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Acute lymphoblastic leukemia (ALL), the most common type of cancer in children, is a heterogeneous disease in which many genetic lesions result in the development of multiple biologic subtypes. Today, with intensive multiagent chemotherapy, most children who have ALL are cured. The many national or institutional ALL therapy protocols in use tend to stratify patients in a multitude of different ways to tailor treatment to the rate of relapse. This article discusses the factors used in risk stratification and the treatment of pediatric ALL.	
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Children with Down syndrome have an increased risk for developing both acute myeloid as well as lymphoblastic leukemia. These leukemias differ in presenting characteristics and underlying biology when compared with leukemias occurring in non-Down syndrome children. Myeloid leukemia in children with Down syndrome is preceded by a preleukemic clone (transient leukemia or transient myeloproliferative disorder), which may disappear spontaneously, but may also need treatment in case of severe symptoms. Twenty percent of children with transient leukemia subsequently develop myeloid leukemia. This transition offers a unique model to study the stepwise development of leukemia and of gene dosage effects mediated by aneuploidy.	
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Acute myeloid leukemia (AML) is a heterogeneous group of leukemias that result from clonal transformation of hematopoietic precursors through the acquisition of chromosomal rearrangements and multiple gene mutations. As a result of highly collaborative clinical research by pediatric cooperative cancer groups worldwide, disease-free survival has improved significantly during the past 3 decades. Further improvements in outcomes of children who have AML probably will reflect continued progress in understanding the biology of AML and the concomitant development of new molecularly targeted agents for use in combination with conventional chemotherapy drugs.	

Neuroblastoma: Biology, Prognosis, and Treatment

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Julie R. Park, Angelika Eggert, and Huib Caron

Neuroblastoma, a neoplasm of the sympathetic nervous system, is the second most common extracranial malignant tumor of childhood and the most common solid tumor of infancy. Neuroblastoma is a heterogeneous malignancy with prognosis ranging from near uniform survival to high risk for fatal demise. Neuroblastoma serves as a paradigm for the prognostic utility of biologic and clinical data and the potential to tailor therapy for patient cohorts at low, intermediate, and high risk for recurrence. This article summarizes our understanding of neuroblastoma biology and prognostic features and discusses their impact on current and proposed risk stratification schemas, risk-based therapeutic approaches, and the development of novel therapies for patients at high risk for failure.

Central Nervous System Tumors

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Roger J. Packer, Tobey MacDonald, and Gilbert Vezina

Central nervous system (CNS) tumors comprise 15% to 20% of all malignancies occurring in childhood and adolescence. They may present in a myriad of ways, often delaying diagnosis. Symptoms and signs depend on the growth rate of the tumor, its location in the central nervous system (CNS), and the age of the child. This article describes the presentation, diagnosis, and management of these tumors.

Cancer Immunotherapy: Will Expanding Knowledge Lead to Success in Pediatric Oncology?

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Terry J. Fry and Arjan C. Lankester

The past 25 years have seen an increase in our understanding of immunology and further expansion in the clinical use of immunotherapeutic modalities. How immunotherapy will be integrated with chemotherapy, radiation, and surgery remains to be established. Although there have been successes in the field of immunotherapy, they have been inconsistent, and it is hoped that increased understanding of the basic principles of immunology will improve the consistency of beneficial effects. In this article, we briefly provide a general overview of our current understanding of the immune system, with a focus on concepts in tumor immunology, followed by a discussion of how these concepts are being used in the clinic.

Challenges After Curative Treatment for Childhood Cancer and Long-Term Follow up of Survivors

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Kevin C. Oeffinger, Paul C. Nathan, and Leontien C.M. Kremer

Childhood cancer survivors are at increased risk of serious morbidity, premature mortality, and diminished health status. Proactive and anticipatory risk-based health care of survivors and healthy lifestyles can reduce these risks. In this article, the authors first briefly discuss four common problems of survivors: neurocognitive dysfunction, cardiovascular disease, infertility and gonadal dysfunction, and psychosocial problems. Second, the

authors discuss the concept of risk-based care, promote the use of recently developed evidence-based guidelines, describe current care in the United States, Canada, and the Netherlands, and articulate a model for shared survivor care that aims to optimize life long health of survivors and improve two-way communication between the cancer center and the primary care physician.

Venous Thromboembolism in Children

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Neil A. Goldenberg and Timothy J. Bernard

With improved pediatric survival from serious underlying illnesses, greater use of invasive vascular procedures and devices, and a growing awareness that vascular events occur among the young, venous thromboembolism (VTE) increasingly is recognized as a critical pediatric concern. This review provides background on etiology and epidemiology in this disorder, followed by an in-depth discussion of approaches to the clinical characterization, diagnostic evaluation, and management of pediatric VTE. Prognostic indicators and long-term outcomes are considered, with emphasis on available evidence underlying current knowledge and key questions for further investigation.

Pediatric Arterial Ischemic Stroke

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Timothy J. Bernard and Neil A. Goldenberg

Arterial ischemic stroke (AIS) is a rare disorder in children. Research suggests that risk factors, outcomes, and presentation are different from those of adult stroke. In particular, prothrombotic abnormalities and large vessel arteriopathies that are nonatherosclerotic seem to play a large role in the pathogenesis of childhood AIS. This review examines the epidemiology and etiologies of neonatal and childhood AIS and provides a detailed discussion of approaches to the clinical characterization, diagnostic evaluation, and management. Long-term outcomes of recurrent AIS and neuromotor, speech, cognitive, and behavioral deficits are considered. Emphasis is on evidence underlying current knowledge and key questions for further investigation.

Advances in Hemophilia: Experimental Aspects and Therapy

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Nidra I. Rodriguez and W. Keith Hoots

This article describes recent clinical and research advances in hemophilia therapy. Different prophylactic regimens for the management of severe hemophilia are described along with the use of adjuvant treatment options to achieve hemostasis. The safety and efficacy of radionuclide synovectomy with phosphorus 32-sulfur colloid to treat existing joint arthropathy also are described. The development of inhibitors to factor VIII or IX remains a challenge for hemophilia care and recent approaches to achieve immune tolerance induction are discussed. Finally, recent advances in hemophilia are mentioned, including the role of iron, inflammation, and angiogenesis in the pathogenesis of hemophilic arthropathy.

- Hydroxyurea for Children with Sickle Cell Disease** 199
Matthew M. Heeney and Russell E. Ware
- Hydroxyurea therapy offers promise for ameliorating the clinical course of children with sickle cell disease (SCD). Hydroxyurea is a prototypic therapeutic option; it can be administered with minimal side effects, has a relatively wide therapeutic window, and has mechanisms of action that address pathophysiologic pathways of sickling, vaso-occlusion, hemolysis, and organ damage. There are limited data regarding hydroxyurea's ability to prevent or diminish organ dysfunction, and the long-term risks of hydroxyurea therapy remain incompletely defined. Although clinical trials are underway to address long-term issues, hydroxyurea remains an effective but underutilized therapy for SCD.
- Update on Thalassemia: Clinical Care and Complications** 215
Melody J. Cunningham
- β -Thalassemia, originally named Cooley anemia, is an inherited blood disease. Various types of thalassemia are inherited anemias caused by mutations at the globin gene loci on chromosomes 16 and 11, affecting the production of α - or β -globin protein, respectively. The combination of early diagnosis, improvements in monitoring for organ complications, and advances in supportive care have enabled many patients who have severe thalassemia syndromes to live productive, active lives well into adulthood.
- Oral Iron Chelators** 229
Janet L. Kwiatkowski
- Effective chelation therapy can prevent or reverse organ toxicity related to iron overload, yet cardiac complications and premature death continue to occur, largely related to difficulties with compliance in patients who receive parenteral therapy. The use of oral chelators may be able to overcome these difficulties and improve patient outcomes. A chelator's efficacy at cardiac and liver iron removal and side-effect profile should be considered when tailoring individual chelation regimens. Broader options for chelation therapy, including possible combination therapy, should improve clinical efficacy and enhance patient care.
- Childhood Immune Thrombocytopenic Purpura: Diagnosis and Management** 249
Victor Blanchette and Paula Bolton-Maggs
- Immune thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by a low circulating platelet count caused by destruction of antibody-sensitized platelets in the reticuloendothelial system. ITP can be classified as childhood versus adult, acute versus chronic, and primary versus secondary. Persistence of thrombocytopenia defines the chronic form of the disorder. Secondary causes of ITP include collagen vascular disorders, immune deficiencies, and some chronic infections. This review focuses on the diagnosis and management of children who have acute and chronic ITP. Emphasis is placed on areas of controversy and new therapies.