental caries is a multifactorial disease with numerous factors that function as participants in the causal chain and increase the probability of the occurrence and progression of dental caries. The goal of risk assessment is to provide information that will help prevent the development and/or progression of the dental caries process by recognizing those factors that are most likely to be a part of the causal chain.

Caries risk is not constant and consistent over time. Substantial variation can occur as the child ages. This variation in the factors that promote and prevent the dental caries process requires ongoing monitoring of risk throughout a child’s development. This is why the American Academy of Pediatrics suggests that pediatricians should be trained to perform an oral health risk assessment on all children beginning by 6 months of age and that these risk assessments continue at each well-child visit [39,40].

<table>
<thead>
<tr>
<th>Target</th>
<th>Scientific paradigm</th>
<th>Technical approach</th>
<th>Potential new therapeutic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tooth enamel</td>
<td>Topical fluoride modulated calcium incorporation into tooth enamel</td>
<td>Increase delivery and retention of fluoride; deliver additional calcium (and phosphate)</td>
<td>Dual component calcium/fluoride dentifrice; slow release fluoride systems, device, encapsulation; Ca delivery systems, protein/peptide carriers, silicate/glass carriers</td>
</tr>
</tbody>
</table>

Several risk factors have been presented as increasing the probability of the development of dental caries, though there is agreement that there is much to do in the way of improving caries risk assessment [41,42]. A valuable risk assessment will include the recognition of factors that increase the risk of the disease as well as factors that decrease risk and allow for intervention and/or referral [43]. This is especially important with regard to dental caries because of the ongoing balance of demineralization and remineralization that goes on at the surface of the tooth. Factors that tip toward demineralization need to be recognized and removed or diminished, whereas factors that promote remineralization must be encouraged and enhanced.

The most predictive of risk factors for the development of dental caries is previous caries experience [42]. Though this does not lend itself to primary prevention, it does let the clinician know that the factors that contribute to the dental caries process do exist in that individual. The challenge, then, is to recognize them and intervene to adjust the risk factors in favor of reversing disease and preventing future disease. Examples of other risk factors that promote the development and progression of dental caries are listed in Box 1.

### Table 2

<table>
<thead>
<tr>
<th>Target</th>
<th>Scientific paradigm</th>
<th>Technical approach</th>
<th>Potential new therapeutic</th>
</tr>
</thead>
</table>
| Plaque bacteria             | Infection caused by endogenous flora; specific (acid producing, acid tolerant) organisms that cause caries; Biofilm is a highly complex entity that behaves differently from its individual constituents | Reduce burden of infection; eliminate causative organisms, especially *S. mutans*; prevent bacterial adhesion; modulate biofilm physiology; disrupt plaque matrix | Topical antimicrobials  
  - Chlorhexidine, Triclosan; *S. mutans* targeted vaccine; replacement therapy, genetically modified organism,  
  - probiotics; targeted antimicrobial enzymes and peptides; coat enamel surface,  
  - agents, sealants; block bacterial adhesion, bacterial surface,  
  - glucosyltransferase and matrix formation, cell–cell signaling; control plaque pH, Xylitol,  
  - Arginine/bicarbonate buffer,  
  - up-regulate arginine deaminase, glucan hydrolase enzymes |

As caries is an etiologically complex disease process, numerous microbial, genetic, immunologic, behavioral, and environmental contributors to risk are at play in determining the occurrence and severity of clinical disease. Assessment tools based on a single risk indicator are therefore unlikely to accurately discriminate between those at high and low risk. Multiple indicators, combined on an appropriate scale and accounting for possible interactions, will certainly be required.

One example of a caries risk assessment tool has been developed by the American Academy of Pediatric Dentistry [18]. The American Academy of Pediatric Dentistry Caries Risk Assessment Tool is intended to be used by dental and nondental health care providers in assessing levels of caries risk in infants, children, and adolescents. The caries risk assessment tool includes risk factors that can be assessed by way of history, clinical evaluation, and supplemental professional assessment and stratifies the patient based on these risk factors into low-, medium-, or high-risk levels (Table 3).

Diet and nutrition
Dental caries is a diet-mediated disease. More specifically, dietary sugars are most important in the process of dental caries [44,45]. These dietary sugars are used by cariogenic bacteria to produce the acids that demineralize the tooth enamel. A systematic review of the literature concluded that the relationship between sugar consumption and caries is weaker now that fluoride exposure has increased [46]. However, the authors stated that controlling consumption of sugars remains an important, if not the most important, aspect of caries prevention. In general, the greater the amount and frequency of intake of dietary sugars, the more at risk for dental caries the child will be [47,48]. This includes not only solid foods, but liquids as well [49].

Beyond limiting the amount and, most importantly, the frequency of intake of foods that contribute to the caries process, there are some foods that seem to

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**Box 1: Risk factors for dental caries**

<table>
<thead>
<tr>
<th>Risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caries presence in the primary caregiver (eg, mother)</td>
</tr>
<tr>
<td>Inadequate exposure to fluoride</td>
</tr>
<tr>
<td>Poor oral hygiene and conditions/oral appliances (eg, cerebral palsy, orthodontia) that prevent the maintenance of good oral hygiene</td>
</tr>
<tr>
<td>Frequent consumption of fermentable carbohydrates</td>
</tr>
<tr>
<td>Medical conditions/medications/interventions that decrease salivary flow</td>
</tr>
<tr>
<td>Low socioeconomic status</td>
</tr>
<tr>
<td>Presence of plaque</td>
</tr>
<tr>
<td>Abnormalities in tooth structure (eg, defective enamel)</td>
</tr>
<tr>
<td>High concentrations of acidogenic bacteria</td>
</tr>
<tr>
<td>Long-term regular doses of medications containing fermentable carbohydrates</td>
</tr>
</tbody>
</table>

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have a beneficial effect on the caries process. One in particular is cheese [50,51].
There is some controversy over other foods, specifically breast milk and its relationship to the caries process. Though the American Academy of Pediatrics and the American Academy of Pediatric Dentistry suggest that ad libitum overnight breastfeeding can contribute to dental caries, a systematic review of the literature on breastfeeding and dental caries concluded that the evidence was equivocal as to the association [52]. The literature on cow’s milk also shows some disagreement on its role in the caries process [49,53].

Oral hygiene
Even today, most preventive regimens are focused on mechanical plaque-control procedures (tooth brushing and flossing) only. These practices are based on the nonspecific plaque hypothesis and do not appreciably affect the incidence of dental caries [36]. Although it is possible to maintain a level of oral hygiene to prevent gingivitis, most individuals cannot maintain that level of oral hygiene for an extended period of time [27]. Certainly, compliance issues with mechanical plaque control procedures in the pediatric population are present and prevalent. It is unrealistic to expect a child to appropriately clean their teeth, yet dentists often hear the proud parent of a two-year-old report, “she brushes her teeth by herself, she won’t let us do it, but she does a good job.”

Oral hygiene procedures are the responsibility of the caregiver of their young child in the same way overall personal hygiene is. It is usually best to provide mechanical plaque-control procedures in a safe environment. Many recommend oral hygiene procedures on a diaper changing table, bed, or parent’s lap [54]. Bathrooms are used for oral hygiene procedures in older children and adults, but because everything in the bathroom is hard, it may not be a safe environment for oral hygiene procedures in infants and toddlers [54].

The difficulty with mechanical plaque-control procedures for infants, toddlers, and preschoolers is that parents and caregivers often do not receive good advice about how to care for their child’s teeth until carious lesions are present, or they are confused about conflicting information they have received from various sources (including health care providers) [20]. Probably the best advice a health care provider can give regarding oral hygiene procedures for infants, toddlers, and preschoolers is: (1) it is normal for an infant, toddler, and a preschooler to be fussy, wiggly, and sometimes cry; (2) find time, usually before bed is best, but kids are often tired then so it is wise to brush more than one time per day (it’s also unrealistic to think a parent or caregiver will brush the teeth well every time); and (3) two adults (one hand-holder and one operator) can do the job much better than one.

Another concept that needs to be addressed is what the parental role is for older children who have the fine motor skills necessary to perform mechanical plaque-control procedures but do not do it. It is a compliance issue. How do you get a child to do something they do not want to do? Parental supervision is important. If it is not getting done well, the parent or caregiver should
<table>
<thead>
<tr>
<th>Risk factors to consider (for each item below, circle the most accurate response found to the right under “Risk Indicators.”)</th>
<th>High</th>
<th>Moderate</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Part 1 — History (determined by interviewing the parent/primary caregiver)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child has special health care needs, especially any that impact motor coordination or cooperation</td>
<td>Yes</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Child has condition that impairs saliva (dry mouth)</td>
<td>Yes</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Child’s use of dental home (frequency of routine dental visits)</td>
<td>None</td>
<td>Irregular</td>
<td>Regular</td>
</tr>
<tr>
<td>Child has decay</td>
<td>Yes</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Time lapsed since child’s last cavity</td>
<td>&lt;12 months</td>
<td>12–24 mo</td>
<td>&gt;24 mo</td>
</tr>
<tr>
<td>Child wears braces or orthodontic/oral appliances</td>
<td>Yes</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Child’s parent and/or sibling(s) have decay</td>
<td>Yes</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Socioeconomic status of child’s parent&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Low</td>
<td>Midlevel</td>
<td>High</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-----</td>
<td>----------</td>
<td>------</td>
</tr>
<tr>
<td>Daily between-meal exposures to sugars/cavity-producing foods (includes on demand use of bottle/sippy cup containing liquid other than water; consumption of juice, carbonated beverages, or sports drinks; use of sweetened medications)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>&gt;3</td>
<td>1–2</td>
<td>Mealtime only</td>
</tr>
<tr>
<td>Child’s exposure to fluoride&lt;sup&gt;f,g&lt;/sup&gt;</td>
<td>Does not use fluoridated toothpaste; drinking water is not fluoridated and is not taking fluoride supplements</td>
<td>Uses fluoridated toothpaste; usually does not drink fluoridated water and does not take fluoride supplements</td>
<td>Uses fluoridated toothpaste; drinks fluoridated water or takes fluoride supplements</td>
</tr>
<tr>
<td>Times per day that child’s teeth/gums are brushed</td>
<td>&lt;1</td>
<td>1</td>
<td>2–3</td>
</tr>
</tbody>
</table>

Part 2—Clinical evaluation (determined by examining the child’s mouth)

<table>
<thead>
<tr>
<th>Visible plaque (white, sticky buildup)</th>
<th>Present</th>
<th>—</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gingivitis (red, puffy gums)&lt;sup&gt;h&lt;/sup&gt;</td>
<td>—</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Areas of enamel demineralization (chalky white spots on teeth)</td>
<td>More than 1</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>Enamel defects, deep pits/fissures&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Present</td>
<td>—</td>
<td>Absent</td>
</tr>
</tbody>
</table>

(continued on next page)
<table>
<thead>
<tr>
<th>Risk factors to consider (for each item below, circle the most accurate response found to the right under “Risk Indicators.”)</th>
<th>High</th>
<th>Moderate</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiographic enamel caries Present — Absent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levels of mutans streptococci or lactobacilli</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Each child’s overall assessed risk for developing decay is based on the highest level of risk indicator circled above (ie, a single risk indicator in any area of the “high risk” category classifies a child as being “high risk”).

- Children who have special health care needs are those who have a physical, developmental, mental, sensory, behavioral, cognitive, or emotional impairment or limiting condition that requires medical management, health care intervention, and/or use of specialized services. The condition may be developmental or acquired and may cause limitations in performing daily self-maintenance activities or substantial limitations in a major life activity. Health care for special needs patients is beyond that considered routine and requires specialized knowledge, increased awareness and attention, and accommodation.

- Alteration in salivary flow can be the result of congenital or acquired conditions, surgery, radiation, medication, or age-related changes in salivary function. Any condition, treatment, or process known or reported to alter saliva flow should be considered an indication of risk unless proven otherwise.

- Orthodontic appliances include both fixed and removable appliances, space maintainers, and other devices that remain in the mouth continuously or for prolonged time intervals and which may trap food and plaque, prevent oral hygiene, compromise access of tooth surfaces to fluoride, or otherwise create an environment supporting caries initiation.

- National surveys have demonstrated that children in low-income and moderate-income households are more likely to have caries and more decayed or filled primary teeth than children from more affluent households. Also, within income levels, minority children are more likely to have caries. Thus, socioeconomic status should be viewed as an initial indicator of risk that may be offset by the absence of other risk indicators.

- Examples of sources of simple sugars include carbonated beverages, cookies, cake, candy, cereal, potato chips, French fries, corn chips, pretzels, breads, juices, and fruits. Clinicians using caries-risk assessment should investigate individual exposures to sugars known to be involved in caries initiation.

- Optimal systemic and topical fluoride exposure is based on use of a fluoride dentifrice and American Dental Association/American Academy of Pediatrics guidelines for exposure from fluoride drinking water and/or supplementation.

- Unsupervised use of toothpaste and at-home topical fluoride products are not recommended for children unable to expectorate predictably.

- Although microbial organisms responsible for gingivitis may be different than those primarily implicated in caries, the presence of gingivitis in an indicator of poor or infrequent oral hygiene practices and has been associated with caries progression.

- Tooth anatomy and hypoplastic defects (eg, poorly formed enamel, developmental pits) may predispose a child to develop caries.

- Advanced technologies such as radiographic assessment and microbiologic testing are not essential for using this tool.

intervene and provide oral hygiene procedures as they would for an infant, toddler, or preschooler.

Prior to the eruption of the teeth, wiping the mouth with cotton finger cloths is recommended. There are commercially available products that function as gum cleaners (and hopefully other oral mucosal surfaces as well) with xylitol (see later discussion). Dental wipes or gum cleansers may be effective in managing the mucosal or soft tissue biofilms and could play a role in decreasing the level of mutans streptococci in the oral cavity.

Dentate children should have their teeth brushed twice daily [19]. Prior to the age of 2 years, the use of a fluoride dentifrice should be used cautiously, if at all [24]. When the child is old enough to not swallow the toothpaste, the use of an appropriate amount of a fluoridated dentifrice (pea sized, size of nail on fifth digit) is recommended irrespective of their caries risk [19]. This reduces the plaque level on the tooth and, more importantly, it provides therapeutic levels of fluoride to the mouth on a regular basis [19].

Flossing is recommended to clean tooth surfaces that are touching and are not able to be cleansed with a toothbrush. Care must be taken to not injure the child during flossing procedures. Direct observation of a dentist or hygienist during an appointment would be most beneficial to learn the proper flossing technique.

Fluoride
The effect of fluoride on the initiation and progression of dental caries has been recognized since the 1920s and 1930s. In the ongoing dynamic balance between demineralization and remineralization at the tooth enamel surface, the presence of fluoride allows for its uptake and incorporation into the mineral structure of the tooth, forming fluoroapatite. This fluoride-enhanced structure is more resistant to the dental caries process. Fluoride can have its effect on dental caries both systemically and topically, though more recent thought points toward the primacy of the topical effects [55].

Systemic fluoride
The two major sources of systemic fluoride come from community water fluoridation and fluoride supplementation. In addition, because many other foods include or are prepared using fluoridated water, these too may be sources of systemic fluoride. Community water fluoridation has been around since the mid 1940s and was recognized by the Centers for Disease Control and Prevention as one of the 10 greatest public health achievements of the twentieth century [56]. Evaluations of community water fluoridation efforts have shown significant caries reduction results [57–59]. Though, more recently, the systemic effect has been questioned [60].

Fluoride supplementation, usually done by way of prescribed drops or chewable tablets, has been available since the 1950s. The evidence for their use, however, has been mixed due to various flaws in the studies [61–64]. The Centers for Disease Control and Prevention, because of these flaws, gave the evidence for fluoride supplementation of children younger than 6 years of age low
marks while giving the highest marks for supplementing children ages 6 to 16 years of age [58]. The biggest concern of supplementation for the younger age group is the possibility of dental enamel fluorosis, a usually minor change in the coloring of the teeth due to increased intake of fluoride in the enamel of the developing tooth [65,66].

Topical fluoride
Fluoride can be delivered topically in various ways including by way of toothpaste, professional and self-applied gels, foams, mouth rinses, and varnish. The most common of these and most accessible to children and families is by way of toothpaste. In the United States, fluoride was first added to toothpaste in the 1950s. The fluoride in toothpaste usually comes in the form of sodium fluoride or sodium monofluorophosphate, and most fluoridated toothpastes contain between 1000 and 1100 ppm of fluoride. Other countries have toothpastes available with lower concentrations of fluoride, but they have not yet been marketed on a large scale in the United States.

Several systematic reviews on fluoridated toothpaste have been published over the past 5 years [67–69]. In general, there is a high level of evidence for the effectiveness of fluoridated toothpaste in the prevention of dental caries in children, specifically in the permanent dentition. There is less evidence for its use in the primary dentition, though there is no evidence to suggest that its use would not also be beneficial for those teeth as well. It is important to remember, however, that in these younger children, the risk of swallowing the toothpaste is higher. Thus, the level of systemic fluoride, which contributes to enamel fluorosis, can be increased. Therefore, parents of these children should be assisting and/or observing tooth brushing and limiting the amount of toothpaste to a pea-sized amount or an amount equal to the size of the child’s pinky fingernail.

Fluoride mouth rinses are available over the counter and by prescription (higher concentration). In many areas of the country, fluoride mouth rinse programs exist in schools. Systematic reviews of the effectiveness of fluoride mouth rinse in the prevention of dental caries have shown some benefit in their use, though they were not able to demonstrate effectiveness of caries prevention in the primary dentition [70,71]. The Centers for Disease Control and Prevention concluded that the quality of evidence supporting fluoride mouth rinse was the highest grade, but they also state that they are best used by children at the highest risk for dental caries, with risk decreasing with increased fluoride exposure from other sources [58].

Fluoride gels and foams are usually professionally applied by way of an application tray, though they can be made available by dental providers to families to use at home. Fluoride foams are similar to gels in the delivery mechanism except that a smaller amount is required in the tray. Systematic reviews of the effectiveness of fluoride gels on the dental caries process have shown a reduction in caries incidence versus control groups [72,73]. Similar to the fluoride toothpaste and mouth rinse findings, evidence to support effectiveness in the
primary dentition was lacking. In addition to the systematic review findings, the Centers for Disease Control and Prevention concluded that the evidence on the use of fluoride gels in preventing and controlling dental caries was at the highest level when specifically used for children at high risk for dental caries [58]. The American Dental Association concluded that fluoride gel is effective in preventing caries in school-aged children, but that the weight of the clinical evidence for the effectiveness of foam is not as strong as that for fluoride gel and varnish [74].

Fluoride varnish is a sticky substance that is easily “painted” directly on the teeth and hardens quickly on contact with saliva. It has been extensively used in Europe and Canada since the 1960s as an anticaries strategy, but in the United States, it is currently considered “off label” for such use. Systematic reviews on the effectiveness of fluoride varnish show that despite the variability in the design and quality of the studies, fluoride varnish provides caries incidence reductions of 18% to 70% [75–78]. Only one, however, found it effective in the primary dentition [78]. A recent randomized controlled trial showed some evidence that fluoride varnish combined with parental counseling does prevent early childhood caries and reduces caries increment in very young children [79]. The Centers for Disease Control and Prevention concluded that there is the highest quality of evidence for the efficacy of fluoride varnish in preventing and controlling dental caries in children at high risk for dental caries [58]. The American Dental Association concluded with the highest level of evidence that fluoride varnish applied every 6 months is effective in preventing caries in the primary and permanent dentition of children and adolescents and that two or more applications of fluoride varnish per year are effective in preventing caries in high-risk populations [74].

Antibacterials
The mechanical plaque control procedures have a limited ability to decrease caries incidence; therefore chemical antibacterials would be a good way to help control plaque biofilms and pathogenic bacteria [36]. The use of therapeutic mouth rinses has recently been based on sound scientific and clinical rationale [27]. It has been demonstrated that the mucosal biofilms can have a significant effect on the colonization of teeth with oral bacteria, and that antibacterial mouth rinses can be a cost-effective adjunct to mechanical plaque control procedures in reducing mucosal and salivary levels of bacteria [27]. Antibacterial mouth rinse regimens are typically age-limited to patients approximately 8 years or older because they have the ability to rinse and expectorate [80]. It is important to remember that the target bacteria are part of a biofilm and the antibacterial mouth rinses can suppress the infection but not totally eliminate it [37,81]. The antibacterial mouth rinses are not effective unless their use is repeated periodically [21]. Currently the best antibacterial mouth rinse available against cariogenic bacteria is chlorhexidine gluconate, and others will be available in the near future [19].
Xylitol

Xylitol is a sugar substitute with a sweetness equal to that of sucrose, but with 40% less calories. Xylitol is a sugar alcohol that is part of the polyol family; others include sorbitol, mannitol, and malitol. It is produced from birch trees and other hardwood trees containing xylan. It has been approved by the Food and Drug Administration since the 1960s and is safe for use in children. Sugar alcohols have been shown to be noncariogenic, and xylitol exhibits a protective effect from dental caries [82]. Short-term xylitol use decreases the level of *S. mutans* in plaque and saliva by way of interference with bacterial adherence, limiting the amount of acid produced, and has a direct inhibitory effect [83,84]. Long-term use of xylitol has a selective effect on *S. mutans* resulting in a decrease in dental caries incidence and positive effects on the vertical transmission of *S. mutans* [83,84]. Polyol sweeteners used in combination can reduce caries incidence, but the effect is dependent on the amount of xylitol present [82]. The other polyol sweeteners may enhance, but will not decrease xylitol’s effectiveness [82]. Six to 10 g per day in at least three consumption periods is the most effective dose and frequency of xylitol in a chewing gum vehicle [85]. Increased dosages have limited utility after 10 g per day. Increased frequency of ingestion is associated with a linear response in decreasing the levels of *S. mutans* in the plaque and saliva.

Studies examining strategies to delay or interfere with the vertical transmission of *S. mutans* found that xylitol consumption by the mother had the greatest effect [23,82,85–87]. Xylitol consumption by caregivers was more effective than chlorhexidine mouth rinse and fluoride in delaying *S. mutans* colonization measured at 2 and 6 years of age. A regimen of xylitol chewing gum (6–10 g/day in three 5-minute consumption periods) in combination with a chlorhexidine mouth rinse (10 mL two times per day for 2 weeks) showed a major decrease in *S. mutans* levels in caregivers [88]. Xylitol containing products are attractive because its effect is not dependent on others sugars in the diet [89]. Xylitol candies and toothpastes are available and are effective in altering the level of *S. mutans* if taken in the appropriate dosages and frequency [90,91]. A major disadvantage of xylitol products is there is no xylitol product available that is suitable for toddlers and preschoolers too young to chew gum [82]. Xylitol food additives and dental wipes with xylitol may be more appropriate for infants, toddlers, and preschoolers. The problem for clinicians is to recommend a product that delivers 6 to 10 g per day, because most products do not specifically state the xylitol content, making decisions about product purchases and consumption difficult [82].

Probiotics

Probiotic therapy consists of selective removal of a pathogen while leaving the ecosystem unaffected [21]. One probiotic strategy is to substitute a genetically modified *S. mutans* that does not produce acid but aggressively competes for a foothold in the ecosystem with acidogenic *S. mutans* [92]. This substitution approach is effective because it stops the disease and prevents repopulation of the
ecosystem with pathogenic bacteria. Another strategy is to target antimicrobials to specific species of bacteria to selectively eliminate those pathogens [93]. One problem with a probiotic approach to dental caries is that there is not just one species of bacteria that contributes to the disease process [21]. Targeted antimicrobials to multiple individual species may prove difficult.

Surgical treatment and a changing paradigm
Removal and repair of demineralized/diseased tooth structure does not remove the cause of the infection nor does it change the oral and external environment that contributed to the disease process [21]. This surgical model of dentistry predates the contemporary understanding of the dental caries process and can be the dominant model in a dental office that has not moved toward the medical model of dental caries management [22]. Within the profession of dentistry, there is slow movement away from the surgical approach to caries management toward the medical model [21]. A comprehensive treatment plan should include eliminating cariogenic bacteria, decreasing plaque acidogenicity, enhancing tooth remineralization, and repairing damaged teeth [22].

An understanding of the ecology of the oral cavity and the interaction between the endogenous and cariogenic bacteria has become the gateway to new therapeutic approaches to the dental caries process [22]. Ongoing research projects evaluating vaccination, bacterial replacement, and targeted antibacterials are revealing new horizons in the treatment of dental caries [94–96]. In the future, dentistry will be a medical-based dental practice focusing on early detection, appropriate prevention, and effective treatment [22].

The dental home
Establishing a dental home by 12 months of age, where a patient can receive all aspects of oral health care in an accessible, comprehensive, coordinated, family-centered way, is recommended by the American Academy of Pediatric Dentistry [97,98]. A dental home provides the following: an accurate risk assessment for dental diseases, a preventive plan based on the risk assessment, anticipatory guidance regarding growth and development, a plan for emergency dental care, age-appropriate oral hygiene procedures, proper nutrition and dietary practices, comprehensive dental care, and referral to other dental specialists as necessary [39]. Evidence suggests that if appropriate preventive measures are initiated in infancy, it may be possible to raise a cavity-free child [97].

Ideally every child should have a dental home established by 12 months of age, but for various reasons (primarily financial), a portion of the population has difficulty accessing dental care. Because access-to-care issues are prevalent, many children are dentally “homeless.” The question then arises: can a nondental health care provider provide a dental home for a patient? This is a simple question, with many, many answers. The reality is that with appropriate training, nondental health care professionals could provide most of the components of a dental home with the exception of providing comprehensive dental care. The challenge for nondental health care providers lies in finding and
incorporating effective, targeted, and developmentally appropriate oral health management into their current health maintenance processes.

THE ROLE OF PEDIATRICIANS IN CHILDREN’S ORAL HEALTH

In a health care environment, where there exists a profession (dentistry) primarily focused on the disease processes of the oral cavity and with the number of health topics to be covered by the practicing pediatrician continually expanding, the question of whether pediatricians have a role to play in children’s oral health is an important one. Several factors contribute to answering that question. These factors include prevalence of disease, opportunity for action, a changing paradigm of disease, knowledge base of pediatricians, and interprofessional communication and collaboration.

Dental caries is an extremely common disease in children and a disease process that begins at a young age. If health maintenance is truly a goal of pediatrics, a disease with such a high prevalence in children should convince providers to make dental caries prevention a priority. Primary prevention strategies do exist to prevent, mitigate, or at least delay the disease process. Risk factors, signs, and symptoms of disease can be assessed and recognized and interventions by a health professional, both medical and dental, can be implemented.

Pediatricians, because of the frequency of interactions with children before and soon after tooth eruption, have the opportunity to shape the oral health knowledge, attitudes, and behaviors of children and their families. Oral health guidance, education, and interventions that are age appropriate, culturally sensitive, evidence based, and risk based can be delivered in ways that fit into the daily practice of pediatrics.

The changing paradigm of dental caries toward a medical model is another factor that makes the role of the pediatrician so important. A more proactive approach that serves to assess risk, provide guidance on prevention of disease, and intervene or refer before or early in the disease process is consistent with the anticipatory guidance, risk-assessment strategy with which pediatricians are familiar. The world of prevention of the disease process rather than the world of treatment (in this case the surgical treatment of dental caries) is a more familiar and appropriate setting for the pediatrician.

It is important, however, that to be competent providers of oral health risk assessment, anticipatory guidance, intervention, and referral, pediatricians must have the knowledge base to understand the disease process and the strategies for prevention and intervention. Historically, medical education has not done well, at all levels, on oral health education [99–101]. Opportunities and models of educating pediatricians and other medical professionals on oral health do exist and are increasing in number [101]. Guidelines for residency training have been developed [102], professional medical organizations have made oral health a top priority and have developed training programs for their members [103,104], and a number of other training efforts have focused on medical professionals [105–107]. However, a recent review of the literature
found insufficient evidence to recommend for or against routine risk assessment of preschool children by primary care clinicians for the prevention of dental disease [108]. This review was done, however, before the marked increase in the development and evaluation of these many oral health training programs for physicians. More studies and evaluation efforts are required.

Finally, it is extremely important, if not obvious, that there be coordination and collaboration between physicians and dentists on children’s oral health. There must be a strong connection and open communication between the medical home and the dental home to ensure the oral and overall health of children. A medical home must be, among other things, comprehensive and coordinated. The absence of oral health or the inability to coordinate care with the dental home makes the medical home model incomplete. Ideally, medical and dental homes will share information to coordinate care and ensure follow-up, educate each other on oral and general health to improve the provision of care, and advocate collaboratively for policies and programs that benefit the health of children. It is the combination of the knowledge, talents, and skills of physicians and dentists alike that will result in positive oral health outcomes.

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Atopic dermatitis is a chronically relapsing dermatosis characterized by pruritus, erythema, vesiculation, papulation, exudation, excoriation, crusting, scaling, and sometimes lichenification [1]. The word *atopic* comes from the Greek word *atopos*, which means “strange” or “unusual.” Atopic eczema is synonymous with atopic dermatitis. The word eczema is from the Greek word *ekzema*, which means to “erupt” or “boil over.” Atopic dermatitis is an “itch that rashes.”

The prevalence of atopic dermatitis in developed countries has increased twofold to threefold over the past 3 decades, and there is evidence to suggest that the prevalence is continuing to increase [2,3]. The increase in prevalence might be due to better access to medical care, improved recognition, enhanced epidemiologic reporting, or increased environmental allergens due to industrialization and pollution [4]. Approximately 70% to 80% of patients who have atopic dermatitis have an extrinsic form that is associated with IgE-mediated sensitization. The other 20% or 30% of patients have an intrinsic form without IgE-mediated sensitization [2]. Atopic dermatitis most often presents in infancy or early childhood [1] and is the initiating atopic factor in more than 50% of those patients who subsequently develop asthma or allergic rhinitis [5,6]. Both forms are associated with eosinophilia [7]. Atopic dermatitis is a frustrating condition for patients and caregivers. The pruritus can be intractable, and the disease has important physical and psychologic implications. Because of the associated emotional stress and sleep disruption, the impact on the quality of life of patients and their families can be appreciable [8]. Although there is no cure, effective control is possible. Effective therapy involves avoidance of triggering factors, optimal skin care, and pharmacotherapy.
**EPIDEMIOLOGY**

Atopic dermatitis affects 10% to 20% of children and 1% to 3% of adults in the United States and Europe [9,10]. The prevalence is higher in developed countries and urban areas and in populations that move from an area of low to high prevalence. Atopic dermatitis is more prevalent in temperate compared with tropical climates, especially dry winter climates [11]. The condition is also more prevalent in children who belong to families with a smaller size, higher socioeconomic class, and who practice meticulous hygiene [12]. Children who have more infections in infancy tend to be less frequently affected [13]. The female to male ratio is 1.5:1 [14].

**PATHOGENESIS AND ETIOLOGY**

The pathogenesis of atopic dermatitis involves complex interactions between susceptible genes, immunologic factors, defects in the skin barrier, skin infection, and environmental factors [1].

There is a strong genetic predisposition. Approximately 30% to 50% of children who have one affected parent and 50% to 80% who have two affected parents develop the disorder [15]. The risk is higher with a family history of maternal compared with paternal atopy [16,17]. Atopic dermatitis has a high concordance in monozygotic twins [1]. The concordance is 85% for monozygotic twins and 21% for dizygotic twins [18]. Based on linkage gene analysis studies and candidate gene studies, numerous gene loci have been identified that are associated with atopic dermatitis and include 1q21, 3p24–26, 3q14, 3q21, 4p14–15, 5q31–33, 11q13, 13q14, 14q11, 17q25, 18q11–12, and 20p [17,19].

Atopic dermatitis involves defective cell-mediated immunity that is related to an imbalance in two subsets of CD4-T cells that creates a predominance of T-memory cells in the T-helper 2 pathways, and preferential apoptosis of interferon-gamma producing T-helper 1 memory and effector T cells [1]. T-helper 2 cells express a set of cytokines that include interleukin-4, -5, -6, -10, and -13 [20]. These cytokines stimulate the proliferation and differentiation of B lymphocytes and contribute to the hypereosinophilia, high serum IgE levels, sustained cutaneous inflammation, histamine release, and pruritus characteristic of the disorder [11]. Compared with extrinsic atopic dermatitis, the intrinsic form is associated with less interleukin-4 and -13 production [2]. Maintenance of chronic inflammation is associated with predominance of interleukin-5 and -12 expression and eosinophils [11].

Loss of the integrity of the skin barrier is an important etiologic factor. Ceramides are reduced in the affected skin and also in the normal skin of patients who have atopic dermatitis [21,22]. Ceramides serve as important water-holding molecules in the extracellular space of the horny layer [2,23]. A deficiency in ceramides results in enhanced transepidermal water loss, dry skin, and increased permeability to environmental irritants and allergens [20,24]. The reduction in ceramides might result from increased sphingomyelin deacylase activity or reduced production of ceramides by keratinocytes [20,21].
Keratinocyte-derived antimicrobial peptides known as cathelicidins and \( \beta \)-defensins are deficient in the skin of patients who have atopic dermatitis [25]. These peptides help in the host defense against bacteria, viruses, and fungi.

Loss of the integrity of the skin barrier makes the stratum corneum susceptible to colonization by *Staphylococcus* (*S.* *aureus*) [26]. *S. aureus* is found on the skin in over 90\% of patients who have atopic dermatitis [27], but in only 5\% of normal subjects. *S. aureus* expresses an array of adhesins known as microbial surface components, which recognize adhesive matrix molecules, and allow the adhesins to bind to extracellular matrix proteins such as fibronectin and fibrinogen [27]. *S. aureus* exacerbates or maintains skin inflammation by secretion of a group of toxins known to act as superantigens and which stimulate T cells, macrophages, eosinophils, and keratinocytes [1,28]. Staphylococcal exotoxins exert proinflammatory effects through inhibition of apoptosis of eosinophils, increased surface antigen expression (CD11b, CD45, CD54, and CD69), and enhanced cytokine-activated oxidative burst, which triggers allergic inflammatory reactions [29]. Toxin-specific IgE levels have been shown to correlate with skin disease severity [30]. Superantigens have also been shown to augment allergen-specific IgE synthesis [31] and to induce glucocorticoid resistance [32].

*Malassezia* (*Pityrosporum orbiculare/ovale*) has been identified as a trigger factor. *Malassezia*-specific IgE antibodies have been found in 50\% to 70\% of adult patients who have atopic dermatitis [33,34]. Patients who have atopic dermatitis that affects the head and neck area are more likely to produce *Malassezia*-specific IgE antibodies [28]. Internalization of *Malassezia* induces maturation of dendritic cells and production of proinflammatory cytokines [28,35]. Antifungal treatment of postpubertal patients who have refractory atopic dermatitis reduces the overall severity [20,23].

The increase in prevalence of atopic dermatitis has been attributed to a decrease in the exposure to microorganisms in early life, especially in developed countries [23,28]. Reduced rates of atopic dermatitis have been observed in individuals who have greater exposure to infections, especially before 1 year of age [13,36]. Other authors suggest that the reduction in the prevalence might be related more to the exposure to specific microbes in the commensal gut microflora than to the frequency of sporadic infection [37,38]. Watanabe and colleagues [38] have reported that patients who have atopic dermatitis have lower counts of *Bifidobacterium* in their stools than healthy control subjects. *Bifidobacterium* is a commensal bacterium that induces T-helper 1 responses [38].

Environmental factors, such as food allergens, aeroallergens, contactants, and stress, trigger or exacerbate atopic dermatitis in susceptible individuals [1].

Food allergy plays an important immunopathogenic role in 30\% to 50\% of young children who have moderate to severe atopic dermatitis [20,36,39,40]. Burks and colleagues [41] evaluated 46 patients who had atopic dermatitis for food hypersensitivity with double-blind placebo-controlled food challenges. Sixty-five food challenges were performed: 27 (42\%) were interpreted as positive in 15 (33\%) patients. Sampson and colleagues studied 350 patients who had severe atopic dermatitis for possible food hypersensitivity [42,43]. Food allergy
was diagnosed by double-blind placebo-controlled food challenges. Cutaneous reactions developed within minutes to 2 hours in 75% of the positive challenges, but only 30% of the positive responses developed cutaneous symptoms alone. Most of the skin manifestations consisted of an intensely pruritic erythematous rash that developed at sites with a predilection for atopic dermatitis. The authors concluded that a single ingestion of a food allergen might not provoke an eczematous lesion, but that chronic ingestion of a food allergen can result in the classic changes of atopic dermatitis [43]. Children who have atopic dermatitis and documented food allergy might develop typical eczematous lesions while the disease is active, but might develop urticaria with ingestion of a food allergen when the atopic dermatitis is in remission [44]. Breuer and colleagues [45] performed 106 double-blind placebo-controlled food challenges to cow’s milk, egg, wheat, and soy on 64 children who had atopic dermatitis. Twenty-eight (57%) of the 49 positive reactions resulted in a late eczematous reaction, either as an isolated event or in combination with an immediate reaction. Hill and Hosking evaluated 487 infants who had skin prick tests to cow’s milk, egg, and peanut, and who had a family history of atopic dermatitis, asthma, or immediate food allergy in a parent or sibling [46]. One hundred and forty-one (28.9%) of these infants had atopic dermatitis by the age of 12 months. These authors found that as the severity of atopic dermatitis increased, so did the prevalence of IgE-mediated food allergy and also the frequency of adverse food allergy reactions. The relative risk of an infant who had atopic dermatitis to develop an IgE-mediated food allergy was 5.9 for the most severely affected group. The most frequently implicated foods include eggs, cow’s milk, tree nut, peanut, soy, wheat, seafood, citrus fruits, and chocolate [47]. Approximately 30% to 40% of children lose their food hypersensitivity after 1 to 2 years of allergen avoidance and 80% to 85% outgrow their food allergies by 10 years of age [40,47]. Hypersensitivity to peanut, tree nut, and shellfish is more persistent [47].

Aeroallergens such as house dust mites, animal dander, pollens, and tobacco smoke might cause exacerbations of atopic dermatitis [1]. Intranasal or bronchial inhalation challenge with these aeroallergens can lead to worsening of the skin lesions in patients who have atopic dermatitis. Tupker and colleagues [48] subjected 20 patients who had atopic dermatitis to bronchial provocations with house dust mite. In 9 of 20 patients, bronchial challenge induced unequivocal skin symptoms after 1.5 to 17 hours. Pruritic erythematous lesions on non-involved sites together with exacerbations of existing lesions were seen in 3 patients. Three patients had an exacerbation only, and 3 other patients had new lesions only. In general, the degree of IgE sensitization is correlated with the severity of atopic dermatitis. Children exposed to environmental tobacco smoke have a higher risk to develop atopic dermatitis [49,50].

The frequency of contact sensitization in atopic dermatitis ranges from 41% to 64% [51–53]. Contact sensitization can provoke or aggravate atopic dermatitis. Nickel, fragrance, and neomycin are the most commonly implicated contactants [51].
Atopic dermatitis can develop consequent to emotional stress [1]. Patients who have atopic dermatitis might respond to emotional stress with increased pruritus and scratching, which will aggravate the lesion of atopic dermatitis [1]. A higher stress-induced increase of cutaneous lymphocyte-associated antigen cells has been demonstrated in the circulation in patients who have atopic dermatitis compared with healthy controls [54]. This suggests that stress might result in an increased ability of T lymphocytes to migrate to the skin [54]. Stress-induced immunomodulation might be mediated by neuropeptides [55].

**IMMUNOPATHOLOGY**

Clinically unaffected skin of patients who have atopic dermatitis shows mild epidermal hyperplasia and sparse perivascular infiltration of T-helper 2 cells in the dermis [2]. Acute skin lesions are characterized by intracellular and intercellular edema of the epidermis (spongiosis), which is a histologic hallmark of atopic dermatitis [56]. There is marked perivascular infiltration of T-helper 2 cells in the dermis. Eosinophils, neutrophils, and mast cells are rarely present [56]. Chronic atopic lesions are characterized by a hyperplastic and hyperkeratotic epidermis with minimal spongiosis and increased IgE-bearing Langerhans cells and inflammatory dendritic epidermal cells [2,56]. Cellular infiltrate in the dermis consists mainly of macrophages and eosinophils [2,56]. The number of mast cells is also increased.

**CLINICAL MANIFESTATIONS**

Approximately 60% of children who have atopic dermatitis manifest the disease during the first year of life, and an additional 30% do so before the age of 5 years [1,57]. Intense pruritus and cutaneous reactivity are the hallmarks of atopic dermatitis [1]. Pruritus increases the susceptibility of the surrounding skin to react to minimal stimuli and to illicit an itch, a phenomenon known as allokinesis [56]. Pruritus is exacerbated by scratching, which causes release of substance P from cutaneous proprioceptor nerves with resultant release of histamine from mast cells in the scratched area [56].

In infants, the eruption often affects the face and scalp (Fig. 1); although the extensor surfaces of the extremities (Fig. 2) and the trunk are also common sites [1,58]. In older children and adolescents, the neck and the antecubital and popliteal fossae are the typical sites (Fig. 3) [1,58]. In a prospective, longitudinal birth cohort study of children born to mothers who had a history of asthma, a total of 411 infants were enrolled and followed for 3 years with scheduled visits every 6 months as well for the acute care visits for new skin symptoms or acute exacerbations [59]. Fifty-five infants had incomplete follow-up and were excluded from the analyses. The cumulative incidence of atopic dermatitis was 44% by the age of 3 years. Atopic dermatitis was found to begin on the scalp, ear, forehead, neck, or cheek; and later to spread to the extensor surfaces of the extremities and trunk; and finally to the flexor surfaces of the extremities [59]. The nose is often spared and is referred to as the “head light” sign [56].
The predilection for the face and cheeks during infancy might be related to the exposure of these skin surfaces to trauma from bed sheets.

Lesions are classified as acute, subacute, or chronic and are usually symmetrical [60]. Acute lesions are intensely pruritic, and include erythematous papules, papulovesicles, or weeping lesions [60]. Subacute lesions include erythematous scaling papules or plaques. Chronic lesions are characterized by prominent scaling, excoriations, and lichenification in commonly affected body areas.

Xerosis results from reduced amount of ceramides in the skin and enhanced transepidermal water loss. Xerosis is seen in 67% to 98% of patients who have atopic dermatitis [61]. Xerosis predisposes to the development of microfissures and cracks in the epithelium, which favor the entry of allergens and microorganisms [10]. Other associated findings include Dennie Morgan lines (infraorbital folds), allergic shiners (periorbital darkening), palmo-plantar hyperlinearity, pityriasis alba (Fig. 4) [62], keratosis pilaris (Fig. 5) [63], ichthyosis vulgaris [64], dermatographism, anterior subcapsular cataract, cheilitis, prurigo nodularis, and lichen simplex [65,66].

**DIAGNOSIS**

The diagnosis of atopic dermatitis is clinical and based on the presence of typical features. Criteria to define atopic dermatitis were first established by Hanifin and Rajka (Table 1) [67]. Although these criteria are useful for
epidemiologic and therapeutic studies, many of the features are not common in children [66], and the minor criteria have not been validated in several studies [66,68,69]. In 1994, the United Kingdom Working Party developed more practical criteria for the diagnosis of atopic dermatitis [70]. This group defined atopic dermatitis as present if a pruritic skin condition is accompanied by at least three features that included history of flexural dermatitis (or history of dermatitis on the cheeks in children younger than 10 years of age), a personal history of asthma or hay fever (or an atopic history in a first-degree relative in children younger than 4 years of age), generalized xerosis in the past year, visible flexural eczema (or eczema on the cheeks, forehead or the extensor extremities in children younger than 4 years of age), and onset before age 2 years for children first diagnosed when they were older than 4 years [70]. More recently the American Academy of Dermatology Consensus Conference on Pediatric Atopic Dermatitis established simplified clinical criteria for the diagnosis of atopic dermatitis (Table 2) [71]. The criteria include pruritus and eczematous lesions as the only essential criteria, but also include supporting criteria that are suggestive of the diagnosis and associated features that are common but nonspecific (see Table 2).

**ASSESSMENT OF SEVERITY AND PSYCHOSOCIAL IMPACT**

Several scoring systems have been developed for the assessment of disease severity in children who have atopic dermatitis. The SCORing of Atopic
Dermatitis (SCORAD) system, Eczema Area and Severity Index (EASI) system, and the Nottingham Eczema Severity Score (NESS) system are user-friendly, reliable, and in popular use [50,72]. These systems generate quantifiable data that are amenable to analysis [72].

The SCORAD score ranges from 0 to 103 and measures the extent and intensity of the skin lesions, and the degree of pruritus and sleep loss over the preceding 3 days [73]. SCORAD uses a body diagram to record the extent and area of involvement, and records the intensity of erythema or darkening, edema or papulation, oozing or crusting, excoriation, lichenification or prurigo, and dryness. SCORAD is a weighted index, with less weight considered for the...
extent (multiplying by a factor of 0.2) but more emphasis on the symptomatology of pruritus and sleep loss (multiplying by a factor of 1) and the most weight for the intensity of the symptoms (multiplying by a factor of 3.5) [73]. Hon and colleagues [74] have shown that subjective symptoms such as scratching and sleep disturbance do not correlate well with the disease extent or intensity. Kunz and colleagues [75] suggest that a modified SCORAD index that does not include the pruritus and sleep-loss components is more objective and accurate to assess the severity of atopic dermatitis. On the modified SCORAD grading scale, only objective items are included with a 20-point extent scale and a 63-point intensity scale. The modified SCORAD scale ranges from 0 to 83 points with higher scores indicative of more severe disease [75].

Scratching lacks objectivity and is difficult to study. Limb-worn digital accelerometers are a useful and practical way to assess nocturnal scratching in the home environment [76–78]. In a recent study, Hon and colleagues [77] demonstrated that nocturnal wrist activities measured with a DigiTrac wrist motion monitor (IM Systems, Baltimore, MD, USA) were closely correlated with objective clinical scores and serum levels of chemokine markers. Pruritus can also be assessed with a video record [74,76].

EASI incorporates body surface area involvement into the assessment. The index assigns proportionate values to four body regions. In patients 8 years and
older, the body regions include the head (10%), trunk (30%), upper limbs (20%), and lower limbs (40%); the values are modified slightly for younger patients [79]. The six signs of atopic dermatitis include erythema, edema/induration/papulation, excoriation, oozing/weeping/crusting, scaling, and lichenification, and are graded on a 4-point scale that ranges from absent (0) to severe (3). The EASI score ranges from 0 (clear) to 72 (very severe).

NESS measures the disease severity over a 12-month period. The disease severity is determined by evaluating the clinical course, disease intensity, and extent of atopic dermatitis [80]. Equal weighting is applied to the three parameters, and each carries a score of 1 to 5. A final score is achieved by adding each score to produce a possible range of scores from 3 to 15; higher scores

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<td>Hanifin and Rajka criteria for the diagnosis of atopic dermatitis</td>
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Must have three or more basic features:

1. Pruritus
2. Typical morphology and distribution:
   - flexural lichenification or linearity in adults;
   - facial and extensor involvement in infants and children
3. Tendency toward chronic or chronically relapsing dermatitis
4. Personal or family history of atopy

Plus three or more of the following:

1. Xerosis
2. Ichthyosis/palmar hyperlinearity/keratosis pilaris
3. Immediate (type 1) skin test reactivity
4. Elevated serum IgE
5. Early age of onset
6. Tendency toward cutaneous infections/impaired cell-mediated immunity
7. Tendency toward nonspecific hand or foot dermatitis
8. Nipple eczema
9. Cheilitis
10. Recurrent conjunctivitis
11. Dennie-Morgan infraorbital fold
12. Keratoconus
13. Anterior subcapsular cataracts
14. Orbital darkening
15. Facial pallor/facial erythema
16. Pityriasis alba
17. Anterior neck folds
18. Itch when sweating
19. Intolerance to wool and lipid solvents
20. Perifollicular accentuation
21. Food intolerance
22. Course influenced by environmental/emotional factors
23. White dermatographism/delayed blanch

indicate more severe disease [80]. The NESS is simple and quick to use and correlates well with the SCORAD scale [50,81].

Problems with interpersonal and intrapersonal variability are unavoidable when subjective clinical scoring systems are used [74]. Objective laboratory markers that correlate with the clinical aspects of atopic dermatitis would be helpful. Hon and colleagues [82–85] have demonstrated that serum levels of macrophage-derived chemokine, thymus and activation-regulated chemokine, interleukin-18, and cutaneous T-cell attracting chemokine, and urinary levels of leukotriene E4 correlate well with the severity of atopic dermatitis. Macrophage-derived chemokine, and thymus and activation-regulated chemokine are not skin-specific and might be altered by other concurrent atopic disorders such as asthma and allergic rhinitis [86,87]. Cutaneous T-cell attracting chemokine is a skin-specific chemokine and therefore more accurate to assess the severity of atopic dermatitis, even in patients who have coexisting atopy [83]. Cutaneous T-cell attracting chemokine functions by providing a skin-specific signal involved in the localization of cutaneous lymphocyte-associated antigen memory T cells to skin, and provides a potential target to regulate cutaneous T-cell trafficking [83,88].

Several indices have been designed to measure the impact of the disease on the quality of life of affected children and their parents. Studies have shown a direct correlation between quality of life and disease severity on cross-sectional and over-time observations [89,90]. The quality of life measurement provides additional information to the objective clinical scoring systems [90]. The Children’s Dermatology Life Quality Index is useful for patients under 16 years of age and is a simple, self-administered, and validated tool that measures the impact of a skin condition on the quality of life over the past 7 days [90]. The index covers 16 areas and includes effects on emotions, social development, sleep

| Table 2 |
| Diagnostic criteria for the diagnosis of atopic dermatitis suggested by the American Academy of Dermatology |

| Essential features (must be present) |
| Pruritus |
| Eczema (with typical morphology for age and a chronic or relapsing history) |

| Important features (seen in most cases and add support to the diagnosis) |
| Early age at onset |
| Atopy (including personal/family history of such and IgE reactivity) |
| Xerosis |

| Associated features (help to suggest diagnosis but are nonspecific) |
| Atypical vascular response (ie, facial pallor, white dermatographism) |
| Keratosis pilaris, hyperlinear palms, or ichthyosis |
| Ocular or periorbital changes |
| Perioral or periauricular lesions |
| Perifollicular accentuation, lichenification, or prurigo lesions |

disturbance, schooling, hobbies, and treatment issues [91]. The score can range from 0 to 30; a high score indicates diminished quality of life [91]. The refined version of the Childhood Atopic Dermatitis Scale consists of five scales that include family and social function, emotion, sleep, symptoms, and activity limitations and behavior [92]. Childhood Atopic Dermatitis Scale has 45 items and a score that ranges from 0 to 180, with higher scores indicative of a more profound effect on quality of life.

The Parents’ Index of Quality of Life in Atopic Dermatitis is a quality-of-life instrument that is specific for parents of children who have atopic dermatitis [93,94]. The Parents’ Index of Quality of Life in Atopic Dermatitis has 28 items that cover a range of parental needs that can be influenced by a child who has atopic dermatitis, such as the need for rest and relaxation, self-respect, independence, and personal space and time [93].

The scoring systems for assessment of disease severity and psychosocial impact are more often used to assess outcomes in clinical trials [91,95,96]. These scoring systems are rarely used in clinical practice. Hon and colleagues [8] proposed a more holistic approach to improve the evaluation of patients who have atopic dermatitis. The approach combines the documentation of acute and chronic symptomatology, and includes an objective assessment of scratching and sleep loss [8]. Hon and colleagues [8] recently found that quality of life, disease severity scores, and laboratory markers of atopy represent different domains in the assessment of atopic dermatitis. These clinical features do not necessarily correlate with each other, and all three aspects should be individually evaluated to assess the well being of the patients. When treating a child who has atopic dermatitis, health care providers should evaluate disease severity and quality of life at the initial consultation, and also at regular intervals during follow-up. This approach ensures a more global and dynamic view of the clinical status of the patient and helps facilitate a more individualized management plan. Treatment should focus more on psychosocial rehabilitation when the impact on daily activities is great notwithstanding minimal evidence of lesion activity [8].

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes seborrheic dermatitis, psoriasis, acrodermatitis enteropathica, scabies, immunodeficiency disorders, nummular eczema, and contact dermatitis [66,97].

The lesion in seborrheic dermatitis is usually asymptomatic and consists of an accumulation of a greasy yellow scale. In contrast, the lesion in atopic dermatitis is pruritic, the scale is dry, and excoriations are frequent. The diaper area might be involved in seborrheic dermatitis, but is typically spared in atopic dermatitis [97].

Psoriasis during infancy and childhood often presents in the diaper area, elbows, knees, and scalp. The lesion is characterized by sharply demarcated erythematous plaques [98]. The thick silvery scale seen in adults is not common in infancy and early childhood. In atopic dermatitis, involvement of the diaper area is unusual, and the lesion is always pruritic and poorly demarcated.
In acrodermatitis enteropathica, the skin eruption consists of vesicobullous, eczematous, dry, scaly or psoriasiform lesions. On the face, the lesion has a typical horseshoe appearance with lesions on the cheeks and around the chin [97]. In the perianal area, the dermatitis is erythematous and diffuse with a peripheral edge of scale [97]. Pruritus is not a feature of acrodermatitis enteropathica. Other associated features include chronic diarrhea, alopecia, stomatitis, glossitis, growth failure, irritability, recurrent skin infections, and superinfection with Candida albicans.

Scabies and atopic dermatitis present with extremely pruritic lesions. In atopic dermatitis, the face is usually involved, whereas in scabies, the face is usually spared. The lesions in scabies are polymorphic with papules, vesicles, pustules, urticaria, and nodules, which can all occur at the same time. Linear burrows are typical of scabietic lesions, but are not features of atopic dermatitis.

The differentiation of an immunodeficiency disorder from atopic dermatitis can be difficult, especially in infants. Pruritus is present in all of these disorders. Immunodeficiency disorders might present with lesions in nonspecific locations, failure to thrive, recurrent infections, lymphadenopathy, and hepatosplenomegaly [60,97].

Nummular eczema is characterized by coin-shaped eczematous plaques [99]. The condition is rare in the first year of life. The onset peaks between 15 and 25 years of age and again between 55 and 65 years of age [99]. The lesions are usually located on the extensor surfaces of the lower extremities and are often symmetrical. The knees, elbows, and scalp are often spared [97]. In contrast to atopic dermatitis, the unaffected skin in patients who have nummular eczema is not xerotic [97].

Contact dermatitis is an inflammatory condition in the skin triggered by direct contact with an environmental agent. The agent might be irritant or allergic in nature. Contact dermatitis and atopic dermatitis are extremely pruritic. An eczematous lesion that conforms to an area exposed to the contactant suggests the diagnosis of contact dermatitis. Patients who have atopic dermatitis are more prone to develop contact dermatitis [51,53,66].

**COMPLICATIONS**

Bacterial infection, most commonly with *S. aureus*, is the main complication of atopic dermatitis [100]. Purulent oozing honey-colored crusts, folliculitis, and pyoderma suggest secondary infection with *S. aureus* (Fig. 6). The anterior nares are an important reservoir of *S. aureus* [101]. Eczema herpeticum (Kaposi varicelliform eruption), caused by herpes simplex virus, is a potentially dangerous complication [57]. Eczema vaccinatum, caused by variola virus, follows smallpox vaccination or exposure to individuals who either have the infection or who were vaccinated for smallpox, but is rare now that smallpox has been eradicated. Children who have atopic dermatitis are also prone to verruca vulgaris (warts), molluscum contagiosum, and superficial fungal infections [56,58].

Ocular complications of longstanding atopic dermatitis include eyelid dermatitis, chronic blepharitis, keratoconjunctivitis, vernal conjunctivitis,
keratoconus, uveitis, and cataracts. It is unclear whether cataracts are due to atopic dermatitis per se or result from the extensive use of corticosteroids [1].

Postinflammatory hypopigmentation might occur at sites of atopic dermatitis [102]. Hypopigmentation might also be a complication of topical corticosteroid therapy.

Atopic dermatitis is uncomfortable and distressing to patients because of the associated pruritus and unsightly appearance of the lesions [11]. Children who have atopic dermatitis might suffer from lack of sleep, irritability, daytime tiredness, emotional stress, lowered self-esteem, and psychologic disturbance [103,104]. Sleep disturbance is common in children who have atopic dermatitis but is inadequately studied. Sleep efficiency is significantly reduced in children who have severe atopic dermatitis [105].

Atopic dermatitis can adversely affect the relationship between the child and caregivers and might have an impact on the whole family. The disruption of school, family, and social interactions can severely impair the quality of life and can have implications in individuals other than the affected child [106–108]. Parents might experience guilt, frustration, resentment, exhaustion, and helplessness [3]. There are considerable economic implications associated with caring for children who have atopic dermatitis [3].

**DIAGNOSTIC TESTING**

The diagnosis is based on a careful history and a thorough physical examination. Laboratory tests are usually not required. The need for further diagnostic work-up should be decided on an individual basis and should depend on the severity of the atopic dermatitis and the suspected factors involved [55,109]. Hypereosinophilia in patients who have atopic dermatitis is
a nonspecific finding and is also seen in patients who have asthma, allergic rhinitis, parasitic infestation, Hodgkin disease, and Löffler syndrome. Although serum levels of macrophage-derived chemokine, thymus and activation-regulated chemokine, interleukin-18, and cutaneous T-cell attracting chemokine, and urinary levels of leukotriene E4 have been shown to correlate well with the severity of atopic dermatitis (vide supra), measurements of these markers are usually performed as a research tool and have limited usefulness in clinical practice.

Approximately 70% to 80% of patients who have atopic dermatitis have elevated IgE levels, which are often high [2]. Conversely, 15% of apparently normal individuals also have elevated IgE levels [110]. As such, routine measurement of serum IgE level is not helpful. IgE to specific allergens does not necessarily correlate with clinical disease or indicate clinical relevance in a given patient [111]. Radioallergosorbent tests can be used to screen for antigen-specific IgE in the serum. Radioallergosorbent tests are most often used in patients who have severe atopic dermatitis who also have severe anaphylaxis [47]. The advantages of radioallergosorbent tests include convenience, safety, and the ability to test the serum for multiple different IgE molecules at one time [112]. The disadvantages include high cost, limited number of antigens available, delay in obtaining results, detection of circulating IgE rather than cell-bound IgE, interference with the test result by circulating IgG antibody, and the use of radiation with the attendant need for precautions [39].

Allergy skin testing with food extracts is often used to screen patients who have suspected IgE-mediated food allergies. A positive skin prick test merely implies the presence of food antigen-specific IgE antibodies and that the symptoms might be related to the particular food allergen tested [39]. Overall, the positive predictive accuracy is around 50% [111]. A negative skin prick test, on the other hand, has an excellent negative predictive value (greater than 95%) and confirms the absence of an IgE-mediated reaction [111,113].

In the atopy patch test, allergens known to elicit IgE-mediated hypersensitivity reactions are applied to the back with large test chambers for 48 to 72 hours, with daily examination of the area [51]. It is important to patch test only those areas that are free of atopic dermatitis and that have not had a recent application of topical therapy [110]. Readings are performed according to the European Task Force on Atopic Dermatitis guidelines [114]. Atopy patch test has a higher specificity (64%–91%) than a skin prick test (50%–85%) [7]. At present, the atopic patch test is used mainly for research purposes.

The double-blind placebo-controlled food challenge is objective and is considered the “gold standard” for the diagnosis of a food allergy [39].

**MANAGEMENT**

Successful treatment requires a comprehensive approach that includes education of patients and caregivers, avoidance of triggering factors, optimal skin care, and pharmacotherapy.
Patient education

Patient and caregiver education and support are important in the management of atopic dermatitis. Compliance is related to understanding of the disease process, and poor compliance is a major reason for treatment failure [115]. Although there is no cure for atopic dermatitis, control is possible. Patients and caregivers should be reassured that modern treatments are safe and effective. Fear of steroid therapy is a significant factor in noncompliance [116]. Patients and caregivers should be taught how to apply topical medications correctly and in adequate amounts. The International Study of Life with Atopic Dermatitis reported that patients who have atopic dermatitis are often not treated for half the duration of time that active lesions are present and that there is a need for patients to be educated so that they are sufficiently confident to use prescribed medications [117]. Studies have shown that age-related educational programs are effective to improve the quality of life of affected children and their caregivers [3,118].

Avoidance of triggering factors

Irritants, allergens, and emotional stress are possible precipitating factors in children who have atopic dermatitis. Soaps, detergents, washing powders, fabric softeners, and perfumed products should be minimized. Soaps should be chosen with minimal defatting activity and a neutral pH. Nonsoap agents are less irritating and preferred. After swimming in a chlorinated pool, children should shower and use a gentle cleanser to remove chlorine on their bodies.

Cotton clothing is preferred to woolen or abrasive clothing. The environment should be kept as cool as possible.

Most individuals try to relieve the sensation of itch by scratching. However, itching abrades or excoriates skin, which leads to a vicious cycle of more itching and increases the risk of secondary infection [110]. Children should be discouraged from scratching. To minimize injury to the skin, fingernails should be kept short, smooth, and clean. Light cotton mittens are occasionally necessary to control scratching at night.

Control of house dust mites might improve atopic dermatitis in patients who are allergic to house dust mites [10]. Among recommended measures are use of allergen-impermeable covers for pillows and mattresses, washing bedding in hot water, removal or frequent vacuuming of carpets and upholstered furniture, and elimination of plants and pets from the house. Smoking should not be permitted in the home.

Food allergy plays an immunopathogenic role in 30% to 50% of children who have moderate to severe atopic dermatitis [1,36,43]. Most children who have food allergy react to only one or two of the most common allergens such as egg, cow’s milk, nut, peanut, soy, and wheat [47]. In a well-designed prospective study of 113 patients who have atopic dermatitis, marked improvement was noted in those who were maintained on an allergen-elimination diet, compared with a similar group of patients who did not have food allergy or who did not adhere to the diet [119]. For children in whom a food allergy...
has been identified, the offending allergen should be eliminated from the diet. Conversely, avoidance of common foods in children who do not have documented food allergy is not recommended and might result in faddism or malnutrition [120].

Infants who have elevated cord serum IgE or a positive family history of atopy are at risk for the development of atopic dermatitis [121,122]. The protective effect of breastfeeding is controversial [123,124]. The American Academy of Dermatology Guidelines Task Force reviewed the subject in 2004 and found no conclusive evidence that exclusive breastfeeding influences the development of atopic dermatitis [123]. There is, however, suggestive evidence that prolonged breastfeeding might delay the onset of atopic dermatitis [123]. The Section of Pediatrics of the European Academy of Allergology and Clinical Immunology critically reviewed the existing literature and concluded that exclusive breastfeeding for at least 4 to 6 months in infants who have a family history of atopy results in a lower incidence of atopic dermatitis [124]. In high-risk infants, exclusive breastfeeding for the first 6 months of life is recommended [124,125]. When breastfeeding is not possible, a partially or completely hydrolysed formula is desirable [126,127].

A Cochrane review reported that allergen avoidance during pregnancy does not minimize the development of atopic dermatitis and increases the risk for preterm births and reductions in birth weight [128]. The present consensus is that dietary intervention in utero is potentially harmful and is not indicated [39,126].

Emotional stress often exacerbates the skin lesions of atopic dermatitis. If stress cannot be avoided, therapy to enhance coping mechanisms should be considered [1].

Optimal skin care
Maintaining optimal skin hydration is critical to prevent and manage atopic dermatitis. Hydration of the skin can be achieved by daily baths in lukewarm, but not hot, water, for approximately 5 to 10 minutes, followed by patting the body dry with a towel. Rubbing should be avoided because this might precipitate the sensation of pruritus. Fragranced bubble baths should be avoided. Showers should be discouraged in favor of bathing because the constant flow of water increases the potential for xerosis, especially in dependant areas such as the calves, ankles, and elbows, which suffer the largest flow of water. Although encouraged, bathing is not practiced by many patients. Hon and colleagues [129] documented that 75% of patients who had atopic dermatitis preferred showering to bathing. Bathing and showering instructions should be individualized for optimal compliance and therapeutic efficacy. A moisturizer or emollient should be applied within 3 minutes of bathing to minimize evaporative losses and to keep the skin soft and flexible [66]. This “soak and seal” method helps to improve the integrity of the skin barrier [6]. Ointments are more effective but messy; creams are better tolerated. The type of moisturizer or emollient should be tailored to the individual skin condition [15]. In areas
rich with sebaceous glands, such as the face, formulations should contain less oil than for other body areas [15]. Lotions, which have a high-water and low-oil content, can worsen xerosis by way of evaporation and should be avoided. More than once a day application of a moisturizer to at-risk areas helps to maintain a high level of hydration in the stratum corneum. Emollient adjunctive therapy has a steroid-sparing effect [130]. Moisturizers that contain urea, alpha-hydroxy acids, or ceramides have been shown to improve the integrity of stratum corneum [6,131].

Topical corticosteroids
Topical corticosteroids are the mainstay of therapy for atopic dermatitis. The choice of potency depends on the severity, site, and extent of the lesions [1]. Corticosteroids mediate an anti-inflammatory effect through binding to a cytoplasmic glucocorticoid receptor in the target cells and forming complexes that enter the nucleus of the cell [132]. Once inside the nucleus, the corticosteroid–receptor complex interacts with glucocorticoid-response elements and alters transcription of various proinflammatory genes, with resultant suppression of inflammatory cell lines and cytokines [133]. Corticosteroids are also effective to reduce the density of S. aureus on affected skin [6]. Topical corticosteroids are available in extremely high (class 1) to low (class 7) potencies [6]. In general, the least potent corticosteroid that can control the symptom should be used, and only low-potency agents should be applied to the face, genitalia, and intertriginous areas. High-potency corticosteroids should only be used for up to 3 weeks for acute exacerbations of atopic dermatitis [10]. Topical corticosteroids should not be applied more than twice a day; frequent use does not improve efficacy and does increase the risk of adverse events. Once daily treatment with topical fluticasone propionate or mometasone furoate is effective [134,135].

The risk of adverse events depends on the potency of the corticosteroid, concomitant use of occlusive dressings, the area being covered, skin integrity, and duration of treatment [1]. Compared with adults, children are at higher risk of local and systemic effects. Local adverse events, particularly on delicate skin areas, include skin atrophy, striae, depigmentation, telangiectasia, decreased subcutaneous adipose tissue, rosacea, perioral dermatitis, folliculitis, and steroid acne [1]. Systemic adverse events include Cushing syndrome, adrenal suppression, cataracts, glaucoma, osteopenia/osteoporosis, and growth retardation. Topical corticosteroids should be used with caution near the eyes to minimize the risk of cataracts and glaucoma. Tachyphylaxis might occur with prolonged treatment.

Systemic immunosuppressants
Systemic corticosteroids should be reserved for recalcitrant cases and used for the shortest time possible while awaiting response to other therapies. Cyclosporine blocks T-cell activation and suppresses cytokine secretion. The drug binds to cyclophilin and the complex inhibits calcineurin. Cyclosporine is beneficial for recalcitrant atopic dermatitis unresponsive to topical corticosteroids, but the dermatitis will return after treatment ceases, although not always as
severely. Nausea, hypertension, gastrointestinal discomfort, hypertrichosis, and hepatic and renal toxicity limit the usefulness. Cyclosporine is not effective when applied locally. Various other systemic immunosuppressants such as azathioprine, mycophenolate mofetil, methotrexate and recombinant interferon gamma have been used in small numbers of patients with variable success. These systemic agents all have significant adverse effects and require careful monitoring, which limits clinical usefulness [6].

**Topical immunomodulators**
The newly introduced tacrolimus ointment and pimecrolimus cream work by binding to a cytoplasmic immunophilin. The complex inhibits the activity of calcineurin to dephosphorylate the nuclear factor of activated T cell, a transcription factor required to activate interleukin-2 gene transcription, and thereby suppresses cytokine production by T cells [1]. The immune responses that stimulate inflammation are therefore down regulated. Both medications have favorable efficacy and safety profiles. Percutaneous absorption has been shown to be low, and there is no evidence of systemic toxicity. Topical immunomodulators significantly improve the quality of life of children and adults who have atopic dermatitis, as well as their family members [95,96]. Effective relief of itch can be prompt, as was objectively documented by Hon and colleagues [78] with the wrist motion monitor. Effectiveness does not decrease with time, and the rebound effect sometimes observed after withdrawal of a topical corticosteroid does not occur [136]. Topical immunomodulators do not decrease collagen synthesis or cause skin abnormalities or depigmentation [137,138], and can be used safely over the entire body, including the face and intertriginous areas [139]. Treatment with a topical immunomodulator might even reverse the steroid-induced skin atrophy in patients who have atopic dermatitis [7,111]. Treatment with either topical immunomodulator is associated with reduced level of *S. aureus* levels in the skin lesions of patients who have atopic dermatitis [133]. Topical immunomodulators, but not corticosteroids, also suppress superantigen-driven immune proliferation [111,140]. The most common adverse effect of topical immunomodulators is a burning or stinging sensation or erythema during the first few days of application. Less-common adverse events include varicella-zoster infection and vesicular rashes [6]. Treatment with a topical calcineurin inhibitor does not affect the normal responses to routine childhood immunization [141,142].

Tacrolimus (FK506), a macrolide lactone produced by the *Streptomyces tsukubaensis*, a fungus found in the soil of Mount Tsukuba in Japan, has 10 to 100 times the potency of cyclosporine [143]. The ointment was the first topical immunomodulator formulated for use in children older than 2 years of age [143]. In addition to its inhibitory effect on cytokine production, tacrolimus inhibits the activation of T cells, fibroblasts, Langerhans cells, mast cells and keratinocytes that might result in decreased immunogenic response to antigens [132,144]. Tacrolimus enhances the production of transforming growth factor-β whereas hydrocortisone does not [145]. Tacrolimus is available in two
strengths: a 0.1% ointment for individuals over the age of 16 years, and a 0.03% ointment for children over the age of 2 years and for adults who do not tolerate the higher dose. The medication can be used twice a day for short or intermittent long-term treatment of moderate to severe atopic dermatitis [6].

Pimecrolimus (SDZ ASM 381), a derivative of the macrolactam ascomycin, is produced by *S. hygroscopicus var. ascomyceticus*. Pimecrolimus 1% cream has been approved by the Food and Drug Administration for short-term and intermittent long-term treatment of mild to moderate atopic dermatitis in individuals older than 2 years. Pimecrolimus selectively inhibits the release of cytokine from activated T cells and mast cells [15,133,146]. In contrast to tacrolimus, pimecrolimus does not affect cytokine release from monocytes, fibroblasts, Langerhans cells, and keratinocytes [15,146–148].

Iskedjian and colleagues [149] performed a meta-analysis of 15 articles that reported on 16 randomized controlled trials with tacrolimus (n = 9) and pimecrolimus (n = 7) and that involved a total of 5301 patients, of whom 2107 received tacrolimus, 1225 received pimecrolimus, and 1969 were controls. Tacrolimus reduced EASI scores by 65.6% at 1 month and 73% at 3 months. In contrast, pimecrolimus reduced EASI scores by 61.5% at 1 month, 60.3% at 6 months, and 61.9% at 12 months. Tacrolimus success was 51.5% above placebo at 1 month. Pimecrolimus was 45.9% higher than placebo at 1 month, 24.9% higher at 6 months, and 16.1% higher at 12 months. The authors concluded that the success rates for tacrolimus and pimecrolimus were statistically similar. However, tacrolimus rates were consistently higher numerically than those for pimecrolimus, and tacrolimus was used in patients who had more severe disease [149].

Ashcroft and colleagues [150] performed a meta-analysis of 25 randomized controlled trials that compared topical tacrolimus or pimecrolimus with active treatment with a topical corticosteroid or a control vehicle in patients who had atopic dermatitis. A total of 4186 (61%) of 6897 participants received tacrolimus or pimecrolimus. Both drugs were significantly more effective than a control vehicle. Tacrolimus 0.1% was as effective as a potent topical corticosteroid at 3 weeks and more effective than combined treatment with hydrocortisone butyrate 0.1% plus hydrocortisone acetate 1% at 12 weeks. Tacrolimus 0.1% was also more effective than hydrocortisone acetate 1%. Tacrolimus 0.03% was more effective than hydrocortisone acetate 1%, but less effective than hydrocortisone butyrate 0.1%. Direct comparisons of tacrolimus 0.03% and tacrolimus 0.1% consistently favored the 0.1% formulation, but efficacy differed significantly between the two strengths only after 12 weeks of treatment (rate ratio 0.80, 95% confidence interval 0.65–0.99). Pimecrolimus was less effective than betamethasone valerate 0.1%. Pimecrolimus and tacrolimus caused significantly more skin burning than topical corticosteroids. The meta-analysis showed that tacrolimus was more effective that pimecrolimus, but the difference was not statistically significant [150,151].

Paller and colleagues [152] randomized 1065 patients to treatment in three multicenter, investigator blinded studies that lasted 6 weeks and compared
the efficacy and safety of tacrolimus ointment and pimecrolimus cream in pediatric and adult patients who had mild to severe atopic dermatitis. Based on the EASI, tacrolimus ointment was more effective than pimecrolimus cream in the combined analysis (52.8% versus 39.1%, respectively; \(P<.0001\)), in adults (54.1% versus 34.9%; \(P<.0001\)), in children who had moderate/severe disease (67.2% versus 56.4%; \(P = .04\)), and after only 1 week of therapy in children who had mild disease (39.2% versus 31.2%; \(P = .04\)). Tacrolimus was also more effective than pimecrolimus based on the results of the Investigator Global Atopic Dermatitis Assessment. It was also more effective on improvement in percentage of total body surface area affected and on improvement in itch scores (\(P<.05\)), and tacrolimus had a faster onset of action. There was no significant difference in the incidence of adverse events, including application site reactions in the two studies that involved 650 children. Adults treated with tacrolimus experienced a greater number of local application site reactions on day 1; both groups reported a similar incidence of application site reactions thereafter. The authors concluded that tacrolimus ointment is more effective and has a faster onset of action than pimecrolimus cream in children and adults who have atopic dermatitis and that the safety profiles were similar.

Kempers and colleagues [153] randomized 141 patients, aged 2 to 17 years, to treatment with 1% pimecrolimus cream (n = 71) or 0.03% tacrolimus ointment (n = 70) twice daily for 6 weeks. At day 4, local, application-site reactions were less common and of shorter duration with pimecrolimus than with tacrolimus. The incidence of erythema or irritation was 8% (6/71) with pimecrolimus compared with 19% (13/70) with tacrolimus (\(P = .039\)). Fewer patients who received pimecrolimus (0%, 0/6) experienced erythema or irritation that lasted more than 30 minutes, compared with those who received tacrolimus (85%, 11/13; \(P<.001\)). Fewer patients reported itching with pimecrolimus (8%; 6/71) than with tacrolimus (20%; 14/70; \(P = .073\)). The incidence of warmth, stinging, and burning was similar in both groups; however, reactions that lasted over 30 minutes were fewer with pimecrolimus (0%, 0/14) than with tacrolimus (67%, 8/12; \(P<.001\)). Although the authors concluded that efficacy was similar in both groups, after 6 weeks, there was a trend toward more complete clearing of atopic dermatitis in those treated with tacrolimus (42% versus 30%, \(P = .12\)) [154]. The study was criticized for the lack of adequate power to detect a significant difference in efficacy response rates [152,154].

On February 15, 2005, the Pediatric Advisory Committee of the Food and Drug Administration recommended that a “black box warning” be placed on the topical calcineurin inhibitors, tacrolimus and pimecrolimus, because of the potential risk of cancer. On March 10, 2005, the Food and Drug Administration issued an alert to health care providers that there might be a potential link between these topical calcineurin inhibitors and cancer [155]. The alert was based on postmarketing case reports of malignancy among adults and children who used these medications, and on an animal study that demonstrated an increased frequency of lymphoma with an oral dose of pimecrolimus that was
to 30 times the maximum recommended human dose \([9,155]\). A Joint Task Force of the American College of Allergy, Asthma, and Immunology and the American Academy of Allergy, Asthma and Immunology reviewed the existing data and concluded that the current data did not support the use of “black box warning” on these medications \([156]\). In spite of this, the Food and Drug Administration issued a black box warning for tacrolimus and pimecrolimus in January 2006 \([9]\). The warning includes the concern that the long-term safety of these medications has not been established and that although no definite causal relationship has been conclusively established between topical calcineurin inhibitors and malignancy, there have been rare case reports in patients treated with these medications. The new labeling advises that these drugs should be recommended as a second-line treatment and that use in children younger than 2 years of age is not recommended \([55]\).

**Antihistamines**

Although pruritus in atopic dermatitis does not appear to be mediated by histamine release, oral antihistamines can provide symptomatic relief at bedtime because of sedative properties and might be effective for intense pruritus refractory to moisturizers and conservative measures \([1]\). Of the \(H_1\) antihistamines, hydroxyzine is more effective than diphenhydramine or cyproheptadine \([157]\). The second-generation antihistamines, such as terfenadine, loratadine, and astemizole, have few central nervous system effects and are nonsedating, but are less efficacious in the treatment of pruritus. Topical antihistamine preparations should be avoided because of the potential for local allergic reactions.

**Antibiotics**

Systemic antibiotics are indicated for secondary bacterial infections that might exacerbate and complicate an acute flare. Cloxacillin, clindamycin, first- or second-generation cephalosporins, or macrolides are most effective against \(S.\) aureus. Topical antibiotics such as mupirocin and fusidic acid are useful to treat impetiginized lesions. Some authors suggest intranasal application of a topical antibiotic twice daily for 5 to 7 days to eradicate \(S.\) aureus in the nares \([111]\). Silk or silver-coated textiles have antimicrobial properties and can reduce \(S.\) aureus colonization and the severity of atopic dermatitis \([158–161]\). The use of silver-coated textiles and silk fabric in the treatment of atopic dermatitis is still experimental.

**Coal tar preparations**

The anti-inflammatory and antipruritic effects of coal tar preparations might help to reduce the amount of topical corticosteroid required in long-term maintenance therapy. There are no randomized, placebo-controlled studies that have demonstrated the efficacy of these preparations. These preparations tend to cause stinging and irritation, which precludes use for acute disease \([10]\). Disadvantages of tars include odor, dark staining color, and side effects such as folliculitis, photosensitization, and contact dermatitis \([1]\). These disadvantages, the lack of proven efficacy, and the potential carcinogenic effects of tar are such that coal tar is now rarely recommended.
**Phototherapy**

Broadband ultraviolet A and UVB, narrowband UVB, combined UVAB, and psoralen plus UVA are effective in the treatment of refractory atopic dermatitis [12]. Their use, however, is limited by the availability of lighting systems, cost, inconvenience, and adverse effects. Adverse effects include acute phototoxicity such as burns and pigmentation, potentially increased risk of skin cancer, and premature photoaging with prolonged treatment. With exceptions, the use of phototherapy should be restricted to patients older than 11 years of age.

**Wet-wrap therapy**

Wet-wrap treatments are a useful adjunct for the short-term relief of pruritus in children who have severe or refractory atopic dermatitis [162, 163]. The evaporation of water from the skin surface results in vasoconstriction with relief of pruritus [66]. Wet-wrap therapy also helps to debride crusts from the skin surface; soften the skin, which enhances the penetration of topical medication; and also serves as a mechanical barrier against scratching [10, 162]. Studies have been performed on only a small number of children, and further studies are warranted. Adverse effects of wet-wrap therapy include maceration of the skin with prolonged treatment and folliculitis [163].

**Probiotics and prebiotics**

The use of probiotics and prebiotics in the treatment of atopic dermatitis is controversial. Probiotics are presumed to mediate antiallergenic effects by stimulating production of T-helper 1 cytokines and transforming growth factor-β and gut IgA [164–166]. Prebiotics work by selectively stimulating the growth or activity of a limited number of bacterial strains in the intestinal flora. Several randomized controlled trials failed to show the beneficial effects of probiotics in the treatment of atopic dermatitis [167]. Other studies yielded different results [167–172]. In a double-blind, randomized placebo-controlled trial, perinatal administration of *Lactobacillus rhamnosus* strain GG reduced the incidence of atopic dermatitis by 50% in children during the first 2 years of life [168]. A follow-up study showed that the preventive effect extended to the age of 4 years [169]. Viljanen and colleagues [172] randomized 230 infants who had suspected cow’s milk allergy in a double-blinded study to receive *L. rhamnosus* GG (n = 80), a mixture of four other probiotic strains (n = 76), or a placebo (n = 74), given twice daily with food for 4 weeks. The authors found that *L. rhamnosus* GG was an effective treatment for atopic dermatitis in IgE-sensitized infants but not in non-IgE sensitized infants. In a double-blind placebo-controlled trial, Weston and colleagues [173] randomized 56 children aged 6 to 18 months who had moderate to severe atopic dermatitis to receive *L. fermen-tum* VRI-033 PCC (n = 28) or placebo (n = 28) twice daily for 8 weeks. Fifty-three children completed the study. The authors found that the reduction in the SCORAD index was significant in the probiotic group (P = .03) but not in the placebo group. In a double-blind study, Passeron and colleagues [174] randomized 48 children to receive either *L. rhamnosus* Lcr 35 plus a prebiotic
preparation \((n = 28)\) or an identically appearing prebiotic preparation alone three times a day for 3 months. In the symbiotic group, the mean total SCORAD score was 39.1 before treatment versus 20.7 after 3 months of treatment \((P < .0001)\). In the prebiotic group, the mean SCORAD score was 39.3 before the treatment versus 24.0 after 3 months of treatment \((P < .0001)\). The authors concluded that symbiotics and prebiotics used alone were effective in the treatment of atopic dermatitis. At present, probiotics or prebiotics are not established treatment alternatives for atopic dermatitis.

**Montelukast**

Montelukast, a specific cysteinyl leukotriene receptor antagonist, has established efficacy for the treatment of asthma. Preliminary studies have shown that oral montelukast might also be helpful as an adjunctive treatment for atopic dermatitis \([175–178]\). Larger randomized controlled trials are necessary to substantiate these preliminary findings.

**Allergen-specific immunotherapy/hyposensitization**

Allergen-specific immunotherapy is not an established therapy for atopic dermatitis \([55]\). Some investigators reported a significant improvement of skin symptoms with allergen-specific immunotherapy \([179,180]\). Other investigators could not confirm these observations \([181,182]\). Well-designed, large-scale, randomized, placebo-controlled studies are necessary to clarify whether this therapy is beneficial.

**Alternative/complimentary therapies**

Traditional Chinese herbal medicine has been studied in controlled trials with variable success \([183–185]\). Some traditional Chinese medicines contain corticosteroids \([186]\). Some are less palatable and have the potential for hepatic and renal toxicity \([185,187]\). Recently, Hon and colleagues \([184]\) randomized 85 patients (aged 5–21 years), who had longstanding moderate to severe atopic dermatitis, to receive a 12-week treatment with twice daily dosing of three capsules that contained either five herbs \((n = 42)\), which included *Flos lonicerae* (*jinyinhua*), *Herba menthae* (*Bohe*), *Cortex moutan* (*Danpi*), *Rhizoma atractylodis* (*Cangzhu*) and *Cortex phellodendri* (*Huangbai*), or a placebo \((n = 43)\). The Children’s Dermatology Life Quality Index in traditional Chinese herbal medicine–treated patients was significantly improved at the end of the 3-month treatment and also 4 weeks after stopping therapy \((P = .008\) and 0.059, respectively) compared with patients who received placebo. Adverse effects were uncommon and were generally mild and self-limiting. In a separate study, Hon and colleagues \([188]\) showed that corticosteroids were not present in the five herbs used in the study.

Dietary essential fatty acid supplementation has been studied as a treatment of atopic dermatitis. However, several randomized, double-blind placebo-controlled trials failed to show the effectiveness of this treatment \([189,190]\). Similarly, borage oil was found to be no better than placebo in the treatment of atopic dermatitis \([191]\).
PROGNOSIS
Atopic dermatitis is characterized by exacerbations and remissions. Ten-year clearance rates vary from 40% to 80% for atopic dermatitis that begins in childhood [126]. Poor prognostic factors include early age at onset, severe disease, family history of atopic dermatitis, and concomitant asthma or allergic rhinitis [36,192].

SUMMARY
Atopic dermatitis is an especially common and frustrating condition, and the prevalence is increasing. The disease can adversely affect the quality of life of patients and caregivers. Significant advances in our understanding of the pathogenesis have led to improvements in therapy. Patient and caregiver education, avoidance of potential triggering factors, optimal skin care, and pharmacotherapy offer the potential for good control for most patients.

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Benefits and Risks of Breastfeeding

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In 2005, the American Academy of Pediatrics extended their position concerning the superiority of human milk for feeding human infants and the reasons for encouraging breastfeeding [1]. Yet questions have been raised whether the benefits of breastfeeding pertain to populations in the industrialized world as well as to those societies in which sanitation is marginal. In the industrialized world, the risks associated with breastfeeding are often better publicized than the benefits. Because of these and certain other concerns, the evidence concerning the benefits and risks of breastfeeding is reviewed. In this article, the authors discuss why the benefits outweigh the risks in the vast majority of cases, how some risks can be minimized or prevented, what conditions preclude breastfeeding, how this information can be clinically applied, and how research might improve understanding of the benefits and risks involved in this key biologic process.

**EVOLUTION AND MILK COMPOSITION**

The complexity of human milk and its superior benefits for recipient human infants are an outcome of many hundreds of thousands of years of evolution [2,3]. Indeed, the human mammary gland provides the optimal types and quantities of nutrients [4,5] and immunologic [6] and other bioactive agents [5] for the human infant. Also, the composition of human milk changes dynamically as lactation proceeds to meet the needs of the developing infant [2,3,6].

One prominent example of the intricacy of human milk is its immune system, which is comprised of many antimicrobial, anti-inflammatory, and immunomodulating agents that are often multifunctional, act synergistically, change dynamically as lactation proceeds, and compensate for delays in the development of the immune system of the infant [2,3,6]. In addition, human milk is replete with growth factors for commensal enteric bacteria [6] and living activated leukocytes [6–8]. Human milk therefore protects the infant not only by

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interfering with microbial pathogens but also by inhibiting inflammation and stimulating the development of key components of the infant’s defense system.

**HEALTH OUTCOMES FOR THE INFANT**

In keeping with the unique composition of human milk, health outcomes of breastfed infants are remarkably superior to non-breastfed infants (Table 1). Although there are limitations to many studies because of an inherent lack of randomization between breastfeeding and non-breastfeeding populations and potential confounding variables, there is widespread agreement among physicians, epidemiologists, and other scientists concerning the following positive health outcomes from breastfeeding.

**Reduction of morbidity**

There is less risk to the recipient infant from common bacterial and viral enteric and respiratory pathogens [1,2,6], bacterial urinary tract infections [9], bacterial sepsis [10], bacterial meningitis [11], necrotizing enterocolitis [12], celiac disease caused by gluten intolerance [13], possibly atopic dermatitis [14], and otitis media [15]. Even in very-low-birth-weight infants, feeding one’s own mother’s milk reduces the morbidity caused by infections [16]. In these cases, the reduction in risks are manifest as a reduced incidence, a delayed onset, or less severity of the disease.

**Reduction in mortality**

Mortality is reduced in breastfed infants [17]. Indeed, it has been suggested that breastfeeding may have a more positive impact on mortality of children in the first 5 years of life than the sum of medical interventions [18]. Support for that position was provided by an investigation of 9424 infants and their mothers in Ghana, India, and Peru [19], which revealed that the risk for dying was much greater in non-breastfed infants than predominantly breastfed infants (risk odds ratio, 10.5; 95% confidence interval, 5.0–22.0) or partially breastfed infants

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<tr>
<td><strong>Superior health outcomes in breastfed infants</strong></td>
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<td>Protection during breastfeeding</td>
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<td>Growth faltering</td>
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<td>Visual acuity</td>
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(risk odds ratio, 2.46; 95% confidence interval, 1.44–4.18). Furthermore, neonates in Ghana who received cow’s milk-based fluids or solid foods in addition to human milk in the immediate postnatal period had a fourfold increase in deaths as compared with those who were solely breastfed [20]. Contaminated water may also be responsible for much of the increased mortality in non-breastfed infants in developing countries.

The effect of breastfeeding on the risk for sudden infant death syndrome has been studied. Although confounding variables may have clouded the interpretation of several studies, a recent meta-analysis suggested that breastfed infants are at less risk for sudden infant deaths [21]. A task force of the American Academy of Pediatrics, however, concluded that breastfeeding does not protect against sudden infant death syndrome [22].

Long-term preventative effects
Prior breastfeeding during infancy may decrease the risk in older children for certain diseases, including non-atopic wheezing [23], inflammatory bowel disease [24], lymphoma [25,26], acute leukemia [25,26], insulin-dependent diabetes mellitus [27], non–insulin-dependent diabetes mellitus [28], and perhaps asthma in the first few years of life [29]. Most associations have been found in case-controlled studies, which are often fraught with long-term recall issues and other confounders [30–32]. Nevertheless, there is growing evidence to support these long-term benefits.

Infant growth and development
Breastfeeding reduces the risk for malnutrition and growth faltering in impoverished populations [33,34]. There is mounting evidence of a small protective effect against obesity [35–37] and a modest but significant increase in cognitive development [38,39] in children breastfed during infancy.

**POTENTIAL RISKS ASSOCIATED WITH BREASTFEEDING**

Because human milk is superior for the health and development of human infants, it has been recommended that no other types of feedings be given to human infants for the first 6 months of postnatal life [1] unless maternal health problems or economic circumstances dictate otherwise. Certain alterations in the environment that occurred during the agricultural and industrial revolutions, however, have undermined the initiation and continuation of lactation and negatively impacted the composition of human milk. These changes may have adverse effects on the health of infants [40]. With some exceptions, risks associated with breastfeeding are caused by external influences that can be avoided or minimized. Although the benefits greatly exceed the risks for breastfeeding, it is important to identify those risks that can be avoided or minimized.

There are several types of potential risks (Table 2). They are (1) insufficient milk transfer caused by primary or secondary lactation failure or poor oral/pharyngeal motor function in the infant; (2) insufficiency of certain micronutrients in human milk, often caused by inadequacies in the maternal diet; (3) foreign food antigens, proinflammatory fatty acids, autoantibodies, infectious
agents, toxic drugs, pesticides, or industrial pollutants in human milk; and (4) T-cells that may colonize immune-deficient infants and thus lead to graft versus host disease. In addition, concentrations of certain agents in human milk in some women may be inadequate for protection and rare genetic diseases manifest in infancy may alter the digestion, assimilation, or metabolism of certain nutrients in human milk and substitute feedings.

**Insufficient milk transfer**

*Pathogenesis*

Normal lactation depends on the anatomy of the mammary gland, a host of growth factors, the production of prolactin and oxytocin in response to the neural stimuli provided by the infant sucking at the breast, and prevention of milk stasis through regular and efficient milk removal [41]. Any disturbance in those requirements may result in an insufficient milk transfer during feedings. Maternal causes include primary lactation failure associated with mammary hypoplasia or hormonal irregularities; breast and nipple abnormalities that impede effective latch-on, such as flat, rigid, abnormally large, multiple, or inverted nipples; inefficient breastfeeding positions; mastitis; emotional stresses that lead to excess secretion of adrenal hormones; inadequate nursing frequencies; and premature termination of nursing episodes. Infant problems that may lead to insufficient milk transfer include anatomic irregularities, such as Pierre-Robin syndrome, cleft lip, or cleft palate, and neurologic/developmental issues, such as hypertonicity, hypotonicity, or poor sucking, swallowing, or breathing coordination. Also, healthcare policies that increase the risk for insufficient milk

<table>
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<th>Potential risks</th>
<th>Clinical consequences</th>
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<td>Poor lactation performance leading to decreased milk production&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Dehydration, growth failure, severe hyperbilirubinemia</td>
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<tr>
<td>Deficiency of micronutrients such as zinc, iron, and vitamins K, D, and B12 in human milk&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Immune deficiency, bleeding, rickets, anemia, CNS damage</td>
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<td>Foreign food antigens in human milk</td>
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<td>Autoantibodies in human milk</td>
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<tr>
<td>HIV-1 in human milk</td>
<td>Acquired immunodeficiency disease&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
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<td>Depends on agent and dose</td>
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<td>Pesticides or industrial pollutants in human milk</td>
<td>Largely undetermined</td>
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<td>Concentrations of agents in human milk at less than protective levels</td>
<td>Wheezing, bacterial enteritis; necrotizing enterocolitis in premature infants</td>
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<tr>
<td>Genetic diseases that alter digestion, assimilation, or metabolism of certain nutrients</td>
<td>Diarrhea, mental retardation, growth failure if untreated</td>
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<sup>a</sup>Most cases are preventable. See text for further information.

<sup>b</sup>Seems to occur primarily in partial breastfeeding. See text for further information.
transfer impede the natural progression of lactogenesis (eg, reduce breast stimulation by separating mother and infant or reduce infant hunger or thirst by introducing unnecessary supplements) or undermine demand feeding. Policies that interfere with early, thorough, and frequent breast emptying and mother-infant contact thus place breastfed infants at risk for poor growth caused by insufficient milk transfer.

**Consequences**

If milk transfer is inadequate, hypernatremic dehydration can occur [42] unless supplemental feedings are given. When breastfeeding meets the water and mineral requirements of the infant but not the caloric and protein needs, the infant may grow poorly [43].

Insufficient ingestion of milk may also lead to hyperbilirubinemia for the following reasons. Serum concentrations of unconjugated bilirubin are usually greater in well-fed breastfed than non-breastfed infants, and the duration of this physiologic hyperbilirubinemia extends into the third or fourth week of life [44]. The increased serum levels in breastfed infants may have a positive effect, because unconjugated bilirubin is an antioxidant [45]. When the volume of ingested milk is significantly diminished, however, intestinal reabsorption of bilirubin by the infant increases and dehydration may occur. Consequently, serum bilirubin levels may become excessive [44,46,47]. High serum bilirubin concentrations associated with inadequate breastfeeding rarely lead to kernicterus [44,47]. In those rare cases, phototherapy or, much less commonly, exchange transfusion, may be warranted [44,47].

**Prevention and resolution of lactation problems**

Many problems with lactation can be anticipated and prevented by appropriate prenatal examinations and professional counseling [48]. Certain problems, such as flat nipples that are unapparent during the prenatal period, can nevertheless be discovered and lessened in the early postpartum period. Observing the feeding may uncover poor breastfeeding techniques or difficulty in nursing by the child. In fact, counseling mothers concerning appropriate breastfeeding techniques and observing a feeding can detect and prevent most cases of poor milk production. Most breastfed infants are normally at or exceeding birth weight by 2 weeks postpartum. When weight loss exceeds 7% of birth weight or continues beyond the fifth day of life, intensive counseling and consideration of supplemental formula are indicated. Monitoring body weight during the first 2 weeks thus provides valuable information regarding breastfeeding adequacy and the need for counseling. In that regard, the American Academy of Pediatrics recommends that infants discharged before 24, 24 to 47.9, and 48 to 72 hours of age should be seen by a qualified health professional by age 72, 96, and 120 hours, respectively [47].

**Deficiencies in micronutrients in human milk**

With a few exceptions, human milk from well-nourished women provides adequate amounts of macronutrients and micronutrients for the growth and
development of the infant. The nutrients that are limiting in human milk are vitamins K [49] and D [50,51], and, in later lactation, iron [52]. Moreover, the concentrations of other micronutrients in human milk, such as vitamin B12, vitamin B6, folic acid, iron, and zinc may be insufficient in women who are malnourished because of nutritionally inadequate diets or problems with intestinal malabsorption.

**Vitamin K**

Vitamin K deficiency in the newborn period leads to serious hemorrhages [53]. The deficiency is less likely to occur in artificially-fed infants, because formulae are supplemented with vitamin K [53] and possibly because of alterations in the intestinal bacterial flora that normally produce menaquinones [54]. The problem has been prevented by routinely administrating vitamin K1 intramuscularly at birth [53].

**Vitamin D**

Even in women who are supplemented with safe amounts of vitamin D, the quantity of that vitamin in human milk does not suffice to prevent rickets in breastfed infants [55]. Rickets, however, can be prevented in breastfed infants by supplementing the infant with a daily oral dose of vitamin D or by exposing the child to enough sunlight (ultraviolet-B radiation) to permit adequate synthesis of vitamin D in the skin [55]. It is difficult to judge, however, how much exposure to sunlight is required, and sunlight exposure is less reliable in the higher latitudes and in more darkly pigmented populations. Furthermore, the diasporas of our distant ancestors from Africa disrupted the match between genotype and environment such that dark-skinned individuals with little ability to absorb ultraviolet light now frequently live in areas that provide inadequate sunlight for the synthesis of vitamin D in the dermis during winter months. Although increased exposure to sunlight would seem to be a reasonable intervention, the proliferation of greenhouse gasses has decreased the ozone layer and thus precludes exposure of the skin to sunlight for long periods because of the risks for skin cancers. Sunscreens are not an answer, because their use decreases the production of vitamin D in the skin by blocking exposure to ultraviolet radiation. Oral supplementation to the infant is thus more reliable. Indeed, in 2003 the American Academy of Pediatrics recommended that all newborn infants be supplemented with 200 international units of vitamin D per day [56]. There is a question as to whether that amount suffices for all infants, not just to prevent rickets but also to provide sufficient vitamin D to stimulate the formation of the intracellular low molecular-weight peptide cathelicidin in macrophages that kills *Mycobacterium tuberculosis* [57]. Some investigators have also questioned whether higher oral vitamin D supplementation of lactating women may achieve protective levels of vitamin D in milk [58], but the present national recommendation is to directly supplement the nursing infant [56].
Vitamin B12
Adequately nourished lactating women have sufficient vitamin B12 stores and excellent levels of that vitamin in their milk, whereas in poorly nourished populations, vitamin B12 deficiency is common in lactating women and their offspring not only because of inadequate dietary intake but also because of gastrointestinal malabsorption caused by intestinal parasites [59]. Among otherwise well-nourished women, vegetarians whose diet is deficient in vitamin B12 may produce milk with insufficient quantities of vitamin B12 to meet the requirements of their infants [51]. Often a symptomatic vitamin B12 deficiency develops in the infant before it occurs in the mother [51]. The inclusion of foods or supplements that supply the recommended daily requirement of the nutrient for the mother prevents the deficiency in herself and her breastfed child [51].

Vitamin B12 deficiency in mothers and breastfed infants may also occur following gastric bypass procedures or partial gastrectomy because of the loss of production of the vitamin B12 transporter, intrinsic factor [60].

Zinc
Zinc deficiency is common in poor, undernourished human populations [61]. Although zinc in human milk has a high bioavailability [62], very low levels of zinc in milk from zinc-deficient women lead to symptomatic deficiencies, including growth stunting in the recipient infants [63]. There are also scattered reports of zinc-deficient breastfed infants whose mothers were not zinc-deficient [64].

Iron
The bioavailability of iron in human milk is much greater than iron in substitute infant feeding formulas [65]. When maternal body stores are adequate, the full-term infant is born with sufficient body iron and the amount of iron in human milk suffices for approximately 4 to 6 months [51,52]. Afterward, iron requirements are met by iron-rich foods, such as iron-fortified cereals or meat products [52]. If those foods are not tolerated, oral elemental iron (1 mg/kg/day) is required. In premature or low birth-weight infants, oral elemental iron (2 mg/kg/day) should be started at 1 month of age [66]. Moreover, because iron deficiency remains widespread in impoverished populations, iron supplementation may be required in breastfed infants from those populations during the neonatal period and afterward.

Polyunsaturated fatty acids
The n-6 and n-3 polyunsaturated fatty acids are constituents of human milk. Large amounts of arachidonic acid are deposited in many tissues, and docosahexaenoic acid (DHA) accumulates in the cerebral cortex and the retina during development [67,68]. Reduced DHA in these sites may result in decreased visual and psychomotor development. The DHA content of human milk varies more than 10-fold. It is lowest in women who have no dietary intake of DHA
and highest in women who have high intakes of DHA. The requirement for n-3 fatty acids during infancy and the balance of n-6 and n-3 fatty acids for optimal growth and development of the brain and retina remains an important question. Decreasing dietary fat in lactating women to reduce the risk for obesity and cardiovascular disease can have a marked effect on the amount and balance of n-6 and n-3 fatty acids secreted in milk.

**Other micronutrients**

Deficiency in other micronutrients, such as folic acid, ascorbic acid, iodine, or carnitine, occurs in infants who are breastfed by women on diets deficient in one or more of those nutrients [69,70]. Furthermore, multiple micronutrient deficiencies are common in impoverished populations, and the nutritional status of women during pregnancy influences the nutritional state of infants at birth [71]. Correction of nutritional deficiencies before pregnancy may thus help to prevent nutrient deficiencies in newborn and young infants. The concentrations of iron, zinc, and copper, however, in human milk collected at 9 months of lactation are independent of the maternal status of those microminerals [72]. This suggests that those microminerals are actively transported by the mammary gland into milk, but thresholds for the secretion of those microminerals into human milk have not been established.

Preterm infants fed human milk usually require a special oral fortifier, because preterm milk usually does not meet the requirements of the premature infant for sodium, calcium, magnesium, copper, zinc, protein, vitamins B6, B12, C, D, E, K, and folic acid [73].

**Human milk and allergic diseases**

*Evolution, infections, and the maternal diet*

There is no consensus regarding whether breastfeeding protects against possible atopic diseases [74], except for atopic dermatitis [14] or when direct exposure to food allergens is avoided by complete breastfeeding. Much of the controversy may be caused by confounding variables, operational definitions of diseases, or the degree of exposure to allergens or to human milk. They include genetic predisposition to atopic disorders, the definition of exposure to breastfeeding (complete, predominant, or partial), dietary exposures not appreciated by caregivers, and exposures to inhalant allergens or irritants that might lead to airway inflammation. Furthermore, there is some evidence that the decrease in infectious diseases in industrialized countries has led to an increase in common allergic diseases. This is explained by a shift in the types of T-helper cell activities. Increased exposures to infectious diseases facilitate Th1 responses that lead to the development of cellular immunity, whereas much exposures engender Th2 responses that lead to antibody formation [75] and hence to possible IgE-mediated hypersensitivity. Because breastfeeding decreases the propensity to common infectious diseases, further augmentation in Th2 responses might be expected. A recent epidemiologic investigation of atopic dermatitis and wheezing in infancy, however, failed to confirm the ‘hygiene’ hypothesis [76]. The effect of breastfeeding on the risk for atopic diseases
thus may depend on factors that are unequally represented in all investigated populations.

In addition, other changes in the maternal environment may have led to the upsurge in allergic diseases in the past several decades. Our species evolved from earlier hominids some 200,000 years ago [77,78]. Stable agricultural communities did not appear until some 10,000 years ago. Until then, nutrients were principally obtained from native plants or wild animals. Exposure to many foods found in modern diets were therefore rare in pre-agrarian societies. Consequently, some populations of our species may be poorly adapted to some foods in modern diets. The high incidence of adult-onset lactose intolerance in African, Asian, Semitic, and certain other human groups attests to that point [79].

According to the principle of natural selection, one would have anticipated that infants of our early ancestors who developed severe allergic reactions to major foods either by direct ingestion or by the transmission of foreign food allergens by way of breastfeeding would have been negatively selected. If there were no exposures to those dietary antigens, however, infants who had a genetic propensity to allergic reactions to those food antigens would not have been negatively selected. The lack of evolutionary restraints may therefore have permitted susceptible populations to persist. In that respect, it is likely that allergic reactions to major foods derived from cultivated plants or from domesticated animals first emerged when those foods became common in the diet.

_Food allergens in human milk_

Food allergy is diagnosed by clinical improvement following dietary elimination of the suspected agent and the reproduction of the symptoms after oral challenge with the same food [80]. Allergic reactions in the infant to foreign dietary allergens in human milk are more difficult to demonstrate because of the complexity of the maternal diet and the necessity of demonstrating the suspected foreign food antigens in human milk. There is some evidence, however, that allergic reactions are produced by foreign food allergens in human milk. Dietary avoidance of cow’s milk, eggs, and fish by breastfeeding mothers prevents certain allergic diseases in some of their nursing infants [81] and the prophylactic effect may last for at least 4 years [82]. Also, certain maternal dietary proteins have been detected immunologically in human milk [83,84], and the levels of one major cow’s milk allergen in human milk, β-lactoglobulin, may decline appreciably after cow’s milk is eliminated from the maternal diet [84].

Dietary antigens, however, are found not only in milk from women whose nursing infants have atopic diseases, but also in those who do not. This suggests that the concentrations or exact molecular structures of the immunoreactive material in human milk or the ability of the infant to catabolize or immunologically react to the detected antigens determine which infants develop atopic disorders. Furthermore, the presence of bovine β-lactoglobulin in human milk may at times be suspect because of antigenic cross-reactivity between that bovine protein and the C-terminal portion of human milk β-casein [85]. Unless it is demonstrated, therefore, that the amounts of such
immunoreactive materials decline when the agent is eliminated from the materna
diet, one should be circumspect concerning the interpretation of such reports.
That is important because elimination diets are frequently recommended for lac-
tating women whose infants have an atopic disorder. The elimination of major
foods such as cow’s milk from the diet is difficult to achieve and maintain and
may lead to deficiencies in essential nutrients such as calcium [51].

Fatty acids in human milk

Certain long chain unsaturated fatty acids found in human milk may have anti-
allergic effects. One of them, the essential fatty acid, α-linolenic acid, may be
much lower in milk obtained from mothers whose infants have atopic disorders
in the first year of life [86]. That is not confirmed, however [87,88], and the con-
verse was evidenced in one study [88]. Be that as it may, some breastfed infants
who have atopic dermatitis improve substantially when their diets are supple-
mented with eicosapentaenoic acid [89] or a mix of fatty acids [90].

Cytokines and chemokines in human milk

High concentrations of certain cytokines and chemokines in human milk have
been hypothesized to cause allergic disease in the infant. In one study, higher
levels of proinflammatory chemokines IL-8 and RANTES were found in milk
from atopic than from non-atopic women [91]. It is unclear, however, whether
the increased concentrations of those agents pose a risk for the infant.

Autoimmune diseases and autoantibodies in human milk

Background

The most common autoimmune diseases are type I diabetes mellitus (see ear-
er discussion), rheumatoid arthritis, and systemic lupus erythematosus. Rheu-
matoid arthritis affects approximately 1% of the population of the United States
annually. Approximately 85% of them are women [92]. Systemic lupus eryth-
ematosus is less common, but approximately 80% to 85% of patients who have
systemic lupus are women [92]. Although the incidence of rheumatoid arthritis
has decreased [92], the incidence of lupus is increasing and the disease is most
common in women during their reproductive years [92].

When those diseases strike in the childbearing years, the possible effects of
the diseases and their treatments on pregnant or lactating women and on the
fetus or the newborn infant must be considered. The problem has become
more widespread, because more women who have autoimmune diseases are
surviving and considering childbirth and breastfeeding.

Rheumatoid arthritis

There are no reports concerning the effects of rheumatoid arthritis on lactation
performance or the composition of human milk. The pathogenesis of rheuma-
toid arthritis involves autoreactive T cells [93], but it is unknown whether
women who have rheumatoid arthritis have such T cells in their milk. Also,
no reports suggest that the disease is passively transferred to breastfed infants.
Indeed, the mother and the infant may have a reduced risk for rheumatoid
arthritis if breastfeeding occurs [94].
**Systemic lupus erythematosus**

Systemic lupus erythematosus is a multisystem disease mediated principally by IgG antibodies to intracellular autoantigens, such as double-stranded DNA [95]. There are no reports that the disease affects lactation performance or the composition of human milk, but certain leukocytes in human milk [6–8] may be decreased in women who have autoimmune cytopenias, such as an autoimmune neutropenia. It is undetermined, however, whether a resultant paucity of neutrophils in human milk lessens the protection afforded by breastfeeding.

Fetal or neonatal lupus is mediated by maternal IgG autoantibodies transmitted by way of the placenta whether or not the mother’s lupus is clinically active. Fetal deaths attributable to maternal lupus are caused by maternal IgG antibodies against phospholipids [96]. Treatment with low molecular-weight heparins alone or in combination with low doses of aspirin in women in early pregnancy with IgG antibodies against phospholipids increases the live birth rate from 0%–40% to 70%–80% [96]. Congenital heart block, the most common life-threatening manifestation of neonatal lupus [97], is caused by the transplacental passage of IgG antibodies directed against the autoantigens SSA/Ro and SSB/La.

**Protection by autoantibodies in human milk**

A late-onset cardiomyopathy also occurs in infants of mothers who have lupus. A few studies have been conducted to determine whether autoantibodies are present in human milk, and if so, whether they instigate or augment autoimmune reactions in breastfed infants. In one study [98], low levels of IgA and IgM antibodies to native DNA and other autoantigens were found in normal human colostrum. Because purified colostral antibodies to DNA also bind to certain environmental antigens, however, perhaps they are formed in response to those antigens and thus may be protective rather than pathogenic.

Other studies have shown that secretory IgA antibodies to DNA are enzymes that cleave DNA and RNA [99]. The DNA is therefore simultaneously recognized as an autoantigen and a substrate by the antibody/enzyme. Because secretory IgA is resistant to enzymatic digestion in the intestinal tract [6], it is likely that secretory IgA antibodies to DNA protect by catabolizing host DNA and RNA released during apoptosis or inflammation or by cleaving nucleic acids from enteric pathogens. Furthermore, secretory IgA antibodies in human milk are not absorbed by the recipient’s intestinal tract [6]. Secretory IgA autoantibodies in human milk thus may be protective enzymes.

There is a small amount of IgG in human milk [6], but receptors for IgG may not be expressed in the intestinal mucosa during postnatal life. Some IgG antibodies in human milk from women who have lupus react with components of the SSA/Ro–SSB/La complex [100]. In contrast to ruminants and rodents [3], however, there is little evidence that IgG in human milk is absorbed into the systemic circulation of recipient infants [3,6]. The upshot is that it is improbable that autoantibodies in human milk are pathogenic.
Some secretory IgA and IgG autoantibodies in human milk are directed against the second extracellular loop of CCR5, which is not only a receptor for a particular chemokine but is also the coreceptor for R5-tropic strains of HIV-1. That permits macrophages and immature dendritic cells to become infected with that retrovirus [101]. The autoantibodies block the in vitro infection of macrophages and dendritic cells by HIV [101], but they are not associated with autoimmune disease. The implications of those findings is considered in the section concerning infectious agents in human milk.

Infectious agents in human milk

General aspects

Although the breast and the lungs share a fractal architecture, their modes of microbiologic exposures are different. The lung is exposed constantly to airborne micro-organisms, whereas the breast is not, because secretions from the mammary gland and its ducts flow principally toward the nipple of the breast. Instead, infections of the mammary gland and its ducts originate from the ectoderm of the areola and the nipples because of local infections or from hematogenous sources during systemic infections. Human milk therefore is not a vector for the transmission of most common respiratory or enteric infections [102].

Even when the pathogens are not in human milk, if the mother has a serious, readily communicable infection such as *Neisseria gonorrhoeae*, *Haemophilus influenzae*, Group B streptococcus, or *Staphylococcus aureus*, breastfeeding should be stopped temporarily. During treatment, the mother should pump her breasts to provide milk for the infant. Once the mother is no longer contagious, breastfeeding can be resumed. A longer period of therapy and abstinence from breastfeeding is required for infections such as *Borrelia burgdorferi*, *Treponema pallidum*, and *Mycobacterium tuberculosis* [102]. Furthermore, certain viruses transmitted by breastfeeding deserve further consideration because of their chronicity and pathogenicity.

Cytomegaloviruses

Cytomegaloviruses are common in human milk [103,104]. Although those viruses commonly infect breastfed infants [103,104], they rarely cause disease [103–105] because of secretory IgA antibodies to the virus and other antiviral agents in human milk [6,103]. In that respect, breastfeeding seems to be a natural immunizing mechanism against cytomegaloviruses in mature infants. Whether exceptionally small preterm infants develop disease because of cytomegalovirus infections transmitted by way of human milk remains controversial.

Hepatitis viruses

There were previous concerns that hepatitis viruses in human milk might cause infections in nursing infants. Studies have shown, however, that the risk of transmitting hepatitis viruses A, B, and C to infants by breastfeeding is negligible [102,106,107].
Rubella
Rubella virus can be transmitted by human milk, but transfer of the infection from infected women [108] or women inoculated with live attenuated rubella virus [109] rarely causes disease in the infant. Because infants are routinely immunized against rubella in the United States, rubella virus in human milk is no longer an issue in this country.

T-cell leukemia virus type I
The retrovirus human T-cell leukemia virus type I (human T-cell lymphotropic virus type-I, HTLV-I) is the main cause of adult T-cell leukemia-lymphoma in southern Japan [110]. Intensive studies in southern Japan revealed that approximately 40% of children breastfed by carrier women became asymptomatic carriers of the virus [111,112]. It is unclear whether children infected by breastfeeding later develop adult T-cell leukemia-lymphoma, but because of the possibility, investigators in southern Japan recommended that breastfeeding be avoided [111,112]. Leukemia or lymphoma, however, develops in less than 1% of adults infected with the virus [110]. The role of HTLV-1 transmitted by breastfeeding in the development of leukemia or lymphoma later in adulthood thus remains uncertain.

Human immunodeficiency virus type I
Infectious human immunodeficiency virus type I (HIV-1) was reported to be present in the acellular part of human milk from three infected women in 1985 [113] and in milk from one woman the next year [114]. Since then there have been no reports of live, infectious HIV-1 in human milk. In many reports, HIV-1 RNA has been detected mainly in cells in human milk. It has been assumed that viral RNA is an indicator of live, infectious virus. It is uncertain, however, whether the virus replicates in the mammary gland or in human milk.

The evidence that breastfeeding transmits HIV-1 infections comes from epidemiologic studies involving infants from HIV-1 infected women who did or did not breastfeed their infants [115]. Such comparative studies were necessary because of the high rates of intrauterine infections and the long latent periods before the disease could be detected. Although there may have been confounding variables, in a randomized trial, the risk for HIV-1 infections seemed to double in breastfed infants [116]. In a recent investigation in Uganda, the effects of HIV transmission in 306 infants from HIV-infected mothers who were exclusively formula fed, exclusively breastfed, or received mixed feedings were compared [117]. HIV transmission was significantly higher in the breastfed infants. In a recent study of more than 4000 infants, however, the cumulative probability of late postnatal transmission at 18 months by breast-feeding from HIV-infected women was only 9.3% [118]. There is a direct relationship between the levels of HIV-1 RNA in human milk and the risk for the recipient infant to contract the infection [119]. The risk also increases with the duration of breastfeeding [119].

In the United States, fewer HIV-1 infections have occurred in infants since the treatment of pregnant women with antiviral medications became widespread in the 1990s and HIV-infected women were advised not to breastfeed.
But should breastfeeding be permitted while the lactating mother is treated with appropriate antiviral agents? In third-world countries, the situation is more complicated in that many women are unaware of their HIV status. Although the mortality in infected, breastfed infants born to HIV-infected women is high [120], a general injunction not to breastfeed will cause more harm than good for the following reasons.

1. The mortality and morbidity of non-breastfed infants is much higher than in breastfed infants [17–20,121]. Indeed, no breastfeeding increased the risk for early mortality by approximately two- to threefold at 6 months, and by approximately 20% in the second year of life [121].

2. Breastfeeding is the principal contraceptive measure in many of those populations [122]. Increased spacing of births decreases the spread of common contagious infections and increases the opportunity for family members to receive better nutrition. Children in smaller families thus usually experience better health outcomes.

3. Human milk contributes most of the nutrient intake of young children greater than 6 months of age in those locales.

4. Only a small segment of those populations are able to afford microbiologically safe artificial infant formulas, to properly store those commercial products, or to have clean water to reconstitute formula powders.

5. Feeding unsafe human milk substitutes and contaminated water further augments the mortality and morbidity caused by a lack of breastfeeding.

6. There may be other long-term risks of not breastfeeding.

It has been suggested that much of the risk of transmission of HIV-1 is inversely related to the degree of breastfeeding. In study of 2060 infants of HIV-1 infected mothers in Zimbabwe, partial (mixed) breastfeeding and predominant breastfeeding was far more of a risk than exclusive breastfeeding [123]. All infants were HIV-1 negative at 6 weeks of age. At age 3 months, 156 were exclusively breastfed, 490 were predominantly breastfed and supplemented with some non-milk liquids, and 1411 were partially breastfed and fed other food. The total transmission rate involving all three groups was approximately 12%, most of which occurred after age 6 months. Early mixed breastfeeding compared with exclusive breastfeeding was associated with a 4.03 (95% CI 0.98–16.61), 3.79 (95% CI 1.40–10.29), and 2.60 (95% CI 1.21–5.55) greater risk for transmission at 6, 12, and 18 months, respectively. Also, predominant breastfeeding compared with exclusive breastfeeding was associated with a 2.63 (95% CI 0.59–11.67), 2.69 (95% CI 0.95–7.63), and 1.61 (95% CI 0.72–3.64) greater risk for transmission at 6, 12, and 18 months. A lower mortality was also found in the exclusively breastfed infants at age 18 months. Whether the increased risk in partial breastfeeding was because of decreased lactation secondary to nipple or mammary gland inflammation or to a shortage in natural antiviral agents in human milk is unclear.

Does the susceptibility of infants to HIV infections transmitted by human milk depend on the precise types and concentrations of naturally produced antiviral agents that are transferred along with the virus in human milk?
Candidate defense agents in human milk include antiviral proteins, sulfated glycolipids and glycosaminoglycans, the polymeric form of Lewis X, antibodies to CCR5, and activated cytotoxic T cells [124–127]. Also, if exclusive breastfeeding is protective, the protection may also include an augmentation of the defense system of the infant’s intestinal tract.

Until these many questions are sorted out, the recommendation not to breastfeed in the face of a proven HIV-1 infection in the mother holds for those regions in which clean water and infant formulae are available. Current UNAIDS guidelines state when replacement feeding is acceptable, feasible, affordable, sustainable, and safe, avoidance of all breastfeeding by HIV-1–infected mothers is recommended. Otherwise, exclusive breastfeeding is recommended during the first 6 months of life [128].

Effects of drugs on lactation and drugs in human milk on infants
Mothers may be exposed to a spectrum of pharmacologic agents. Some are well characterized and others are not in respect to their effects on lactation, their ability to be transferred by the mammary gland into human milk, and their potential effect on the recipient infant [129,130].

Most drugs are safe to use during breastfeeding, but some are not because of their negative effects on lactation or toxicity to the infant. Agents such as ergot alkaloids, estrogens, progestogens, and perhaps pseudoephedrine inhibit lactation. Others such as domperidone stimulate milk production, but their effects on milk composition are unknown. Herbal compounds are commonly used to promote lactation, but such effects are unproven.

Despite the assumption that alcohol is a galactogogue, acute alcohol consumption lowers the plasma levels of oxytocin and consequently decreases milk secretion [131]. The negative effect of tobacco during lactation is also striking [132]. Although children of mothers who smoked and breastfed did not experience the expected cognitive deficits seen in children of mothers who did not breastfeed but smoked, passive exposure to cigarette smoke should be avoided because it increases the risk for respiratory illness in infants and children [133], passive exposure to cigarette smoke increases the risk for respiratory illness in infants and children [134]. This risk is reduced if the child is breastfed [135]. Mothers who cannot stop smoking should be advised to breastfeed and to exercise extreme caution to avoid passive smoke exposure to their offspring.

When breastfeeding women require medications, the potential risk to the infant must be evaluated. The likelihood of untoward side effects in the infant depends on (1) the degree of absorption of the agents from the gastrointestinal tract or other sites, (2) their toxicity, (3) molecular size, (4) acidity, (5) solubility in water or lipids, (6) concentrations in human milk, (7) duration of exposure, (8) developmental status of the catabolic and elimination pathways in the infant, and (9) genetic variations in those pathways [129,130,136,137]. The decision to use a potentially toxic agent during lactation also depends on clinical factors, such as whether a safe, effective substitute is available or if the medication can be given at a time to avoid peak levels in the milk. Some anti-seizure and anti-psychotic
medications may be problematic if used during lactation. Blood levels of such drugs may have to be monitored in the mother and child.

It should be re-emphasized that most pharmaceutical agents are safe to use during breastfeeding. For further information about the safety and risks of specific drugs, two sources can be consulted: a publication by the American Academy of Pediatrics [136] and a peer-reviewed, referenced database from the National Institute of Health on the website of the US National Library of Medicine [138].

Pesticides and industrial pollutants in human milk

During the second half of the twentieth century, new chemical agents were produced in large quantities for commercial purposes. Many were toxic and therefore banned in many industrialized countries, but some continue to be used in less developed countries. Furthermore, throughout the world these compounds are detectable in human tissues and in human milk.

Xenobiotics are often lipophilic and therefore are often easily secreted by the mammary gland into human milk [139–142]. The presence of toxins in human milk raises concerns about potential detrimental effects on the breastfed infant, particularly with respect to mental and psychomotor development. The problem is compounded by the difficulty in separating the effects of exposure by way of breastfeeding from exposure during fetal life [142].

Many harmful effects to the infants have been attributed to these compounds in human milk, but a precise correlation between those effects and the degree of exposure to the infant to those compounds in human milk has not been made [143]. Furthermore, one investigation suggests that breastfeeding prevents the neurodevelopmental toxicity caused by polychlorobiphenyls [144].

Although there is no compelling evidence that halogenated organic compounds in human milk are injurious [139,143,144] or that they interfere with lactation, given the uncertainties of long-term exposures by prolonged breastfeeding, a more intensive prospective monitoring of xenobiotic agents in human milk, body burdens in infants and children, and neurodevelopment of those infants and children has been recommended [145].

Variations in quantities of defense agents in human milk

The concentrations of the defense agents in human milk produced by most lactating women protect the recipient infant against many infectious and inflammatory diseases. When the levels of these agents are low, however, the breastfed infant may be as susceptible to certain diseases as the non-breastfed infant. In addition to questions that have been raised about the effects of variations in the quantities of certain fatty acids in human milk [86,89,90], some studies have suggested that variations that result in marked quantitative decreases in three other agents in human milk are associated with an increased risk for certain diseases in human infants.

\[\text{TGF-\(\beta\)}\]

A negative relationship between the risk for wheezing at age 1 year and the concentration of TGF-\(\beta\)1 in human milk collected at approximately 11 days
postpartum (risk odds ratio, 0.22; 95% confidence interval 0.05–0.89) has been reported [146]. In that respect, the findings recall the inflammatory reactions in the lungs of TGF-β1-null gene infant mice that are prevented by administration of TGF-β1 [147]. The effects of low exposures to TGF-β1 during breastfeeding on other respiratory problems in childhood are undetermined.

**Fucosyloligosaccharides**

In one investigation it was found that the severity of Campylobacter or calicivirus enteritis in breastfed infants was inversely proportional to the concentrations of certain 2-linked fucosyloligosaccharides in the maternal milk [148]. It is unclear whether quantitative variations in other oligosaccharides in human milk are associated with an increased risk for other enteropathogens.

**IL-10**

Recently two distinct populations of women were found with respect to the concentrations of IL-10 in their milk, high producers in approximately 72% and very low producers in approximately 28% [149]. In women whose infants developed necrotizing enterocolitis while receiving their own mother’s milk, IL-10 was barely detected or undetected in milk from more than 90% of them. These clinical findings mimic those in IL-10 null-gene mice [150], in which null-gene infant mice develop a serious enterocolitis after weaning unless they are promptly given IL-10.

**Genetic diseases in infancy**

The feeding of human milk is precluded in four rare genetic diseases involving the digestion, assimilation, and metabolism of certain nutrients.

**Lactose digestion and glucose and galactose absorption**

Genetic defects in intestinal lactase that are manifest at birth [151] do not permit the hydrolysis of dietary lactose. Because lactose is not digested, glucose and galactose from that disaccharide are not available for absorption. Consequently, a profuse watery acidic diarrhea develops when lactose is ingested. Similar clinical problems occur in infants who are unable to absorb glucose or galactose because of genetic defects in the intestinal Na⁺-glucose co-transporter [152].

**Galactose metabolism (galactosemia)**

Galactosemia is caused by genetic defects in galactose-1-phosphate uridylyltransferase [153], uridine diphosphate galactose 4′-epimerase [154], or galactokinase [155]. As a result, galactose is not metabolized. In untreated classic galactosemia, liver damage, developmental abnormalities, including speech abnormalities, ataxia, cognitive impairment, cataracts, septicemias, growth delay, bone alterations, and ovarian failure are frequent [156]. A complete molecular evaluation of the enzymes in that metabolic pathway is required to determine the exact type of the disease and the appropriate treatment. The clinical consequences of the disease can be prevented in part by avoiding foods containing galactose for the first few years of life [156,157]. Human milk contains large
amounts of lactose and is therefore contraindicated in infants who have classic galactosemia.

**Phenylalanine metabolism (phenylketonuria)**

Phenylketonuria is caused by a genetic deficiency in the enzyme phenylalanine hydroxylase [158]. Chronic dietary exposure to phenylalanine leads to a cerebral injury and consequently to mental retardation. Because human milk contains a significant amount of phenylalanine, human milk should be restricted in those cases to the amount required to provide sufficient phenylalanine for protein synthesis and growth [159].

**Graft versus host disease**

Do T cells in human milk transferred to the recipient sometimes cause graft versus host disease (GVH)? This question arose from observations that certain infants who have genetic T-cell deficiencies were colonized during fetal life by placentally transferred maternal T-cells [160]. In these cases, the transferred maternal T-cells react against the infant’s tissues, but the ensuing dermatitis and hepatitis are mild as compared with such reactions that follow the infusion of foreign T cells in blood transfusions. Because human milk contains activated T-cells, it was logical to ask whether GVH could be caused by breastfeeding. Furthermore, GVH caused by the transfer by way of the intestinal tract was demonstrated experimentally in highly in-bred strains of rats [161]. Nevertheless, there is no published evidence that such reactions occur in human infants because of breastfeeding.

**CLINICAL APPLICATIONS: OBSTACLES TO BE OVERCOME**

For the information regarding the benefits and risks of breastfeeding to be relevant, it must be clinically applied. Yet there are several obstacles to attaining that goal.

1. Physician education. The American Academy of Pediatrics stressed the importance of education of medical students and graduate physicians in their most recent recommendations concerning breastfeeding [1]. Information concerning human lactation, the composition and health effects of human milk, and the potential risks of breastfeeding, however, may not be presented in sufficient detail to trainees in all medical schools. Many practicing physicians therefore may not be well prepared to understand the benefits and risks of human milk or appropriate strategies for supporting successful breastfeeding.

2. Time for patient care. Because of time limitations imposed by third-party payers, comparatively few physicians devote sufficient time to these matters. The participation of other types of healthcare professionals in primary care settings may help to alleviate this problem.

3. Educational material for mothers. Little visual educational material regarding these subjects is available to women during pregnancy and immediate postpartum periods.
4. Postpartum care. Because most new mothers are discharged from the hospital within 48 hours postpartum, there is little time for postpartum education concerning breastfeeding. Yet the first few postpartum days are crucial for the establishment of lactation, and the early initiation of breastfeeding may significantly decrease morbidity caused by enteric and respiratory infections.

5. Laboratory support. Few clinical diagnostic laboratories are equipped to measure nutrients, drugs, environmental pollutants, fatty acids, or dietary food antigens that may be in human milk.

FUTURE STUDIES

The benefits of breastfeeding or of expressed human milk usually far exceed the potential risks posed by most infections, commonly used drugs, and commonly encountered levels of xenobiotics in human milk (see Tables 1 and 2). There are, however, many questions concerning potential risks associated with breastfeeding. Some are as follows.

Levels of bioactive agents in human milk

Low levels of certain key bioactive agents in human milk, such as polyunsaturated fatty acids [86], TGF-β1 [146], oligosaccharides [148], and IL-10 [149], may increase the susceptibility of the breastfed infant to certain diseases. Further investigations are required to confirm whether that is the case and whether genetic variations in other bioactive compounds in human milk confer protection or pose a risk for the recipient infant.

Foreign food antigens in human milk

The risks posed by foreign food antigens in human milk are not fully understood, although some studies suggest that they play a role in triggering certain atopic diseases in recipient infants [81–83]. Multifaceted investigations of the pro- and anti-inflammatory compounds in human milk and more precise understanding of the genetic bases of allergic diseases are probably required.

Role of enteric commensal flora

Does the commensal enteric flora that is encouraged by agents in human milk help to keep Th1 and Th2 responses in balance, as has been recently shown experimentally for a specific polysaccharide from Bacteroides fragilis [162]?

HTLV-1 in human milk

HTLV-1 in human milk leads to asymptomatic infections during infancy. It is unknown exactly how the virus is passed, however, and whether the infections acquired by breastfeeding lead to protective immune responses or set the stage for leukemic transformation of T cells in adulthood of some individuals. In southern Japan where the infection is endemic, it has been recommended that women of childbearing age not breastfeed. Further studies may shed additional light on that public health dilemma and ascertain whether that recommendation is valid.
HIV-1 and breastfeeding

The scope of HIV-1 infections is massive and the epidemic continues to increase in Africa and Asia. Because the vast majority of the infections are occurring in poorly developed countries, the problem is compounded on the one hand by evidence that the infection may be transmitted to infants by breastfeeding and on the other hand by the increased mortality and morbidity in non-breastfed infants. It is therefore important to learn why some women are more at risk than others in transmitting the virus by breastfeeding. Whether the risk factors are genetic variations in antiviral agents in human milk or preventable inflammatory processes in the breast or nipples needs to be defined. Also more studies are needed to determine whether antiretroviral agents given during lactation lessen the transmission of HIV-1 to the infant [163,164].

New drugs

As new drugs are developed, it is important to ascertain whether they may be secreted into human milk and whether their presence poses a threat to the recipient infant.

Xenobiotics

It is also important to identify and reduce the exposure of the population to existing and future xenobiotic agents that potentially pose a risk to the fetus and the breastfed infant. A recent study from the north of France is a case in point. In that investigation, breastfeeding was found to be associated with an increased risk for Crohn disease [165], although a recent meta-analysis showed a protective effect from breastfeeding [166]. One possible explanation that was offered by the investigators was the inordinately high level of airborne industrial pollutants in the region in which the study was conducted and the possibility that pollutants in human milk may have played a role in the negative outcome. Because the study was retrospective, it was impossible to be sure. A monitoring system might help determine what role that xenobiotics in human milk play in the production of disease in later childhood and beyond. Also because comparatively few xenobiotics in the environment are being measured in the United States, more of these agents should be monitored by state and national agencies, including the Environmental Protection Agency and the Food and Drug Administration.

Genetic risks from toxic drugs and xenobiotics

It is important to identify those infants who are genetically more at risk from potentially toxic drugs or xenobiotics in human milk.

Positive effects of human milk

There is also a need to examine the extent and mechanisms of the positive effects of breastfeeding. These include (1) modifications of the structure and function of defense agents by partial digestion in the alimentary tract as occurs with lactoferrin [167], (2) molecular interactions of bioactive agents in human milk with each other and with their counter-structures in the recipient infant, (3) absorption of
certain bioactive agents in human milk, (4) prospective epidemiologic studies of the long-term effects of breastfeeding, (5) better definitions at the molecular genetic level of certain chronic diseases that may be prevented or lessened by breastfeeding, and (6) further exploration of what components of human milk are responsible for those effects. Such research may also benefit non-breastfed infants, because some salutary bioactive agents in human milk may be tested for their effects in non-breastfed infants.

Moreover, epidemiologic investigations that compensate for inherent bias because of maternal characteristics in different socioeconomic groups or the problem in randomizing subjects will be valuable. For example, in a recent study the relationship between breastfeeding and cognitive development was examined in a population in which breastfeeding was inversely correlated with socioeconomic advantages and other healthy maternal behaviors [168]. Yet the duration of breastfeeding seemed to have a positive effect on cognition during the early school-age period. In a second study, the problem of individual subject randomization was partially overcome by randomizing breastfeeding educational programs in different hospitals in a single region [14].

**CODA**

**Evolution: benefits and risks**

An important evolutionary event that distinguished early mammals from their reptilian ancestors was the development of the mammary gland [2,3]. Milk from each mammalian species became most suited to infants of that same species [3]. Through natural selection, nutritional, immunologic, and other bioactive compounds in human milk arose to optimally meet the needs of the developing human infant.

Our species has, however, altered the environment in many ways, and those changes influence the initiation and continuance of lactation, the composition of human milk, and risks for adverse outcomes among non-breastfed infants. Women are commonly employed in occupations and professions that separate them from their infants. The replacement of extended families with nuclear families limits the counseling that new mothers receive from family members concerning breastfeeding. Foods that were not in our diet during Paleolithic times are now staples for many populations. Paradoxically, although our species is omnivorous, some choose to be vegetarian and thus may inadvertently become deficient in certain essential micronutrients, such as vitamin B12. The recently emerged HIV-1 would have been confined to a small part of west central Africa, where it originated. Because of rapid movements of populations over great distances, however, it became pandemic. Many potentially toxic drugs and pesticides in our current environment were unknown less than a century ago, and some are secreted into human milk. Many potential risks associated with breastfeeding thus are new.

Simultaneously in well-developed countries, housing, hygiene, good nutrition, and access to quality healthcare has improved for much of the population. Those beneficial changes have reduced the morbidity and mortality of...
non-breastfed infants who receive infant formulas. The reductions, however, do not compensate for the health benefits of breastfeeding.

Decision-making by mothers
Weighing the benefits and risks of breastfeeding is not difficult for women who understand breastfeeding techniques, are adequately nourished, do not have the previously discussed risk factors, are reasonably informed about the benefits of breastfeeding, including the long-term advantages to her child and herself, and are able to take the time required to maintain lactation. Most of those women choose breastfeeding.

Women who might otherwise breastfeed, however, may not, because they have no paid maternity leave or because they are unsure whether they will be able to readapt to the workplace after an absence of several months. This leads to a two-tiered system in which wealthy professional women are usually able to breastfeed, whereas low-income women in entry-level positions are not. Clearly further reforms in the workplace will help to insure that all infants have equal access to their mother’s milk. Also counseling services, such as those offered by lactation consultants or other trained personnel, need to be more available to underserved populations. In addition, the development and implementation of clinical practice guidelines, including laboratory evaluations of the nutritional and immunologic qualities of human milk to support successful lactation, would further extend the benefits of breastfeeding.

Human milk for premature infants
Expressed preterm milk from the mother may supply greater benefits than pasteurized donor human milk [16]. There are, however, problems for women who wish to provide their own milk for their hospitalized premature infants. Such mothers require considerable support to initiate and maintain lactation.

Laboratory support
Many women are unaware of potential dangers associated with breastfeeding, or if they are, they are often unable to find out whether their apprehensions are realistic because of a lack of counseling or diagnostic analytic methods. Also possible genetic variants may change the production of defense agents in milk. Laboratories thus should be established that specialize in identification and quantitation of risk factors.

National and international support
A continued commitment by international and national public health leaders is needed to support and further develop health services for women and children that encourage and ensure the safety of breastfeeding. The best nutrition and health care should be provided for infants who cannot be breastfeed, while realizing that artificial feedings have potential dangers, including their allergenicity, certain proteins that are not readily digested, high solute loads, and lipids not well adapted to the human infant. Although the risks are highest in infants fed unprocessed cow’s milk or other unprocessed animal milks, current infant formulas that are adjusted to be more similar to human milk do not support the
optimal developmental outcomes of human infants. Risks associated with breastfeeding thus must be weighed against risks of formula feeding.

Economics
Throughout this overview, biologic advantages of breastfeeding have been stressed. Economic advantages are also important. Breastfeeding is less expensive than artificial infant formulas and costs for medical care of breastfed infants are significantly lower than for non-breastfed infants [169].

SUMMARY
In the absence of significant, unpreventable risks, breastfeeding should be the norm for the nourishment of human infants and should, therefore, be encouraged for populations in all countries. Continued efforts of international and national agencies and healthcare professionals to aid and abet breastfeeding, reduce the risks that occur in some women during breastfeeding, provide the safest substitutes for human milk when that is necessary, and encourage further research into the posed questions should considerably improve the health of many children.

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