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Nancy E. Kline
(Eds.)

Pediatric Oncology Nursing

**Advanced Clinical
Handbook**

With 43 Figures and 203 Tables

 Springer

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Dedication

To the nurses, and others,
who use the information in this book,
and to the children they serve,
we dedicate this work.

To my husband Chris and our children,
Vivian, Sam and Suzanne –
to the moon and back.
Deborah Tomlinson

To my parents, and Michael.
I am forever grateful for your love and support.
Nancy E. Kline

Preface

“Pediatric Oncology Nursing: Advanced Clinical Handbook” is a joint effort between nurses in Canada, the UK, and the USA. This is a first-time collaboration between pediatric hematology and oncology nurses from two continents and represents a blending of knowledge from these experts. The book is designed to be a comprehensive clinical handbook for nurses in advanced practice working with pediatric hematology / oncology patients. Specific issues related to young children and adolescents with cancer and hematologic disorders are discussed.

Twenty-two contributors and two editors participated in the writing of this text. Nurses in advanced practice and academic roles – nurse practitioners, clinical nurse specialists, clinical instructors, lecturers, and educators – were involved. One of the most appealing features of this text is the varied experience represented by nurses from different countries and different educational backgrounds.

The book is divided into five sections: pediatric cancers, hematologic disorders, treatment of childhood cancer, side effects of treatment and disease, and supportive and palliative care. Many tables and illustrations are included for quick reference in the clinical setting. Future perspectives and opportunities for new treatment options and research are discussed.

Part One focuses on pediatric cancers: the leukemias and solid tumors. The most common pediatric tumors, as well as some rare tumors, are discussed with regard to epidemiology, etiology, molecular genetics, symptoms and clinical signs, diagnostic and laboratory testing, staging and classification, treatment, prognosis, and follow-up care.

Part Two focuses on pediatric hematology. The anemias, bleeding disorders, neutropenia, and thrombocytopenia are discussed in detail. Epidemiology,

etiology, symptoms and clinical signs, diagnostic and laboratory procedures, treatment, prognosis, and follow up care are included for each of the disorders.

Part Three covers cancer treatment, including chemotherapy, radiation therapy, peripheral stem cell transplantation, surgery, gene therapy, and complementary and alternative medicine. The principles and description of treatment, method of treatment delivery, potential side effects, and special considerations for each type of treatment are discussed.

Part Four focuses on the side effects of cancer treatment in relation to metabolic processes and the gastrointestinal, hematologic, respiratory, urinary, cardiovascular, neurologic, musculoskeletal, integumentary, and endocrine systems. The incidence, etiology, treatment, prevention, and prognosis are included for each side effect reviewed.

Part Five includes essential information regarding supportive and palliative care of pediatric cancer patients. Nutrition, hydration, pain, transfusion therapy, growth factors, and care of the dying child are covered. The principles of treatment for these conditions, method of delivery, and special considerations for certain conditions are included.

As the editors of “Pediatric Oncology Nursing: Advanced Clinical Handbook” we want to recognize and thank everyone who participated in the development of this text. We are profoundly aware of the personal time and commitment that was devoted to make this an outstanding resource, and we are grateful. It is our hope that nurses in advanced clinical practice will find this publication useful and that it will enrich knowledge and improve care for young people with cancer and hematologic disorders.

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Contents

PART I

1 Leukemia

Deborah Tomlinson

1.1 Acute Lymphoblastic Leukemia	2
1.1.1 Epidemiology	2
1.1.2 Etiology	4
1.1.2.1 Genetic Factors	4
1.1.2.2 Environmental Factors	4
1.1.3 Molecular Genetics	6
1.1.4 Symptoms and Clinical Signs	7
1.1.5 Diagnostics	8
1.1.6 Staging and Classification	8
1.1.6.1 Risk Classification	8
1.1.6.2 Cell Morphology	10
1.1.6.3 Cytochemistry	10
1.1.6.4 Immunophenotyping	10
1.1.6.5 Cytogenetics	11
1.1.7 Treatment	12
1.1.7.1 Induction	12
1.1.7.2 Intensification/Consolidation	13
1.1.7.3 CNS-directed Therapy	13
1.1.7.4 Maintenance/Continuing Treatment	14
1.1.7.5 Allogeneic Stem Cell Transplant	14
1.1.8 Prognosis	15
1.1.9 Follow-up	15
1.1.10 Future Perspectives	15
1.2 Acute Myeloid Leukemia	16
1.2.1 Epidemiology	16
1.2.2 Etiology	16
1.2.2.1 Genetic Factors	16
1.2.2.2 Environmental Factors	16
1.2.3 Molecular Genetics	16
1.2.4 Symptoms and Clinical Signs	17
1.2.5 Diagnostics	17
1.2.6 Staging and Classification	17
1.2.7 Treatment	19
1.2.8 Prognosis	19
1.2.9 Follow-up	19
1.2.10 Future Perspectives	20

1.3 Chronic Myeloid Leukemia	20
1.3.1 Epidemiology and Etiology	20
1.3.2 Molecular Genetics	20
1.3.3 Symptoms and Clinical Signs	20
1.3.4 Diagnostics	21
1.3.5 Treatment	21
1.3.6 Prognosis	21
1.3.7 Future Perspectives	21
1.4 Juvenile Myelomonocytic Leukemia	21
1.5 Langerhans Cell Histiocytosis	22
References	23

2 Solid Tumors

Eleanor Hendershot

2.1 Hodgkin's Disease	26
2.1.1 Epidemiology	26
2.1.2 Etiology	27
2.1.3 Molecular Genetics	27
2.1.4 Symptoms and Clinical Signs	27
2.1.5 Diagnostics	27
2.1.6 Staging and Classification	28
2.1.7 Treatment	28
2.1.8 Prognosis	29
2.1.9 Follow-up	30
2.1.10 Future Perspectives	30
2.2 Non-Hodgkin's Lymphoma	30
2.2.1 Epidemiology	30
2.2.2 Etiology	30
2.2.3 Molecular Genetics	31
2.2.4 Symptoms and Clinical Signs	31
2.2.5 Diagnostics	31
2.2.6 Staging and Classification	34
2.2.7 Treatment	35
2.2.8 Prognosis	36
2.2.9 Follow-up	36
2.2.10 Future Perspectives	37

2.3 Ewing's Sarcoma Family of Tumors	37	2.8 Retinoblastoma	62
2.3.1 Epidemiology	37	2.8.1 Epidemiology	62
2.3.2 Etiology	37	2.8.2 Etiology	62
2.3.3 Molecular Genetics	37	2.8.3 Molecular Genetics	62
2.3.4 Symptoms and Clinical Signs	38	2.8.4 Signs and Symptoms	62
2.3.5 Diagnostics	38	2.8.5 Diagnostics	63
2.3.6 Staging and Classification	38	2.8.6 Staging and Classification	63
2.3.7 Treatment	39	2.8.7 Treatment	65
2.3.8 Prognosis	40	2.8.8 Prognosis	66
2.3.9 Follow-up	40	2.8.9 Follow-up	66
2.3.10 Future Perspectives	41	2.8.10 Future Directions	66
2.4 Osteosarcoma	41	2.9 Rhabdomyosarcoma	66
2.4.1 Epidemiology	41	2.9.1 Epidemiology	66
2.4.2 Etiology	41	2.9.2 Etiology	66
2.4.3 Molecular Genetics	41	2.9.3 Molecular Genetics	67
2.4.4 Signs and Symptoms	42	2.9.4 Symptoms and Clinical Signs	67
2.4.5 Diagnostics	42	2.9.5 Diagnostics	68
2.4.6 Staging and Classification	43	2.9.6 Staging and Classification	68
2.4.7 Treatment	43	2.9.7 Treatment	69
2.4.8 Prognosis	44	2.9.8 Prognosis	70
2.4.9 Follow-up	44	2.9.9 Follow-up	70
2.4.10 Future Perspectives	44	2.9.10 Future Perspectives	70
2.5 Liver Tumors	45	2.10 Non-rhabdomyosarcomatous Soft Tissue Sarcomas	71
2.5.1 Epidemiology	45	2.11 Germ Cell Tumors	73
2.5.2 Etiology	45	2.11.1 Epidemiology	73
2.5.3 Molecular Genetics	45	2.11.2 Etiology	73
2.5.4 Symptoms and Clinical Signs	45	2.11.3 Molecular Genetics	73
2.5.5 Diagnostics	46	2.11.4 Symptoms and Clinical Signs	73
2.5.6 Staging and Classification	47	2.11.5 Diagnostics	74
2.5.7 Treatment	48	2.11.6 Staging and Classification	75
2.5.8 Prognosis	49	2.11.7 Treatment	75
2.5.9 Follow-up	49	2.11.8 Prognosis	76
2.5.10 Future Perspectives	49	2.11.9 Follow-up	76
2.6 Neuroblastoma	50	2.11.10 Future Perspectives	77
2.6.1 Epidemiology	50	2.12 Rare Tumors	77
2.6.2 Etiology	50	2.12.1 Adrenocortical Carcinoma (ACC)	77
2.6.3 Molecular Genetics	50	2.12.2 Melanoma	77
2.6.4 Symptoms and Clinical Signs	51	2.12.3 Nasopharyngeal Carcinoma	78
2.6.5 Diagnostics	52	2.12.4 Thyroid Carcinoma	78
2.6.6 Staging and Classification	53	References	79
2.6.7 Treatment	53	Bibliography	82
2.6.8 Prognosis	55		
2.6.9 Follow-up	55		
2.6.10 Future Perspectives	57		
2.7 Renal Tumors	57		
2.7.1 Epidemiology	57		
2.7.2 Etiology	57		
2.7.3 Molecular Genetics	58		
2.7.4 Symptoms and Clinical Signs	58		
2.7.5 Diagnostics	58		
2.7.6 Staging and Classification	60		
2.7.7 Treatment	60		
2.7.8 Prognosis	60		
2.7.9 Follow-up	61		
2.7.10 Future Perspectives	61		
		3 Common Central Nervous System Tumours	
		Nicki Fitzmaurice · Sharon Beardsmore	
		3.1 Causes/Epidemiology	86
		3.2 Distribution/Classification	86
		3.3 Staging	87
		3.4 Molecular Genetics of Brain Tumours	87
		3.5 Diagnosis	87
		3.6 Specialist Referral	89
		3.7 Hydrocephalus	89

3.8 Treatment	89
3.8.1 Surgery	90
3.8.2 Radiotherapy	90
3.8.3 Chemotherapy	91
3.9 Prognosis	91
3.10 Specific Tumours	92
3.10.1 PNETs/Medulloblastomas	92
3.10.2 Astrocytomas/Glial Tumours	93
3.10.3 Malignant Gliomas	94
3.10.4 Other High-grade Gliomas	95
3.11 Follow-up	100
3.12 The Late Effects and Rehabilitation of Survivors	100
3.13 Palliative Care	100
3.14 Future Perspectives/New Innovations	100
References	101
Bibliography	101

PART II

4 Anemias

Rosalind Bryant

4.1 Anemia	104
4.2 Iron Deficiency Anemia	106
4.2.1 Epidemiology	106
4.2.2 Etiology	107
4.2.3 Molecular Genetics	107
4.2.4 Symptoms/Clinical Signs	107
4.2.5 Diagnostic Testing	107
4.2.6 Treatment	108
4.2.7 Transfusion	109
4.2.8 Erythropoietin (Epotin Alfa, Epogen)	109
4.2.9 Prognosis	109
4.3 Sickle Cell Disease	109
4.3.1 Epidemiology	109
4.3.2 Etiology	109
4.3.3 Molecular Genetics	110
4.3.4 Symptoms/Clinical Signs	110
4.3.5 Diagnostic Testing	110
4.3.6 Complications of SCD	111
4.3.6.1 Vaso-occlusive Crisis/Episode (VOE)	112
4.3.6.1.1 <i>Diagnostic Test/Differential</i>	112
4.3.6.1.2 <i>Treatment</i>	112
4.3.6.2 Acute Sequestration Crisis	112
4.3.6.3 Aplastic Crisis	114
4.3.6.4 Infection	114
4.3.6.5 Acute Chest Syndrome	115
4.3.6.6 Acute Abdominal Pain	116
4.3.6.7 Acute Central Nervous System Event	117
4.3.7 Preparation for Surgery	117
4.3.7.1 Hydroxyurea Therapy	118
4.3.8 Prognosis	118
4.3.9 Future Perspectives	118

4.4 Thalassemia	118
4.4.1 Alpha (α)-Thalassemia	118
4.4.1.1 Epidemiology	118
4.4.1.2 Etiology	118
4.4.1.3 Molecular Genetics	118
4.4.2 Beta (β)-Thalassemia (Cooley Anemia)	119
4.4.2.1 Epidemiology	119
4.4.2.2 Etiology	119
4.4.2.3 Molecular Genetics	119
4.4.3 Diagnostic Testing	119
4.4.4 Treatment	120
4.4.5 Treatment of Hemosiderosis (Iron Overload)	120
4.4.6 Chelation Therapy	120
4.4.6.1 Initiation of Chelation Therapy	120
4.4.6.2 Chelation Regimens	121
4.4.6.3 Complications of Desferrioxamine	121
4.4.7 Clinical Advances (Hemosiderosis)	121
4.4.8 Prognosis	121
4.4.9 Follow-up	121
4.4.10 Future Perspectives	121
4.5 Hemolytic Anemia	121
4.5.1 Hereditary Spherocytosis (HS)	122
4.5.1.1 Epidemiology	122
4.5.1.2 Etiology	122
4.5.1.3 Molecular Genetics	122
4.5.1.4 Symptoms/Clinical Signs	122
4.5.1.5 Diagnostic Testing	122
4.5.1.6 Treatment	122
4.5.1.7 Prognosis	123
4.5.1.8 Follow-up	123
4.5.1.9 Future Perspectives	123
4.5.2 Autoimmune Hemolytic Anemia (AIHA)	123
4.5.2.1 Epidemiology	123
4.5.2.2 Etiology	123
4.5.2.3 Molecular Genetics	123
4.5.2.4 Symptoms/Clinical Signs	123
4.5.2.5 Diagnostic Testing	124
4.5.2.6 Treatment	124
4.5.2.7 Prognosis	124
4.5.2.8 Future Perspectives	125
4.5.3 Glucose-6-phosphate dehydrogenase deficiency (G-6PD)	125
4.5.3.1 Epidemiology	125
4.5.3.2 Etiology	125
4.5.3.3 Molecular Genetics	125
4.5.3.4 Symptoms/Clinical Signs	126
4.5.3.5 Diagnostic Testing	126
4.5.3.6 Treatment	126
4.5.3.7 Prognosis	126

4.6 Bone Marrow Failure Syndromes	126
4.6.1 Aplastic Anemia	126
4.6.1.1 Acquired Aplastic Anemia	126
4.6.1.1.1 Epidemiology	127
4.6.1.1.2 Etiology	127
4.6.1.1.3 Molecular Genetics	127
4.6.1.1.4 Symptoms/Clinical Signs	127
4.6.1.1.5 Diagnostic Testing	127
4.6.1.1.6 Treatment	128
4.6.1.1.7 Supportive Treatment	128
4.6.1.1.8 Prognosis	129
4.6.1.2 Inherited Aplastic Anemia	129
4.6.1.2.1 Epidemiology	129
4.6.1.2.2 Etiology	129
4.6.1.2.3 Molecular Genetics	129
4.6.1.2.4 Symptoms/Clinical Signs	129
4.6.1.2.5 Diagnostic Testing	129
4.6.1.2.6 Treatment	130
4.6.1.2.7 Prognosis	130
References	130

5 Neutropenia

Cara Simon

5.1 Epidemiology	133
5.2 Etiology	134
5.3 Symptoms and Clinical Signs	135
5.4 Diagnostic Testing	135
5.5 Treatment	135
5.6 Prognosis	137
5.7 Follow-up	137
Reference	137
Bibliography	137

6 Thrombocytopenia

Cara Simon

6.1 Epidemiology	139
6.2 Etiology	140
6.3 Symptoms and Clinical Signs	140
6.4 Diagnostic Testing	142
6.5 Treatment	143
6.6 Prognosis	144
6.7 Follow-up	145
6.8 Future Perspectives	145
References	145
Bibliography	145

7 Bleeding Disorders

Nicole M. Sevier

7.1 Hemophilia	147
7.1.1 Epidemiology	147
7.1.2 Etiology	147
7.1.3 Genetics	148
7.1.4 Symptoms and Clinical Signs	148
7.1.5 Diagnostic Testing	150
7.1.6 Treatment	150
7.1.7 Prognosis	153
7.1.8 Follow-Up	153
7.1.9 Future Perspectives	154
7.2 Von Willebrand Disease	154
7.2.1 Epidemiology	154
7.2.2 Etiology	154
7.2.3 Genetics	155
7.2.4 Symptoms and Clinical Signs	155
7.2.5 Diagnostic Testing	156
7.2.6 Treatment	156
7.2.7 Prognosis	159
7.2.8 Follow-up	159
References	159

PART III

8 Chemotherapy

Christine Chordas

8.1 Introduction	162
8.2 Chemotherapy Principles	162
8.2.1 Cell Cycle Phase-Specific Agents	164
8.2.2 Cell Cycle Phase-Nonspecific Agents	164
8.3 Clinical Trials	165
8.3.1 Phase I Clinical Trials	165
8.3.2 Phase II Clinical Trials	165
8.3.3 Phase III Clinical Trials	165
8.3.4 Phase IV Clinical Trials	165
8.4 Types of Chemotherapy Agents	165
8.4.1 Antimetabolites	165
8.4.1.1 Mechanism of Action	165
8.4.1.2 Side Effects	166
8.4.2 Alkylating Agents	166
8.4.2.1 Mechanism of Action	166
8.4.2.2 Side Effects	166
8.4.2.3 Long-Term Effects	167
8.4.3 Antitumor Antibiotics	167
8.4.3.1 Mechanism of Action	167
8.4.4 Plant Derivatives	167
8.4.4.1 Mechanism of Action	167

8.4.5	Antiangiogenic Agents	168	8.9	Extravasation	184
8.4.5.1	Mechanism of Action	168	8.9.1	Pathophysiology of Extravasation	184
8.4.6	Miscellaneous Agents	168	8.9.2	Risk Factors of Peripheral Extravasation	185
8.4.7	Corticosteroids	169	8.9.3	Risk Factors of Extravasation with Central Venous Access Devices	185
8.4.7.1	Mechanism of Action	169	8.9.4	Administration Techniques That May Help Prevent Extravasation	185
8.4.7.2	Common Side Effects	169	8.9.4.1	Peripheral Administration	185
8.4.8	Asparaginase/Peg-asparaginase	169	8.9.5	Central Venous Access Device Administration	186
8.4.8.1	Mechanism of Action	169	8.9.6	Assessment and Treatment of Extravasation	186
8.4.8.2	Common Side Effects	169	8.9.6.1	Signs and Symptoms of Extravasation	186
8.4.9	Hydroxyurea	169	8.9.6.2	Treatment for Extravasation	186
8.4.9.1	Mechanism of Action	169	8.9.6.3	Peripheral Access	186
8.5	Administration of Chemotherapy Agents	169	8.9.6.4	Central Venous Access	187
8.5.1	Preparation	169	8.9.6.5	Follow-Up Guidelines	189
8.5.2	Planning	173	8.9.6.6	Patient Education	189
8.5.3	Presentation	173	8.10	Acute Hypersensitivity Reactions to Chemotherapy	189
8.5.4	Follow-up	173	8.10.1	Risk Factors for Hypersensitivity, Flare Reactions, or Anaphylaxis	189
8.5.5	Nursing Preparation	173	8.10.2	Chemotherapy Agents That Can Cause HSRs	189
8.5.6	Infusion Preparation	174	8.10.2.1	L-Asparaginase (<i>E. coli</i> , <i>Erwinia</i> , Pegaspargase)	189
8.6	Routes of Administration and Practice Considerations	174	8.10.2.2	Etoposide/Teniposide	189
8.6.1	Topical	174	8.10.2.3	Taxanes (Paclitaxel/Docetaxel)	190
8.6.2	Oral	174	8.10.2.4	Carboplatin	190
8.6.3	Intramuscular	174	8.10.3	Recommended Steps to Prevent HSRs	190
8.6.4	Subcutaneous Injection	176	8.10.4	Emergency Management of HSR/Anaphylaxis	190
8.6.5	Intravenous	177	8.10.5	Patient and Family Education	191
8.6.6	Peripheral IV Administration	177	References		191
8.6.7	Intrathecal/Intraventricular	177	Bibliography		192
8.6.8	Post-administration Guidelines	177			
8.6.9	Professional Guidelines to Minimize the Risk of Medication Errors	178			
8.6.9.1	Prescribing Errors	178			
8.6.9.2	Compounding	178			
8.6.9.3	Dispensing	178			
8.6.9.4	Administration	178			
8.7	Safe Practice Considerations	178			
8.7.1	Mixing Chemotherapeutic Agents	178			
8.7.2	Transporting Cytotoxic Agents	180			
8.7.3	Safe Handling After Chemotherapy	180			
8.7.4	Disposal of Cytotoxic Materials	180			
8.7.5	Spill Management	180			
8.7.6	Procedures Following Accidental Exposure	181			
8.7.7	Storage	181			
8.7.8	Medical Management	181			
8.8	Administration of Chemotherapy in the Home	181			
8.8.1	Eligibility Guidelines for Home Chemotherapy	182			
8.8.2	Home Care Agency Chemotherapy Safety Guidelines	182			
8.8.3	Management of Home Chemotherapy Guidelines	183			
8.8.4	Evaluation of Home Administration of Chemotherapy	184			
8.8.5	Immediate Complications of Chemotherapy Administration	184			

8.9	Extravasation	184
8.9.1	Pathophysiology of Extravasation	184
8.9.2	Risk Factors of Peripheral Extravasation	185
8.9.3	Risk Factors of Extravasation with Central Venous Access Devices	185
8.9.4	Administration Techniques That May Help Prevent Extravasation	185
8.9.4.1	Peripheral Administration	185
8.9.5	Central Venous Access Device Administration	186
8.9.6	Assessment and Treatment of Extravasation	186
8.9.6.1	Signs and Symptoms of Extravasation	186
8.9.6.2	Treatment for Extravasation	186
8.9.6.3	Peripheral Access	186
8.9.6.4	Central Venous Access	187
8.9.6.5	Follow-Up Guidelines	189
8.9.6.6	Patient Education	189
8.10	Acute Hypersensitivity Reactions to Chemotherapy	189
8.10.1	Risk Factors for Hypersensitivity, Flare Reactions, or Anaphylaxis	189
8.10.2	Chemotherapy Agents That Can Cause HSRs	189
8.10.2.1	L-Asparaginase (<i>E. coli</i> , <i>Erwinia</i> , Pegaspargase)	189
8.10.2.2	Etoposide/Teniposide	189
8.10.2.3	Taxanes (Paclitaxel/Docetaxel)	190
8.10.2.4	Carboplatin	190
8.10.3	Recommended Steps to Prevent HSRs	190
8.10.4	Emergency Management of HSR/Anaphylaxis	190
8.10.5	Patient and Family Education	191
References		191
Bibliography		192

9	Radiation Therapy Joan M. O'Brien · Deborah Tomlinson	
9.1	Principles of treatment	195
9.2	Description of treatment	196
9.2.1	Cell radiosensitivity	196
9.2.2	Units of radiation	196
9.3	Methods of delivery	196
9.3.1	External Beam/Teletherapy	196
9.3.1.1	Fractionation	197
9.3.1.2	Total Body Irradiation (TBI)	197
9.3.2	Interstitial implants/brachytherapy (Sealed source)	197
9.3.3	Unsealed source of radioisotope	198
9.3.4	Treatment planning	198
9.3.5	Simulation	198
9.3.6	Protection of health care professionals	198

9 Radiation Therapy

Joan M. O'Brien · Deborah Tomlinson

9.1	Principles of treatment	195
9.2	Description of treatment	196
9.2.1	Cell radiosensitivity	196
9.2.2	Units of radiation	196
9.3	Methods of delivery	196
9.3.1	External Beam/Teletherapy	196
9.3.1.1	Fractionation	197
9.3.1.2	Total Body Irradiation (TBI)	197
9.3.2	Interstitial implants/brachytherapy (Sealed source)	197
9.3.3	Unsealed source of radioisotope	198
9.3.4	Treatment planning	198
9.3.5	Simulation	198
9.3.6	Protection of health care professionals	198

9.4	Potential side effects	198
9.5	Special considerations	199
9.5.1	Ensuring accuracy of treatment:	
	Patient issues	199
9.5.1.1	Marking	199
9.5.1.2	Patient immobilisation	199
9.5.1.3	Sedation and general anaesthesia	199
9.5.1.4	Preparation of children and young people	200
9.5.2	Brachytherapy	200
9.5.3	Unsealed sources of radiation treatment	200
9.6	Future Perspectives	200
	References	200

10 Hematopoietic Stem Cell Transplantation

Robbie Norville

10.1	Principles of Treatment	201
10.2	Description of Treatment	204
10.2.1	Stem Cell Collection (Harvest)	205
10.3	Potential Side Effects	207
10.3.1	Early Side Effects	207
10.3.2	Intermediate Side Effects	210
10.3.3	Late Side Effects	212
10.4	Special Considerations	215
10.5	Future Perspectives	216
	References	216
	Bibliography	216

11 Surgical Approaches to Childhood Cancer

Jill Brace O'Neill

11.1	Principles of Treatment	219
11.2	Description of Treatment	219
11.3	Method of Delivery	220
11.3.1	Preoperative Evaluation	220
11.3.2	Postoperative Nursing Care	221
11.4	Potential Side Effects	222
11.4.1	Complications of Medical Therapy Requiring Surgical Evaluation	222
11.4.2	Complications Arising from Surgical Management of Solid Tumors	223
11.5	Special Considerations	223
11.5.1	Vascular Access Devices	223
11.6	Future Perspectives	224
11.6.1	New Surgical Techniques and Directions for Future Research	224
	References	225
	Bibliography	225

12 Gene Therapy

Kathleen E. Houlahan · Mark W. Kieran

12.1	Introduction	227
12.2	Principles of Treatment	228
12.3	Method of Delivery	229
12.4	Potential Side Effects	230
12.5	Special Considerations	230
12.6	Future Perspectives	231
	References	231

13 Complementary and Alternative Therapy

Nancy E. Kline

13.1	Principles of Treatment	233
13.2	Description of Treatment	234
13.3	Method of Delivery	234
13.3.1	Alternative Medical Systems	234
13.3.2	Mind–Body Interventions	234
13.3.3	Biologically Based Treatments	235
13.3.4	Body Manipulation	235
13.3.5	Energy Therapies	235
13.4	Potential Side Effects	235
13.5	Special Considerations	237
13.6	Future Perspectives	238
	References	238

PART IV

14 Metabolic System

Deborah Tomlinson

14.1	Cancer Cachexia	239
14.1.1	Incidence	239
14.1.2	Etiology	240
14.1.3	Treatment	240
14.1.4	Prognosis	240
14.2	Obesity	241
14.2.1	Incidence	241
14.2.2	Etiology	241
14.2.3	Treatment	241
14.2.4	Prognosis	241
14.3	Tumour Lysis Syndrome	242
14.3.1	Incidence	242
14.3.2	Etiology	242
14.3.3	Treatment	244
14.3.3.1	Patient Assessment	244
14.3.3.2	Preventative Measures	245
14.3.3.3	Management of Metabolic Abnormalities	246
14.3.4	Prognosis	247

14.4 Hypercalcaemia	247
14.4.1 Incidence	247
14.4.2 Etiology	247
14.4.3 Treatment	248
14.4.4 Prognosis	248
14.5 Impaired Glucose Tolerance	
Following Bone Marrow Transplant	249
14.5.1 Incidence	249
14.5.2 Etiology	249
14.5.3 Treatment	249
14.5.4 Prognosis	249
References	249

15 Gastrointestinal Tract

Anne-Marie Maloney

15.1 Mucositis	252
15.1.1 Incidence	252
15.1.2 Etiology	252
15.1.2.1 Iatrogenic	252
15.1.2.2 Bacterial	254
15.1.2.3 Viral	254
15.1.2.4 Fungal	254
15.1.3 Prevention	254
15.1.4 Treatment	254
15.1.5 Prognosis	255
15.2 Dental Caries	255
15.2.1 Incidence	255
15.2.2 Etiology	255
15.2.2.1 Iatrogenic	255
15.2.3 Prevention and Treatment	255
15.2.4 Prognosis	256
15.3 Nausea and Vomiting	256
15.3.1 Incidence	256
15.3.2 Etiology	256
15.3.3 Prevention	258
15.3.4 Treatment	258
15.3.4.1 Delayed Nausea and Vomiting	259
15.3.4.2 Anticipatory Nausea and Vomiting	260
15.3.4.3 Radiation-Induced Nausea and Vomiting	260
15.3.4.4 Other Causes of Nausea and Vomiting	260
15.3.4.5 Nonpharmacological Management	260
15.3.5 Prognosis	260
15.4 Constipation	260
15.4.1 Incidence	260
15.4.2 Etiology	261
15.4.2.1 Iatrogenic	261
15.4.2.2 Primary Constipation	261
15.4.2.3 Secondary Constipation	261
15.4.3 Prevention	261
15.4.4 Treatment	262
15.4.5 Prognosis	263
15.5 Diarrhoea	263
15.5.1 Incidence	263
15.5.2 Etiology	264
15.5.2.1 Iatrogenic	264
Chemotherapy	264
Radiation	264
Other Iatrogenic Cause of Diarrhoea	264
15.5.2.2 Fungal	264
15.5.2.3 Viral	264
15.5.2.4 Bacterial	265
15.5.2.5 Other Infectious Aetiologies of Diarrhoea	265
15.5.3 Prevention	265
15.5.4 Treatment	265
15.5.5 Prognosis	266
15.6 Typhlitis	266
15.6.1 Incidence	266
15.6.2 Etiology	266
15.6.2.1 Iatrogenic	266
15.6.2.2 Fungal	266
15.6.2.3 Viral	266
15.6.2.4 Bacterial	267
15.6.3 Prevention	267
15.6.4 Treatment	267
15.6.5 Prognosis	267
15.7 Perirectal Cellulitis	267
15.7.1 Incidence	267
15.7.2 Etiology	268
15.7.2.1 Iatrogenic	268
15.7.2.2 Bacterial	268
15.7.3 Prevention	268
15.7.4 Treatment	268
15.7.5 Prognosis	268
15.8 Acute Gastrointestinal Graft Versus Host Disease	268
15.8.1 Incidence	268
15.8.2 Prevention	269
15.8.3 Treatment	269
15.8.4 Prognosis	270
15.9 Chemical Hepatitis	270
15.9.1 Incidence	270
15.9.2 Etiology	270
15.9.3 Prevention	270
15.9.4 Treatment	270
15.9.5 Prognosis	271
References	271

16 Bone Marrow

Sandra Doyle

16.1 Anemia	274
16.1.1 Incidence and Etiology	274
16.1.2 Treatment	274
16.1.2.1 Transfusion	274
16.1.2.2 Use of Recombinant Human Erythropoietin	275
16.2 Neutropenia	275
16.2.1 Incidence and Etiology	275
16.2.1.1 Fever (Pyrexia) and Neutropenia	275
16.2.2 Treatment	276
16.2.2.1 Antibiotic Management	277
16.2.2.2 Special Consideration for the Management of Indwelling Intravenous Catheters	278
16.2.2.3 Management of Candidiasis (Oropharyngeal Candidiasis and <i>Candida</i> Esophagitis)	278
16.2.2.4 Infections Due to <i>Aspergillus</i> Species	278
16.2.2.5 Management of Viral Infections	278
16.2.2.6 Infections Due to <i>Pneumocystis jiroveci</i> (Formerly <i>Pneumocystis carinii</i>)	280
16.2.2.7 Use of Colony Stimulating Factors (CSF) in Children with Neutropenia	280
16.2.2.8 Isolation	280
16.3 Thrombocytopenia	281
16.3.1 Incidence and Etiology	281
16.3.2 Treatment	281
16.4 Transfusion Issues	281
16.4.1 Granulocyte Transfusions	281
16.4.2 Transfusion-associated Graft-Verses-Host Disease	282
16.4.3 Cytomegalovirus and Transfusions	282
16.4.3.1 Treatment	282
16.4.4 Platelet Refractoriness	283
16.4.4.1 Treatment	283
16.5 Disseminated Intravascular Coagulation	283
16.5.1 Etiology and Manifestation	284
16.5.1.1 Diagnosis	285
16.5.2 Treatment	285
16.6 Septic Shock	285
16.6.1 Etiology	285
16.6.2 Treatment	286
16.6.3 Prognosis	286

16.7 Immune Suppression	286
16.7.1 Polymorphonuclear Leukocytes	286
16.7.2 Lymphocytes	287
16.7.3 Spleen and Reticuloendothelial System	287
16.7.4 Other Factors Contributing to Immunocompromised States	288
References	288

17 Respiratory System

Margaret Parr

17.1 <i>Pneumocystis</i> Pneumonia	291
17.1.1 Incidence	291
17.1.2 Etiology	291
17.1.3 Prevention	292
17.1.4 Treatment	292
17.1.5 Prognosis	294
17.2 Pneumonitis	294
17.2.1 Incidence	294
17.2.2 Etiology	294
17.2.3 Prevention	295
17.2.4 Treatment	295
17.2.5 Prognosis	295
17.3 Fibrosis	295
17.3.1 Incidence	295
17.3.2 Etiology	296
17.3.3 Prevention	296
17.3.4 Treatment	296
17.3.5 Prognosis	296
17.4 Compromised Airway	296
17.4.1 Incidence	296
17.4.2 Etiology	296
17.4.3 Prevention	297
17.4.4 Treatment	297
17.4.5 Prognosis	298
References	298

18 Renal System

Fiona Reid

18.1 Nephrectomy	302
18.1.1 Incidence	302
18.1.2 Etiology	302
18.1.2.1 Neoplasms	302
18.1.2.2 Bacterial	302
18.1.3 Treatment	302
18.1.3.1 Preoperative	302
18.1.3.2 Surgery	303
18.1.3.3 Postoperative Care	305
18.1.4 Prognosis	305

18.2 Cytotoxic Drug Excretion	306
18.2.1 Pharmacokinetics/Dynamics	307
18.2.2 Metabolism	307
18.2.3 Excretion	309
18.2.4 Drug Interactions	311
18.2.5 Dose Modification	311
18.2.6 Safe Handling of Cytotoxic Excreta	312
18.3 Nephrotoxicity	313
18.3.1 Incidence	313
18.3.2 Etiology	314
18.3.2.1 Iatrogenic	314
Radiation	314
Chemicals	314
18.3.2.2 Fungal	314
18.3.2.3 Viral	316
18.3.2.4 Bacterial	316
18.3.3 Prevention	316
18.3.4 Treatment	316
18.3.4.1 Fluid Overload	318
18.3.4.2 Metabolic Acidosis	318
18.3.4.3 Electrolyte Imbalance	318
18.3.5 Prognosis	318
18.4 Hemorrhagic Cystitis	319
18.4.1 Incidence	319
18.4.2 Etiology	320
18.4.2.1 Iatrogenic	320
Radiation	320
Chemical	320
18.4.2.2 Fungal	320
18.4.2.3 Viral	321
18.4.2.4 Bacterial	321
18.4.3 Prevention	321
18.4.4 Treatment	322
18.4.5 Prognosis	323
References	324

19 Cardiovascular System

Ali Hall

19.1 Cardiotoxicity/Cardiomyopathy	327
19.1.1 Incidence	327
19.1.1.1 On Treatment Recommendations	328
19.1.1.2 Modification Therapy	328
19.1.2 Etiology	328
19.1.3 Treatment	331
19.1.4 Prevention	331
19.1.4.1 Limiting the Effects of Myocardial Concentrations of Anthracyclines and Their Metabolites	331
19.1.4.2 Concurrent Administration of Cardioprotective Agents	332

19.1.4.3 Developing Less Cardiotoxic Therapies	332
19.1.4.4 Lifestyle Advice	332
<i>Guidelines for Long-term Follow-up Post-completion of Anthracycline Therapy</i>	332

19.1.5 Prognosis	332
------------------	-----

19.2 Veno-occlusive Disease

19.2.1 Hepatic Veno-occlusive Disease	332
19.2.1.1 Incidence	333
19.2.1.2 Diagnostic Tests	333
19.2.1.3 Etiology	333
19.2.1.4 Treatment	334
19.2.1.5 Prevention	334
19.2.1.6 Prognosis	335
19.2.2 Pulmonary Veno-occlusive Disease	335
19.2.2.1 Incidence	335
19.2.2.2 Etiology	335
19.2.2.3 Treatment	335
19.2.2.4 Diagnosis	335
19.2.2.5 Prognosis	335

References	336
-------------------	-----

Bibliography	336
---------------------	-----

20 Central Nervous System

Jane Belmore · Deborah Tomlinson

20.1 Spinal Cord Compression	337
20.1.1 Incidence	337
20.1.2 Etiology	337
20.1.3 Treatment	338
20.1.4 Prognosis	338
20.2 Fatigue	338
20.2.1 Incidence	338
20.2.2 Etiology	339
20.2.3 Treatment	340
20.2.4 Prognosis	340
20.3 Cognitive Deficits	341
20.3.1 Incidence	341
20.3.2 Etiology	342
20.3.3 Treatment	342
20.3.4 Prognosis	342
20.4 Diabetes Insipidus	343
20.4.1 Incidence	343
20.4.2 Etiology	343
20.4.3 Treatment	343
20.4.4 Prognosis	343
References	343

21 Musculoskeletal System

Chris M. Senter · Deborah Tomlinson

21.1 Limb Salvage Procedures	345
21.1.1 Incidence	345
21.1.2 Procedure	345
21.1.2.1 Management	348
21.2 Amputation	348
21.2.1 Incidence	348
21.2.2 Procedure	349
21.2.3 Rotationplasty	349
21.2.3.1 Management	349
21.2.3.2 Comparison of Limb Salvage and Amputation	350
<i>Duration of Survival</i>	350
<i>Immediate and Ultimate Morbidity</i>	350
<i>Function</i>	350
<i>Quality of Life</i>	351
21.3 Altered Bone Density and Increased Risk of Fracture	351
21.3.1 Incidence	351
21.3.2 Etiology	351
21.3.3 Treatment	352
21.3.4 Prognosis	352
References	352

22 Skin

Cutaneous Toxicities

Deborah Tomlinson · Nan D. McIntosh

22.1 Alopecia	355
22.1.1 Incidence	355
22.1.2 Etiology	355
22.1.3 Treatment	356
22.1.4 Prognosis	356
22.2 Altered Skin Integrity Associated with Radiation Therapy	357
22.2.1 Incidence	357
22.2.2 Etiology	357
22.2.3 Prevention	357
22.2.4 Treatment	358
22.2.5 Prognosis	358
22.3 Radiation Sensitivity and Recall	358
22.3.1 Incidence	358
22.3.2 Etiology	358
22.3.3 Treatment	359
22.3.4 Prognosis	359
22.4 Photosensitivity	359

22.5 Cutaneous Reactions Associated with High-dose Cytosine Arabinoside	359
22.5.1 Incidence	359
22.5.2 Etiology	359
22.5.3 Prevention and Treatment	359
22.6 Nail Dystrophies	360
22.7 Graft Versus Host Disease	360
22.7.1 Incidence and Etiology	360
22.7.2 Treatment	361
22.7.3 Prevention	362
22.7.4 Treatment	362
22.7.5 Prognosis	362
References	363

23 Endocrine System

Deborah Tomlinson · Ethel McNeill

23.1 Hypothalamic-Pituitary Dysfunction	365
23.1.1 Incidence and Etiology	365
23.2 Growth Hormone Deficiency	366
23.2.1 Treatment	367
23.2.1.1 Investigation	367
23.2.1.2 Growth Hormone Replacement Therapy	367
23.2.2 Prognosis	367
23.3 Hypothalamic-Pituitary-Gonadal Axis	367
23.3.1 Gonadotrophin Deficiency	367
23.3.2 Early or Precocious Puberty	368
23.3.2.1 Treatment	368
23.3.2.2 Prognosis	368
23.4 Thyroid Disorders	369
23.4.1 Treatment	369
23.5 Hypothalamic-Pituitary-Adrenal Axis	369
23.6 Other Pituitary Hormones	370
23.6.1 Fertility	370
23.6.1.1 Testicular Failure	370
23.6.1.2 Ovarian Failure	370
23.6.2 Treatment	370
23.6.2.1 Assessment of Gonadal Function	370
23.6.2.2 Treatment for Gonadal Dysfunction	370
23.6.3 Prognosis	371
References	373

24 Ototoxicity

Colleen Nixon

24.1 Incidence	375
24.2 Prevention and Treatment	378
References	381

25 Eyes – Ocular complications

Deborah Tomlinson

25.1 Ocular Toxicity Associated with High-dose Cytarabine Arabinoside	383
25.1.1 Incidence and Etiology	383
25.1.2 Prevention	384
25.1.3 Treatment	384
25.1.4 Prognosis	384
25.2 Cataracts	384
25.2.1 Incidence	384
25.2.2 Etiology	384
25.2.3 Prevention	385
25.2.4 Treatment	385
25.2.5 Prognosis	385
References	385

PART V

26 Nutrition and Hydration in Children with Cancer

Elizabeth Kassner

26.1 Introduction	387
26.2 Principles of Treatment	388
26.2.1 Nutritional Assessment	388
26.3 Method of Delivery	389
26.3.1 Oral and Enteral Replacement Strategies	389
26.3.2 Selection of Supplemental Enteral Nutritional Solutions	389
26.4 Special Considerations	390
26.4.1 Common Complications of Oral/Enteral Nutritional Supplementation	390
26.4.2 Total Parental Nutrition (TPN)/Hyperalimentation	391
26.4.3 Complications of TPN/Hyperalimentation	393
26.4.4 Glutamine	393
26.4.5 Intravenous Fluid and Electrolyte Requirements	393
26.4.6 Specific Nutritional Concerns During Palliative Care	394
References	396
Bibliography	396

27 Pain in Children with Cancer

Debbie Rembert

27.1 Introduction	397
27.2 Causes of Pain in Childhood Cancer	398
27.3 Assessment	398
27.4 Cultural Issues	402
27.5 Principles of Treatment	404
27.6 Treatment	404
27.6.1 By the Ladder	404
27.6.1.1 Step I: Mild Pain	404
27.6.1.2 Step II: Mild to Moderate Pain	405
27.6.1.3 Step III: Moderate to Severe Pain	405
27.6.1.4 Step IV: Intractable Pain	405
27.6.2 By the Route	408
27.6.3 By the Clock	409
27.6.4 Opioids	409
27.6.5 Equianalgesia	409
27.6.6 Procedure-related Pain	409
27.6.7 Patient-controlled Analgesia (PCA)	410
27.6.8 Adjuvant Medications	410
27.6.9 Nonpharmacologic Treatment	410
27.7 Summary	411
References	412
Bibliography	412

28 Blood Transfusion Therapy

Elizabeth Kassner

28.1 Introduction	414
28.2 Blood Screening Guidelines	414
28.2.1 Blood Product Processing	415
28.3 Transfusion Complications	416
28.3.1 Hemolytic Reactions	416
28.3.2 Nonhemolytic Reactions	417
28.3.3 Allergic Reactions	417
28.3.4 Graft Versus Host Disease (GvHD)	417
28.3.5 Fluid Overload	418
28.3.6 Transfusion-acquired Infections	418
28.3.6.1 Bacterial Infections	418
28.3.6.2 Cytomegalovirus (CMV)	418
28.4 Erythrocyte Transfusion	419
28.4.1 Erythrocyte Transfusion Options	420
28.4.2 Special Transfusion Considerations	420
28.4.2.1 Partial Exchange Transfusion	420
28.4.2.2 Specific Risks of Erythrocyte Transfusion	420
28.5 Platelet Transfusion Options	420
28.5.1 Procurement and Storage	421
28.5.2 Transfusion Guidelines	421
28.5.3 Dosing Recommendations	421
28.5.4 Infusion Guidelines	421

28.5.5	Platelet-specific Transfusion Risks	421
28.5.6	Platelet Alloimmunization	421
28.5.7	Treatment Options	421
28.6	Granulocyte Transfusion	421
28.6.1	Indications	422
28.6.2	Dosing Guidelines	422
28.6.3	Specific Risks	422
28.7	Albumin	422
28.7.1	Volume	422
28.7.2	Transfusion	422
28.8	Fresh Frozen Plasma (FFP)	422
28.8.1	Indications	422
28.8.2	Volume	422
28.8.3	Transfusion	422
28.9	Cryoprecipitate	423
28.9.1	Indications	423
28.9.2	Volume	423
28.9.3	Transfusion	423
28.10	Intravenous Immunoglobulin (IVIG)	423
28.10.1	Indications	423
28.10.2	Volume	423
28.10.3	Side Effects	423
28.11	Recombinant Human (rHu) Erythropoietin Alpha	423
28.12	Palliative Care Issues for Transfusion Therapy	423
28.12.1	Erythrocyte Transfusion	423
28.12.2	Platelet Transfusion	423
References		424
Bibliography		424

29 Growth Factors

Nancy E. Kline

29.1	Principles of Treatment	425
29.2	Method of Delivery	427
29.3	Future Perspectives	428
References		429

30 Care of the Dying Child and the Family

Angela M. Ethier

30.1	Children's Understanding of Death	431
30.1.1	Infants and Toddlers (0–36 Months)	431
30.1.2	Preschool Children (3–5 Years)	431
30.1.3	School-age Children (6–12 Years)	433
30.1.4	Adolescents (13–20 Years)	433
30.2	Explaining Death to Children	433
30.3	Pediatric Palliative Care	433
30.3.1	Principles	433
30.3.2	Location of Care	434
30.4	Grief	434
30.4.1	Principles	434
30.4.2	Assessment of Child and Family	436
30.4.3	Interventions	436
30.5	Cultural and Spiritual Care	438
30.5.1	Principles	438
30.5.2	Assessment of Child and Family	438
30.5.3	Interventions	438
30.6	Bereavement	439
30.6.1	Principles	439
30.6.2	Assessment of Child and Family	440
30.6.3	Interventions	440
30.7	Resources	440
30.7.1	Resources for Children	440
30.7.2	Resources for Adults	441
References		441
Bibliography		442

Subject Index	443
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PART I

Leukemia

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Contents

1.1 Acute Lymphoblastic Leukemia	2
1.1.1 Epidemiology	2
1.1.2 Etiology	4
1.1.2.1 Genetic Factors	4
1.1.2.2 Environmental Factors	4
1.1.3 Molecular Genetics	6
1.1.4 Symptoms and Clinical Signs	7
1.1.5 Diagnostics	8
1.1.6 Staging and Classification	8
1.1.6.1 Risk Classification	8
1.1.6.2 Cell Morphology	10
1.1.6.3 Cytochemistry	10
1.1.6.4 Immunophenotyping	10
1.1.6.5 Cytogenetics	11
1.1.7 Treatment	12
1.1.7.1 Induction	12
1.1.7.2 Intensification/Consolidation	13
1.1.7.3 CNS-directed Therapy	13
1.1.7.4 Maintenance/Continuing Treatment	14
1.1.7.5 Allogeneic Stem Cell Transplant	14
1.1.8 Prognosis	15
1.1.9 Follow-up	15
1.1.10 Future Perspectives	15
1.2 Acute Myeloid Leukemia	16
1.2.1 Epidemiology	16
1.2.2 Etiology	16
1.2.2.1 Genetic Factors	16
1.2.2.2 Environmental Factors	16
1.2.3 Molecular Genetics	16
1.2.4 Symptoms and Clinical Signs	17
1.2.5 Diagnostics	17
1.2.6 Staging and Classification	17
1.2.7 Treatment	19
1.2.8 Prognosis	19
1.2.9 Follow-up	19
1.2.10 Future Perspectives	20
1.3 Chronic Myeloid Leukemia	20
1.3.1 Epidemiology and Etiology	20
1.3.2 Molecular Genetics	20
1.3.3 Symptoms and Clinical Signs	20
1.3.4 Diagnostics	21
1.3.5 Treatment	21
1.3.6 Prognosis	21
1.3.7 Future Perspectives	21
1.4 Juvenile Myelomonocytic Leukemia	21
1.5 Langerhans Cell Histiocytosis	22
References	23

Leukemia is the most common malignancy that affects children, accounting for approximately a third of cancer diagnoses. It may be defined as a neoplastic disease that involves the blood-forming tissues of the bone marrow, lymph nodes, and spleen.

Normal hematopoiesis occurs in these blood-forming tissues; the development of blood cells is shown in Fig. 1.1. A range of extracellular protein factors regulates the growth and differentiation of pathways of developing cells. This ensures that the mature blood cell types are produced in appropriate proportions. Leukemia is a clonal disease that is due to genetic mutations and transformation of a single early progenitor myeloid or lymphoid cell during hematopoiesis. The type of leukemia that results is therefore dependent on the cell lineage that is affected by the mutation. Table 1.1 shows the blood cells that can be affected from either stem cell lineage. In leukemia, there is an overproduction of immature white blood cells that cannot function effectively. These immature white blood cells, such as the myeloblasts, lymphoblasts, and monoblasts, are commonly called “blasts.” An abnormal population of immature white blood cells decreases the space available for the production of other healthy blood cells produced by the bone marrow. The blast cells may then enter the blood and may also infiltrate the central nervous system (CNS).

The two broad classifications of leukemia are acute and chronic. The most common types of leukemia are

- Acute lymphoblastic leukemia (ALL), which accounts for 75–80% of childhood leukemia

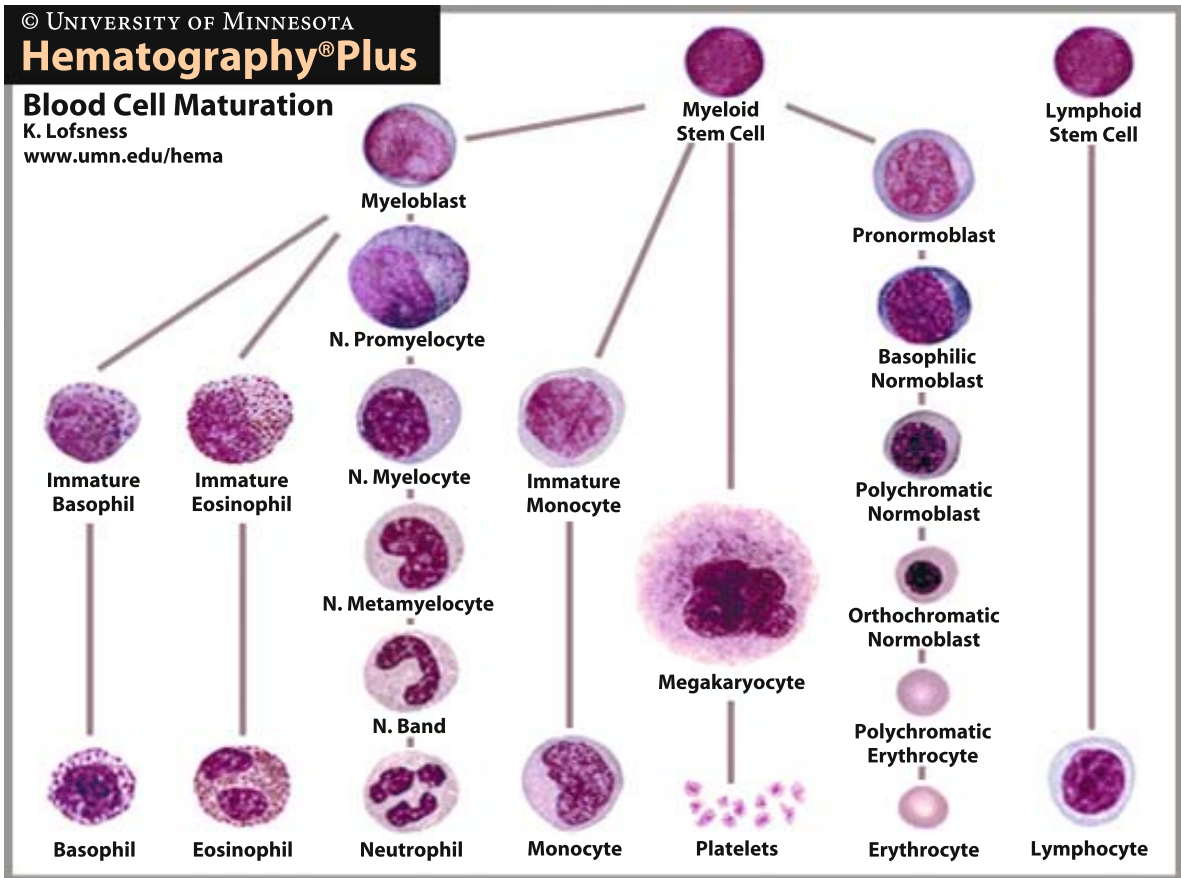


Figure 1.1

Hemopoiesis: The lymphoid stem cell differentiates into T-lymphocytes and B-lymphocytes. Natural Killer (NK) cells are also thought to derive from the lymphocyte stem cell. Image credit: K. Lofsness, University of Minnesota

- Acute myeloid leukemia (AML), also known as acute nonlymphoblastic leukemia (ANLL), which accounts for 20–25% of childhood leukemia
The most common type of chronic leukemia is
- Chronic myeloid (or myelocytic) leukemia (CML), which accounts for less than 5% of childhood leukemia

1.1 Acute Lymphoblastic Leukemia

1.1.1 Epidemiology

ALL affects slightly more males than females (1.2:1) and peaks between the ages of 2 and 6 years. In infants there is a higher number of females affected.

Globally, the highest incidence of ALL appears to be in Europe and North America, with about 5 cases in 100,000 of 0–14-year-old children. The lowest incidence, of about 0.9 in 100,000, is in Kuwait and Bombay. There may be a lack of clarity regarding some

Table 1.1. Lineage and function of major types of blood cells

Blood cell	Lineage	Function	Half-life
Red blood cells (erythrocytes)	Myeloid stem cells	Transport oxygen from lungs to tissue Transport some carbon dioxide from tissues to lungs	About 120 days
Platelets (thrombocytes)	Myeloid stem cells	Repair blood vessels and participate in clotting mechanism	7–10 days
White blood cells (leucocytes)		Crucial in immunity	
Monocytes	Myeloid stem cells	Can differentiate into macrophages; phagocytosis; antigen presentation; immune regulation	1–3 days in blood 3 months in tissues
Granulocytes			
– Neutrophils	Myeloid stem cells	Phagocytosis, killing bacteria	6–12 hours in blood
– Eosinophils	Myeloid stem cells	Detoxify products from allergic response; phagocytosis	2–3 days in tissues
– Basophils	Myeloid stem cells	Involved in allergic response; source of immune inhibitors (e.g., histamine)	Minutes to hours in blood, then in tissue for about 12 days
– Monocytes	Myeloid stem cells	Contain enzymes that kill foreign bacteria	Undetermined
Lymphocytes	Lymphoid stem cells	Role in immunity	Undetermined; cells can move between blood and lymphoid tissues
– T lymphocytes		Attack invaders directly	
– B lymphocytes		Produce antibodies	
– Others: null cells, natural killer cells, lymphokine-activated killer cells, tumor-infiltrating lymphocytes			

incidence figures due to the lack of true population-based registration of cancer. However, ALL generally has a higher incidence in affluent industrialized nations within white populations. The incidence tends to be lower among the black populations of the same nations.

In a study in the United States, Pan et al. (2002) compared the incidence of leukemia in Asian-Americans and their descendents and in Caucasians. This study reported a lower incidence of leukemia in Asian-Americans irrespective of birthplace. In 1991,

Stiller et al. reported that children of Asian and West Indian ethnic origin had patterns of ALL incidence that were similar to those of Caucasians. Interestingly, other later studies of ALL incidence in areas of the United Kingdom have reported an increased risk, although not significantly so, of ALL among South Asian children compared with non-Asian children (McKinney et al. 2003; Powell et al. 1994). However, these increases may be due to socioeconomic status, which has been linked to childhood cancers.

Table 1.2. Syndromes with a predisposition to leukemia

Genetic bone marrow failure syndromes predisposed to leukemia:
Fanconi's anemia
Diamond-Blackfan anemia
Shwachman-Diamond syndrome
Congenital dyskeratosis
Kostmann's infantile genetic agranulocytosis
Genetic syndromes predisposed to leukemia as one of the illnesses:
Chromosomal abnormality:
Down's syndrome (trisomy 21)
Chromosome 8 trisomy syndrome
DNA repair/tumor suppressor deficiency:
Ataxia telangiectasia
Li-Fraumeni syndrome
Neurofibromatosis type 1
Bloom syndrome
Nijmegen/Berlin breakage syndrome
Retinoblastoma:
RB1 gene is important in the histiogenesis of ALL

(Table compiled from Mizutani 1998)

1.1.2 Etiology

The factors involved in the cause of childhood cancers are unclear. Many different etiologies have been suggested and investigated, but few are well established. It would be misleading to associate the cause of any childhood malignancy wholly to genetic or environmental factors, but the study of various factors can improve the understanding of events that may lead to leukemia in children.

1.1.2.1 Genetic Factors

Syndromes that have a component of hereditary or genetic predisposition to leukemia have been identified and are listed in Table 1.2. A study by Mellekjaer et al. in 2000 has shown that children of parents with autoimmune disease are slightly more susceptible to leukemia.

1.1.2.2 Environmental Factors

It is accepted that ionizing radiation is a causal factor in leukemia. Following the atomic bombs in Japan, children who were exposed acquired an increased risk of developing leukemia. Individuals exposed in utero, however, showed no increase in incidence of leukemia. This finding is in contrast to the suggested results of various studies that showed an increased risk of leukemia and other cancers (by about 40%) to children exposed in utero to diagnostic radiography (Doll and Wakeford 1997). There is no doubt that ionizing radiation is a causal factor in leukemia; however, there are uncertainties regarding various aspects of its effect on leukemogenesis.

A significant change in thought surrounds the clusters of reported childhood ALL around nuclear installations. The suspicion that background radiation was the cause of these clusters has moved towards Kinlen's theory (1995) that population mixing, herd immunity, and abnormal response to infection of unusually susceptible children increases the risk of ALL. This "delayed infection" or "hygiene" hypothesis suggests that ALL in children is caused by a lack of exposure to infection in infancy, with an abnormal response to a later common infection incurred after mixing with other children in playgroups or schools. Therefore, circumstances that alter the pattern of infections in infants may contribute to the etiology of ALL.

Table 1.3 highlights studies that have been undertaken to investigate various possible factors in the etiology of childhood leukemia and other cancers. All theories surrounding the causes of ALL, or indeed the majority of childhood cancers, leave much unexplained, and further studies are necessary to confirm or reject the conclusions of those available.

Because of the public interest that surrounds the majority of these potential risk factors, parents will continue to form theories regarding their children's illnesses (Ruccione et al. 1994). Nurses have a role in eliciting parents' causal explanations so that the content of these concerns can be related to the parents' adjustment and management of their experience of childhood cancer.

Table 1.3. Reported environmental links to childhood leukemia and current conclusions

Possible environmental link	Current conclusions
Parental use of tobacco	Paternal smoking before pregnancy may be a potential risk factor for the generality of childhood cancers. Studies do not provide significant evidence (Pang et al. 2003; Sorahan et al. 2001)
Vitamin K prophylaxis in infants	Inconsistent associations reported. However, confirmed benefits of vitamin K outweigh the hypothetical association with any childhood cancer (Parker et al. 1998; Passmore et al. 1998; Roman et al. 2002; Ross and Davies 2000).
Living near landfill sites	No excess risk of any cancer reported (Jarup et al. 2002)
Proximity to railways	No association reported between risk of childhood leukemia and railway proximity (Dickinson et al. 2003). Small association with railway density assumed consequence of population mixing and proximity of railways in deprived urban areas
Children born after in-vitro fertilization	No increased risk of childhood cancer reported in studies published (Bergh et al. 1999; Klip et al. 2001)
Prenatal ultrasound	No association with childhood leukemia found (Naumburg et al. 2000)
Supplementary oxygen	Resuscitation with 100% oxygen immediately postpartum is associated with childhood ALL; further studies warranted (Naumburg et al. 2002a)
Breastfeeding	Contradicting reports of association with a reduced risk of acute leukemia (Lancashire and Sorahan 2003; UK Childhood Cancer Study Investigators 2001; Shu et al. 1999)
Pet (healthy or sick) ownership	No relationship (Swensen et al. 2001)
Family cancer history	May be a risk factor for childhood acute leukemia (Perrillat et al. 2001)
Electromagnetic fields (EMF)/ power lines	Do not support hypothesis of an association (Skinner et al. 2002; Steinbuch et al. 1999)
Natural radionucleotides in drinking water, including uranium	Results do not indicate increased risk of leukemia (Auvinen et al. 2002)
In utero exposure to metronidazole	No reported increased risk (Thapa et al. 1998)
Allergies or family history of allergies	Reduced risk of ALL; no such pattern seen with AML (Schuz et al. 2003)
Exposure to pesticides	May increase risk (Ma et al. 2002); further studies needed
Perinatal exposure to infection	Some association reported between maternal lower genitourinary tract infection in utero and risk of childhood leukemia (Naumburg et al. 2002b). This supports hypothesis that an infectious agent is involved in etiology of ALL (Kinlen 1995)
Population mixing	Increased risk of ALL in children 1–6 years old in high tertile of population mixing (Alexander et al. 1999; Boutou et al. 2002). Further support for infectious agents possessing direct or indirect cause

1.1.3 Molecular Genetics

Clonal chromosomal abnormalities (originating in a single cell) are detectable in around 90% of childhood ALL cases. The leukemia then evolves by the accrual of mutations within a clone. The abnormalities are responsible for a loss of controlled cell growth, division, and differentiation.

To review the biology of chromosomes:

- Genes carry instructions to make proteins essential for cell growth, division, and differentiation.
- A deoxyribonucleic acid (DNA) molecule carries the genetic information in coded form.
- DNA is a nucleic acid made of chains of nucleotides.
- Nucleotides have three components – a phosphate group, a pentose sugar, and a base.
- In DNA the sugar is deoxyribose, and the bases are adenine, guanine, thymine, and cytosine.
- DNA consists of two chains of nucleotides linked across their bases by weak hydrogen ions. These two complementary strands of nucleotides are linked in a double helix formation.
- The bases have specific affinities with each other, so that thymine pairs only with adenine, and cytosine pairs only with guanine.
- The base sequence is the key to the control of the cell and is referred to as the genetic code.
- The length of DNA in cells is so great that there is a significant risk of entanglement and breakage. During mitosis, proteins called histones bind to DNA and wrap it into 46 compact manageable chromosomes (23 pairs).
- The complete chromosome complement of a cell is referred to as the karyotype.

Some genes are associated with the transformation of a normal cell to a malignant cell. These are known as oncogenes (or proto-oncogenes) and tumor suppressor genes. Mutations in the DNA of these genes may cause them to produce an abnormal product or disrupt their control so that they are expressed inappropriately, making products in excessive amounts or at the wrong time. Some oncogenes may cause extra production of growth factors, which are chemicals that stimulate cell growth. Other oncogenes may

cause changes in a surface receptor, causing it to send signals as though it were being activated by a growth factor.

The exact number of mutations required to transform a normal cell into a malignant cell is unknown, but research indicates that two or more mutations, or “hits,” are involved. The first hit is thought to occur in the womb, which in ALL is likely to be a developmental accident affecting a chromosome. This would then suggest that a second hit after birth is necessary before ALL develops. This theory has arisen mainly from observed high concordance rates of leukemia in infant monozygotic twins (that is, if one twin has leukemia, so will the other) and the study of neonatal blood spots or Guthrie cards. In twins, it is considered that the leukemogenic event arises in one twin, and the cells from the abnormal clone then spread to the other via shared placental anastomosis. Polymerase chain reaction (PCR) has been used to identify the same fusion gene sequence in neonatal blood spots as is in patients’ leukemic cells at diagnosis. In all cases of infant leukemia, there are fusions of the MLL gene; in many cases of childhood ALL, there are fusions of the TEL-AML 1 gene. These gene fusions would indicate the first hit or mutation. Table 1.4 shows the classification of types of mutation that can occur. In childhood ALL, reciprocal translocations account for approximately 25% of the chromosomal abnormalities. The translocations involve exchanges of tracks of DNA between chromosomes, resulting in the generation of chimeric or fusion genes. There may also be changes in chromosome number (ploidy), gene deletions, or single nucleotide base changes in genes. (The chromosome number is also measurable as the DNA index, in which 46 chromosomes equals a DNA index of 1).

As discussed earlier, the process by which a normal cell transforms into a leukemic cell is unclear. However, improved molecular analysis techniques have assisted in identifying mechanisms regulating cell growth and differentiation. These include the following:

- Polymerase chain reaction (PCR)
- Fluorescence in situ hybridization (FISH)
- Flow cytometry for immunophenotyping

Table 1.4. Types of mutation to genetic code

Mutation	Description	Presentations
Point mutation	Change in DNA sequence Can occur in base substitution, deletion, or addition May result in wrong amino acid being inserted into protein	Mis-sense mutation, usually a decrease in function
Chromosomal mutation	Alteration in the gross structure of chromosomes Results from cell breakage and reunion of chromosomal material during the cell cycle	Translocation Rearrangement
Genomic mutation	Change in number of chromosomes in the genome	Amplification Aneuploidy (loss or gain of single chromosome)

- Digitized karyotype imaging/multicolor spectral karyotyping
- Microarray profiling
- Southern blotting
- Western blotting

Molecular analysis has proved indispensable for identifying prognostic factors and therapeutically important genetic subtypes of childhood ALL. The ranges of subtypes are based on gene expression, antigens that delineate cell type, and chromosomal and molecular abnormalities. There is currently a relatively sophisticated understanding of the genetic basis of ALL, which will be discussed further in the following sections.

1.1.4 Symptoms and Clinical Signs

ALL usually presents as an acute illness of short onset, but symptoms are occasionally slow and insidious. Symptoms relate to the infiltration of the bone marrow and other affected organs by the proliferation of lymphoblastic cells. The presenting features often appear like many childhood illnesses. Parents or children may describe the following:

- irritability
- night sweats
- fatigue
- bone pain, which may present as limping
- loss of appetite

Initially, symptoms may fluctuate daily, with the child feeling exhausted one day and fine the next. The child may have suffered from repeated ear or other infections that have been frequently resistant to treatment. This is often associated with a history of frequent visits to the family general practitioner.

Physical findings may include the following:

- pallor and lethargy
- pain at the sites of disease infiltration, especially in long bones
- petechiae
- bruising or unusual bleeding (including nose bleeds)
- enlarged liver or spleen, causing the abdomen to protrude
- enlarged lymph nodes and fever

In less than 10% of cases the disease has spread to the CNS at diagnosis. This may cause related symptoms of

- headache
- poor school performance
- weakness
- vomiting
- blurred vision
- seizures
- difficulty maintaining balance

In 60–70% of children with the T-cell type of ALL, there is involvement of the thymus. Enlargement of the thymus caused by an accumulation of white blood cells can give rise to an anterior mediastinal

mass that can cause pressure on the trachea, causing coughing, shortness of breath, pain, and dysphagia. In some cases the pressure may also compress the superior vena cava and cause swelling of the head and arms.

In rare circumstances acute leukemia may present with extremely high blast cell counts, known as hyperleukocytosis. This state of the disease can cause respiratory failure, intracranial bleeding, and severe metabolic abnormalities, conditions that are the main causes of high early mortality. The process that leads to these complications has become known as leukostasis. It had been thought that leukostasis was caused by overcrowding of leukemic blasts. However, it is now evident that leukostasis results from adhesive interactions between blasts and the vascular endothelium. Damage to the endothelium is likely due to cytokines that are released. The adhesion molecules displayed by the blasts and their response to the environment are probably more important factors in leukostasis formation than numbers of cells. Leukopheresis is routinely used to reduce the leukocyte count in the initial phase when there is hyperleukocytosis. It remains unclear whether this is the most efficient method of treating leukostasis. However, further research should indicate the most appropriate use of this procedure.

1.1.5 Diagnostics

If ALL is suspected following the history and physical examination of the child, initial investigations include a complete blood count, urea and electrolyte counts, and a chest x-ray. The blood count may point to a diagnosis of leukemia with blast cells present or an elevated white blood cell count. Figure 1.2a shows a normal blood film, and Fig. 1.2b is a blood film from a child with ALL. However, the necessary diagnostic investigation is a bone marrow examination. The bone marrow is usually taken from the iliac bone at the iliac crest. Despite the new technologies available, ALL is still usually diagnosed by an experienced pediatric oncologist and/or pathologist examining a Romanowsky-stained bone marrow smear with a high-powered microscope. More than a 25% blast cell count in the marrow confirms a diagnosis of

leukemia. A portion of the bone marrow aspirate and the chloroma biopsy/trephine are then analyzed to detect other features of the leukemic cells to help determine what type of leukemia is present. Other techniques are used to extend the diagnosis.

A lumbar puncture is performed to determine any CNS involvement; a sample of cerebrospinal fluid (CSF) is examined for blast cells.

These procedures are most often performed using sedation or anesthetic. Therefore, because of the potential anesthetic difficulties that could develop, a chest x-ray is vital to assist in diagnosing infection or detecting a mediastinal mass.

1.1.6 Staging and Classification

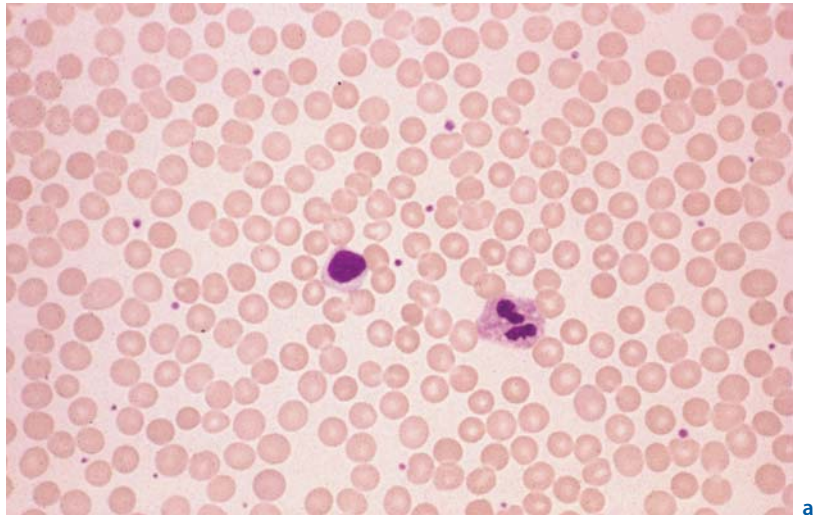
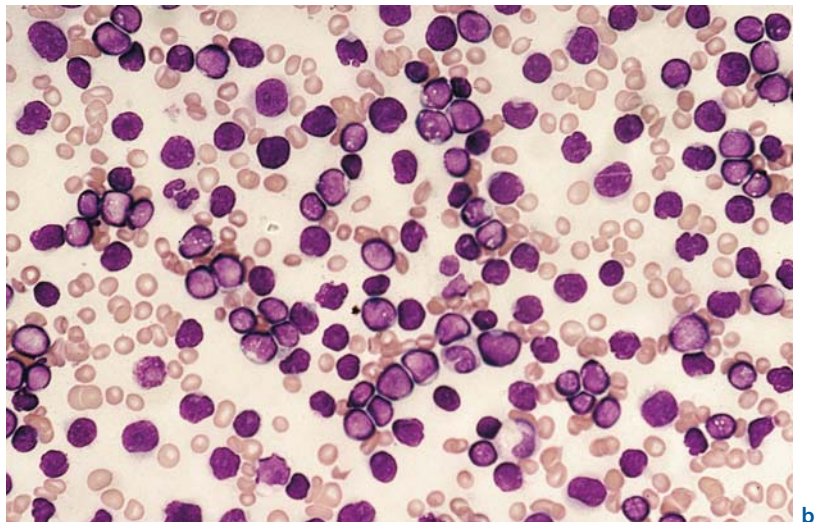
1.1.6.1 Risk Classification

Once a diagnosis of ALL has been confirmed, cell morphology, cytogenetics, and immunophenotyping are determined to elicit more defined prognostic factors. Treatment can then focus on “risk-directed” protocols developed through well-designed clinical trials. This strategy uses the child’s likelihood of relapse or resistance to treatment to intensify or reduce the treatment to ensure adequate cell kill within acceptable levels of toxicity. The significance of various reported risk factors has led to some debate. Difficulty also arises when comparing results between different countries and centers using locally-assigned risk categories. However, over the past few decades several features have been determined to be more favorable prognostic factors. In 1993, following a previous initiative in Rome, collaborative groups met to establish those features that would indicate “standard risk” ALL. These are known as the Rome/NCI (National Cancer Institute) criteria:

- WBC <50,000/mm³
- Female
- 1–9 years of age
- non-T/non-B

Figure 1.2 a, b**a** Normal blood film (×25)**b** ALL blood film (×25).

Image credit: Dr Angela Thomas, RHSC, Edinburgh

**a****b**

All other patients are “high risk.”

Other factors are used to determine risk classification, but the number and array of factors used to classify ALL make it difficult to establish any one system. Consequently, there is a lack of precision within most risk classification systems. Varying conclusions have been reported with regard to the prognostic significance of other characteristics, including the presence of Down's syndrome; liver and spleen size; the presence of an anterior mediastinal mass; French-American-British subtype; body mass index; and CNS in-

volvement, hemoglobin level, platelet count, and number of blast cells in the CSF at diagnosis. However, subgroups of patients with different outcomes can be predicted by blast karyotype, molecular abnormalities, and early response to treatment, with response to treatment proving to be increasingly more important. The persistence of lymphoblasts in bone marrow following a week of induction therapy is associated with a poor prognosis, with less than 30% survival at 5 years no matter what subsequent therapy is given (Hann 2001).

Table 1.5. French-American-British Classification of acute lymphoblastic leukemia

Category	Definition	Features	% of patients
L1	Small cells with scant cytoplasm	Associated with good treatment response	90%
L2	Large cells with abundant cytoplasm	Indicates more refractory to therapy if 10–20% L2 cells are present	9%
L3	Large cells with prominent nucleoli	Mature B-cell phenotype; frequently presents as lymphoma; poor prognosis	1%

Interestingly, a study by Gajjar and colleagues in 2000 found that traumatic lumbar puncture at diagnosis of childhood ALL indicated adverse outcomes and was an indication to intensify intrathecal (IT) therapy.

1.1.6.2 Cell Morphology

Despite other ways of looking at cells, a morphological classification that is still widely applied is the French-American-British (FAB) system. This classification is based on the morphology (appearance, structure, and cytochemistry) and number of cells, and it defines three categories (Table 1.5). This system is limited due to very unevenly divided numbers of patients in each category and to a morphological feature that correlates with responsiveness to conventional therapy – the presence of cytoplasmic vacuoles – not included in the FAB system. Vacuoles are present in 25–30% of patients and are associated with a lower presenting white cell count and the “common” ALL immunophenotype.

1.1.6.3 Cytochemistry

Several biochemical markers have been identified to assist in the classification of leukemia. However, little is added to the morphology of ALL, with the exception of

- Periodic-acid Schiff positivity, seen in around 15% of cases correlating with common ALL
- Acid phosphatase positivity in T-ALL

Table 1.6. Categories of acute lymphoblastic leukemia

Category of ALL	Percentage (approximately)
Common or pre-B	80%
T-cell	10%
Mature B	7%
Null (early B-precursor)	3%

All forms other than T-cell are considered as B-precursor cell ALL

1.1.6.4 Immunophenotyping

ALL is probably best classified on the basis of immunophenotyping. Antigens on the surface of normal hematopoietic cells express changes as the cells mature in the bone marrow. Technology has produced monoclonal antibodies to many of these cell cluster-of-differentiation (CD) antigen groups. These are each given a classification number prefixed with CD. Some CD antigen groups relate to lymphocyte sublineage (CDs 1–8 mark various stages of T-cell lineage; CDs 19–22, 24, and 79a mark B cells) and some to myeloid lineage, whereas others mark more primitive features (CD10 and CD34). Other useful immunologically defined cell characteristics include the following:

- Cytoplasmic immunoglobulins found in pre-B-cell ALL
- Surface immunoglobulins found in mature B-ALL
- Terminal deoxynucleotidyl transferase (TdT) found in immature lymphoid cells

Using these markers enables the classification of ALL into major categories (Table 1.6).

Table 1.7. Outcome prediction associated with ploidy status of acute lymphoblastic leukemia

Ploidy status	Number of chromosomes per malignant cell	Percentage of childhood ALL cases	Predicted response to treatment
Hyperdiploidy	>50	25–30%	Favorable
Hypodiploidy	<50	5–10%	Poor
Near-haploidy	<30	<1%	Very poor

ALL cells occasionally express cell antigens more usually associated with myeloid lineage. Opinion is divided as to whether this is clinically significant.

1.1.6.5 Cytogenetics

Cytogenetic abnormalities are detectable in most cases of childhood ALL. They can be categorized either by the number of chromosomes (ploidy) or by the structural changes and rearrangements based on detailed analysis of the karyotype. The assessment of ploidy status is clinically useful in predicting prognosis (Table 1.7).

With regard to structural changes, the identification of translocations and marker chromosomes and the delineation of complex chromosome aberrations have been possible with multicolor spectral karyotyping. The most significant chromosome (Ch') translocations identified in childhood ALL include the following:

- Ch'12 and Ch'22; i.e., t(12;22), resulting in the ETV6/AML1 fusion gene
- the Philadelphia chromosome, which is translocation t(9;22) and gives rise to the BCR/ABL fusion gene in ALL that indicates a poor prognosis
- t(1;19), giving rise to E2A/PBX1 which is a translocation of pre-B ALL
- t(12;21), giving rise to TEL/AML1 (also termed ETV6/CBFA2 fusion gene), which has been commonly reported as indicating a good prognosis
- t(4;11), giving rise to MLL/AF4, which is a typical translocation occurring in infant leukemia

Other significant abnormalities include

- rearrangements of the MLL gene
- rearrangements of the MYC gene with immunoglobulin genes
- rearrangements of T-cell receptor genes
- mutations of p16 (a tumor suppressor gene)
- mutations of p53 gene (although uncommon in childhood ALL, these mutations are associated with relapse or refractory leukemia)

The effects of these genetic alterations in leukemia help to explain adverse clinical outcomes. For example, the Philadelphia chromosome results in the production of an active kinase enzyme that drives cell proliferation independently of normal requirements for growth factor and blocks apoptosis (programmed cell death). Therefore, drug responsiveness pathways may be blocked. Normal p53 protein is required to induce cell death following anoxia or DNA damage from exposure to drugs or irradiation. Mutations in the p53, common in relapse of leukemia, may explain drug resistance in more advanced disease.

Although the risk criteria features must be considered important predictors of outcome, it would appear that they are most beneficial in predicting risk groups in B-cell lineage but not consistently in T-cell disease (Eden et al. 2000). Overall, 30–40% of children with T-lineage ALL relapse within the first 18 months after diagnosis, and approximately 20% of children with “standard risk” ALL relapse. Some groups of patients require further intensification of therapy. Consequently, more sophisticated approaches to risk classification that incorporate the molecular genetic findings and minimal residual disease measurement have the potential for identifying higher-risk children.