

Shalea Piteau
Editor

Update in Pediatrics

 Springer

Update in Pediatrics

Shalea Piteau
Editor

Update in Pediatrics

 Springer

Editor

Shalea Piteau
Chief/Medical Director of Pediatrics at Quinte Health Care
Assistant Professor at Queen's University
Belleville, ON
Canada

ISBN 978-3-319-58026-5 ISBN 978-3-319-58027-2 (eBook)

<https://doi.org/10.1007/978-3-319-58027-2>

Library of Congress Control Number: 2017964312

© Springer International Publishing AG, part of Springer Nature 2018

This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.

The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

The publisher, the authors and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, express or implied, with respect to the material contained herein or for any errors or omissions that may have been made. The publisher remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Printed on acid-free paper

This Springer imprint is published by the registered company Springer International Publishing AG part of Springer Nature

The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

Pediatrics is evolving with new advancements in knowledge, research, and technology, making it challenging to keep up-to-date with current information. This concise and comprehensive volume provides a review of the latest advances and current literature in Pediatrics, so health professionals can get a summarized overview of the different subspecialties in Pediatrics. Update in Pediatrics includes chapters ranging from traditional disciplines such as Infectious Disease and Cardiology, to more current disciplines such as Adolescent Medicine and Child Maltreatment. The target audience for this book includes any practitioner who cares for children, including pediatricians, family doctors, nurses and nurse practitioners, allied health professionals, and health researchers. My hope is that Update in Pediatrics will serve as a valuable resource for the busy clinician who wishes to stay up-to-date with the latest advances in the field.

ON, Canada

Shalea Piteau

Contents

| | |
|---|-----|
| 1 Update in Adolescent Medicine | 1 |
| Raina V. Voss and Emily Ruedinger | |
| 2 Update in Pediatric Allergy | 39 |
| Amanda Ciccolini, Shannon French, Mark Tenn, and Anne K. Ellis | |
| 3 Update in Pediatric Cardiology | 61 |
| Jane Lougheed and Jenna Ashkanase | |
| 4 Update in Child Maltreatment | 83 |
| Michelle G.K. Ward, Amy E. Ornstein, Tanya Deurvorst Smith, and Karla Wentzel | |
| 5 Update in Pediatric Critical Care | 117 |
| Lisa A. DelSignore, Traci A. Wolbrink, and Niranjan Kissoon | |
| 6 Update in Development: Section A—Infant Development | 133 |
| Madhavi Moharir and Chaya Kulkarni | |
| 7 Update in Development: Section B—Autism Spectrum Disorder | 207 |
| R.G. Smith and D. Samdup | |
| 8 Update in Pediatric Emergency Medicine: Pediatric Resuscitation, Pediatric Sepsis, Interfacility Transport of the Pediatric Patient, Pain and sedation in the Emergency Department, Pediatric Trauma | 223 |
| Tania Principi, Deborah Schonfeld, Laura Weingarten, Suzan Schneeweiss, Daniel Rosenfield, Genevieve Ernst, Suzanne Schuh, and Dennis Scolnik | |
| 9 Update in Pediatric Endocrinology | 251 |
| Seth D. Marks and Brandy A. Wicklow | |
| 10 Update in Pediatric Gastroenterology, Hepatology and Nutrition | 267 |
| A. Jay Freeman, Tatyana Hofmekler, John-Paul Berauer, and Sirish Palle | |

| | |
|---|-----|
| 11 Update in Pediatric Hematology | 313 |
| Ziad Solh, Anthony K.C. Chan, and Mihir D. Bhatt | |
| 12 Update in Pediatric Hospital Medicine | 331 |
| Elizabeth J.N. Davis and Ricardo Quinonez | |
| 13 Update in Pediatric Infectious Disease | 349 |
| Archana Chatterjee and Maya Gogoi | |
| 14 Update in Clinical Genetics and Metabolics | 369 |
| Christine M. Armour and Matthew A. Lines | |
| 15 Update in Pediatric Nephrology | 391 |
| Darcy Weidemann and Martin Bitzan | |
| 16 Update in Neonatology | 415 |
| Faiza Khurshid and Imtiaz Ahmad | |
| 17 Update in Pediatric Neurology | 439 |
| Andrea Andrade and Asuri N. Prasad | |
| 18 Update in Pediatric Oncology: Section A—New Developments in the Treatment of Pediatric Acute Lymphoblastic Leukemia | 461 |
| Shannon L. Maude and Stephen P. Hunger | |
| 19 Update in Pediatric Oncology: Section B—Solid Tumors of Childhood | 485 |
| Allison F. O’Neill | |
| 20 Update in Pediatric Psychiatry | 513 |
| Sabina Abidi | |
| 21 Update in Pediatric Rheumatology | 537 |
| Roberta A. Berard and Ronald M. Laxer | |
| Index | 553 |

Contributors

Sabina Abidi, M.D., F.R.C.P.C. Department of Psychiatry at IWK, Halifax, NS, Canada

Imtiaz Ahmad, M.B.B.S., M.Sc. Department of Biomedical and Molecular Sciences, Queen's University, Kingston, ON, Canada

Andrea Andrade Department of Neurology, LHSC, London, UK

Christine M. Armour, M.D., M.Sc., F.R.C.P.C. Regional Genetics Unit, Children's Hospital of Eastern Ontario, Ottawa, ON, Canada

Jenna Ashkanase Division of Pediatric Cardiology, Department of Pediatrics, Children's Hospital of Eastern Ontario, University of Ottawa, Ottawa, ON, Canada

Roberta A. Berard Division of Rheumatology, Department of Paediatrics, Children's Hospital, London Health Sciences Centre, Western University, London, ON, Canada

John-Paul Berauer Division of Pediatric Gastroenterology, Emory School of Medicine, Atlanta, GA, USA

Mihir D. Bhatt, B.H.Sc., M.D., F.R.C.P.C. Pediatric Hematology/Oncology, McMaster Children's Hospital, McMaster University, Hamilton, ON, Canada

Martin Bitzan Division of Nephrology, Department of Pediatrics, McGill University Health Center, Montreal Children's Hospital, Montreal, QC, Canada

Anthony K.C. Chan, M.B.B.S., F.R.C.P.C. Division of Hematology/Oncology, Department of Pediatrics, McMaster University, Hamilton, ON, Canada

Archana Chatterjee, M.D., Ph.D. Department of Pediatrics, University of South Dakota Sanford School of Medicine, Vermillion, SD, USA

Amanda Ciccolini, M.D. Queen's University, Kingston, ON, Canada

Elizabeth J.N. Davis, M.D., F.A.A.P. Division of Pediatric Hospital Medicine, Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA

The Children's Hospital of San Antonio, San Antonio, TX, USA

Lisa A. DelSignore, M.D. Division of Critical Care Medicine, Department of Anesthesia, Perioperative and Pain Management, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

Anne K. Ellis, M.D., M.Sc., F.R.C.P.C. Queen's University, Kingston, ON, Canada

Division of Allergy and Immunology, Department of Medicine,
Queen's University, Kingston, ON, Canada

Genevieve Ernst Department of Pediatrics, Division of Pediatric Emergency Medicine, University of Toronto, Toronto, ON, Canada

A. Jay Freeman Division of Pediatric Gastroenterology, Emory School of Medicine, Atlanta, GA, USA

Shannon French, M.D. Queen's University, Kingston, ON, Canada

Maya Gogoi Department of Pediatrics, University of South Dakota Sanford School of Medicine, Vermillion, SD, USA

Tatyana Hofmekler Division of Pediatric Gastroenterology, Emory School of Medicine, Atlanta, GA, USA

Stephen P. Hunger Division of Oncology and Center for Childhood Cancer Research, The Children's Hospital of Philadelphia, Philadelphia, PA, USA
Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Faiza Khurshid, M.D., F.C.P.S., M.Sc. (H.Q.) Department of Pediatrics, Queen's University, Kingston, ON, Canada

Niranjan Kissoon, M.D. Division of Critical Care and the Child and Family Research Institute, Department of Pediatrics, British Columbia's Children's Hospital, University of British Columbia, Vancouver, BC, Canada

Chaya Kulkarni Infant Mental Health Promotion, HSC, Toronto, ON, Canada

Ronald M. Laxer, M.D.C.M., F.R.C.P.C. Division of Rheumatology, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada

Matthew A. Lines, M.D., M.Sc., F.R.C.P.C. Metabolics, Clinical Biochemical Geneticist, Children's Hospital of Eastern Ontario, Ottawa, ON, Canada

Jane Lougheed Division of Pediatric Cardiology, Department of Pediatrics, Children's Hospital of Eastern Ontario, University of Ottawa, Ottawa, ON, Canada

Seth D. Marks Pediatric Endocrinology and Metabolism, University of Manitoba, Winnipeg, MB, Canada

Shannon L. Maude Division of Oncology and Center for Childhood Cancer Research, The Children's Hospital of Philadelphia, Philadelphia, PA, USA
Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Madhavi Moharir Infant Mental Health Promotion, HSC, Toronto, ON, Canada

Allison F. O'Neill, M.D. Department of Pediatrics, Division of Pediatric Emergency Medicine, University of Toronto, Toronto, ON, Canada

Amy E. Ornstein, M.D.C.M., M.Sc., F.R.C.P.C., F.A.A.P. Department of Pediatrics, Dalhousie University, Halifax, NS, Canada

Sirish Palle Division of Pediatric Gastroenterology, Emory School of Medicine, Atlanta, GA, USA

Asuri N. Prasad Department of Neurology, LHSC, London, UK

Tania Principi Department of Pediatrics, Division of Pediatric Emergency Medicine, University of Toronto, Toronto, ON, Canada

Ricardo Quinonez, M.D. Division of Pediatric Hospital Medicine, Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA
Texas Children's Hospital, Houston, TX, USA

Daniel Rosenfield Department of Pediatrics, Division of Pediatric Emergency Medicine, University of Toronto, Toronto, ON, Canada

Emily Ruedinger, M.D. Division of Adolescent Medicine, Department of Pediatrics, Seattle Children's Hospital and University of Washington, Seattle, WA, USA

D. Samdup KidsInclusive Centre for Child and Youth Development, Hotel Dieu Hospital, Kingston, ON, Canada

Queen's University, Kingston, ON, Canada

Suzan Schneeweiss, M.D., M.Ed., F.R.C.P.C Department of Pediatrics, Division of Pediatric Emergency Medicine, University of Toronto, Toronto, ON, Canada

Suzanne Schuh, M.D., F.R.C.P.(C.), F.A.A.P. Division of Paediatric Emergency Medicine, Research Institute, Hospital for Sick Children, University of Toronto, Toronto, ON, Canada

Deborah Schonfeld Department of Pediatrics, Division of Pediatric Emergency Medicine, University of Toronto, Toronto, ON, Canada

Dennis Scolnik, F.R.C.P.(C.), D.C.H., M.Sc. Department of Paediatrics, Faculty of Medicine, University of Toronto, Toronto, ON, Canada

Divisions of Paediatric Emergency Medicine and Clinical Pharmacology and Toxicology, The Hospital for Sick Children, Toronto, ON, Canada

R.G. Smith KidsInclusive Centre for Child and Youth Development, Hotel Dieu Hospital, Kingston, ON, Canada

Queen's University, Kingston, ON, Canada

Tanya Deurvorst Smith, M.N., N.P.-Paediatrics The Suspected Child Abuse and Neglect (SCAN) Program, The Hospital for Sick Children, Toronto, ON, Canada

Adjunct Lecturer, Lawrence S. Bloomberg Faculty of Nursing, The University of Toronto, Toronto, ON, Canada

Ziad Solh, M.D., M.Sc., F.R.C.P.C. Department of Pathology and Molecular Medicine, McMaster University, Hamilton, ON, Canada

Division of Hematology/Oncology, Department of Pediatrics, McMaster University, Hamilton, ON, Canada

Medical Services and Innovation, Canadian Blood Services, Hamilton, ON, Canada

Mark Tenn, B.H.Sc., M.Sc. Candidate Queen's University, Kingston, ON, Canada

Raina V. Voss, M.D. Division of Adolescent Medicine, Department of Pediatrics, Seattle Children's Hospital and University of Washington, Seattle, WA, USA

Michelle G.K. Ward, M.D., F.A.A.P., F.R.C.P.C. Department of Pediatrics, University of Ottawa and Children's Hospital of Eastern Ontario, Ottawa, ON, Canada

Darcy Weidemann Section of Pediatric Nephrology, Department of Pediatrics, University of Missouri – Kansas City School of Medicine, Children's Mercy Hospital and Clinics, Kansas City, MO, USA

Laura Weingarten Pediatric Emergency Physician and Assistant Clinical Professor, Department of Pediatrics, McMaster University, Hamilton, ON, Canada

Karla Wentzel, M.N., N.P.-Paediatrics The Suspected Child Abuse and Neglect (SCAN) Program, The Hospital for Sick Children, Toronto, ON, Canada
Adjunct Clinical Appointment, Lawrence S. Bloomberg Faculty of Nursing, The University of Toronto, Toronto, ON, Canada

Brandy A. Wicklow Pediatric Endocrinology and Metabolism, University of Manitoba, Winnipeg, MB, Canada

Traci A. Wolbrink, M.D., M.P.H. Division of Critical Care Medicine, Department of Anesthesia, Perioperative and Pain Management, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA



Update in Adolescent Medicine

1

Raina V. Voss and Emily Ruedinger

Introduction

Adolescence is a time of enormous physical, cognitive, social and emotional transformation recognized as a distinct developmental stage across cultures. This period of rapid change is perhaps rivaled only by the changes that occur in infancy. Chronologically, it can be difficult to definitively define, but roughly occurs from around the age of onset of secondary sexual characteristics (roughly age 9 or 10) through the early 20s. Adolescence has historically been categorized as a stormy time, but in fact most adolescents transition from childhood to adulthood smoothly, maintaining generally healthy behaviors and good relationships with their caregivers (Christie and Viner 2005; Hazen et al. 2008).

Because adolescence is a distinct developmental stage, caregivers are also presented with some challenges that are unique to this population. As youth transition from childhood to adulthood, they take on increasingly active roles as autonomous decision-makers in many arenas,

including healthcare. Providers can help shepherd adolescents and their caregivers more successfully through this transition by understanding the developmental nuance of adolescence, and by communicating with youth and their caregivers in a sensitive manner. In this chapter, we will touch upon topics for which healthcare providers in general have developed new or more detailed understanding over the past decade. Topics include development, interviewing, substance use, reproductive health, sexual and gender identity, technology and media, and transitioning to adult healthcare.

Adolescent Development

Adolescence is commonly divided into three phases: early, middle and late. Though there are not exact age cutoffs for each of these stages, in typically developing individuals early adolescence is roughly ages 10–13 (the middle school years in the United States); middle adolescence encompasses roughly ages 14–17 (the high school years); and late adolescence is from ages 18 through the early 20s (late high school through the next 4 years or so). The end of adolescence is generally marked by attainment of independent adult behaviors rather than a numerical indicator, though there remains a good deal of controversy over this endpoint. Conversation in the lay community about “prolonged adoles-

R.V. Voss, M.D. (✉) • E. Ruedinger, M.D.
Division of Adolescent Medicine, Department of
Pediatrics, Seattle Children’s Hospital and University
of Washington, 4540 Sand Point Way NE, Seattle,
WA 98105, USA
e-mail: raina.voss@seattlechildrens.org;
emily.ruedinger@seattlechildrens.org

cence” of the current generation abounds—simply enter the term into any search engine to come up with myriad articles and opinions. While there is evidence to substantiate the assertion that traditional markers used to signify transition into adulthood (e.g., living independently from childhood family unit, finishing schooling, first job, entering into marriage or stable partnership, childbearing) have shifted later in the life course, many experts in the field contend that this shift should not necessarily be viewed in a negative light and may have a neutral or even positive impact (Hayford and Furstenberg 2008; Steinberg 2014).

While much of the commentary on prolonged adolescence refers to cognitive, social and emotional development, concern about earlier physical development, particularly among girls, has also been raised. The age of onset of Tanner 2 breast development may have declined negligibly over recent years, though increased adipose tissue may be mistaken for early breast development and confound the issue (Walvoord 2010). The age of menarche, which is probably a better marker of true pubertal timing, has, indeed, declined in modern times—but the importance of this is unclear, particularly when taken in a broader historical context. During the industrial revolution, often used as a marker for the beginning of “modern times,” menarche was delayed relative to previous eras. This was likely due to remarkably poor living and sanitation conditions. With improved living conditions over the past century, the current age of menarche has become relatively re-aligned with historical norms from eras prior to the industrial revolution (Papadimitriou 2016). Furthermore, the age of menarche seems to generally have stabilized over the past half-century (Walvoord 2010; Papadimitriou 2016). A complete review of physical developmental milestones is beyond the scope of this chapter, but can be readily found elsewhere (Rosen 2004; American Academy of Pediatrics Section on Endocrinology 2015).

With regard to cognitive, social and emotional development, there are fewer outwardly visible markers to help clinicians determine a patient’s stage of development. These developmental

domains can develop in a dyssynchronous manner, and development often does not occur in a linear fashion. Further, development along these domains is context- and culture-dependent; considering context and culture is, in many regards, more important than chronology when determining whether or not a youth’s development is normal. See Table 1.1 for a summary of important cognitive, social and emotional developmental considerations for early, middle and late adolescents.

In general, adolescents in all stages of development have a reputation for taking more risks than adults. Imaging studies have shown that adolescents have particularly active reward centers; youth often perceive similar, or at times even greater, levels of risks as adults. However, the potential reward, or benefit, to engaging in many behaviors is perceived as greater among adolescents than among adults. Thus, adolescents’ perception of risk-to-benefit ratios is skewed compared to adults (Sanders 2013; Ahmed et al. 2015; Chick and Reward processing in the adolescent brain: individual differences and relation to risk taking 2015). Because teens are particularly sensitive to their peers, they are also generally more likely to participate in risky behaviors when surrounded by peers than if they are alone (Ahmed et al. 2015; Chick 2015). Although there does appear to be a population-level correlation between greater reward perception and increasing risk taking behavior, the causality of this relationship has not been firmly established and remains an area of ongoing research; some studies show that adolescents who perceive the greatest reward are not necessarily the same ones who take the greatest risk (Chick 2015).

Functional MRI studies have started to provide greater insight into how physiologic developmental changes may correspond with cognitive, psychosocial and emotional development. In general, gray matter in the frontal lobes peaks around early adolescence and declines over middle and late adolescence, with increasing white matter over the same timeframe. This may represent synaptic proliferation early in adolescence followed by synaptic pruning

Table 1.1 Cognitive, psychosocial and emotional changes throughout adolescence (Christie and Viner 2005; Hazen et al. 2008; Sanders 2013; Dixon and Stein 2006)

| Cognitive | Early (10–13 years old) | Middle (14–17 years old) | Late (18 years old–early/mid 20s) |
|---|--|---|-----------------------------------|
| <p><i>Concrete and Literal:</i> Youth in this stage remain very concrete. They often have difficulty answering vague questions, such as, “Tell me about yourself.” More concrete questions, like “What did you do yesterday?” will likely be more comfortable for these kids and yield more information. Adolescents this age may be more likely to perceive the interview as a test of sorts, with right or wrong answers, and provide the answer that they think will please the clinician. They often have difficulty organizing tasks, and usually still need concrete directions. They may perceive questions about their peers as more conversational and less threatening than direct, sensitive questioning (for example, asking “Are any of your friends doing XYZ...” and then asking, “What about you? Have you tried XYZ?”). Early adolescents tend to have very little understanding of future consequences of their current actions</p> | <p><i>Abstract Thinking:</i> Many teens this age have just developed the ability to introspect and have more “big concept” understanding—this allows middle adolescents to begin exploring concepts such as spirituality and love at a personal level, and grasp advanced academic concepts such as allegory or calculus. Development of abstract thinking may also contribute to increased egocentrism. Executive functioning remains poor, with relatively low ability to understand long-term consequences or impact of actions on others; on organizing tasks; and on self-control. However, this is often better than it is in an early adolescent. It can also vary by task or domain. This seeming ability to think long-term in some areas but not others can be frustrating to parents and clinicians. However, the ability to think toward the future develops over time. This apparent ability to apply this sort of reasoning and executive functioning in one area but not another often represents that they are progressing along this continuum, rather than a deliberate choice to ‘understand’ the future in one area but not in another</p> | <p><i>Maturing Prefrontal Cortex:</i> The prefrontal cortex is still developing during this stage, but executive function and future thinking is more mature. Often young people in this stage of development are able to participate in deep conversations about abstract topics and draw complex connections. Developing this ability is exciting and young people in this age group are often great activists and can be quite passionate. “Gray” areas can still be challenging when it comes to morals and values—many older adolescents are often still concrete about what is right and wrong from a big-picture perspective. For example, it may be hard for them to recognize why it may ever be acceptable for a politician to act in a way that they feel is “immoral”</p> | |

(continued)

Table 1.1 (continued)

| | | | |
|----------------------------|--|---|--|
| | <p>Early (10–13 years old)</p> <p><i>Establishing identity separate from family:</i> Early adolescents are just starting to view themselves as separate from their family. They often “try on” different personas, often still in a very literal sense (for example, by changing outward appearance). They will usually start to test limits with parents; they still desire support, but this can create an internal sense of conflict with their desire for independence. As a result, some teens act resistant. They are still usually very concrete about rules, values and morals—things are very black and white; something is good or bad, with little room for middle ground, gray area, or understanding nuance</p> | <p>Middle (14–17 years old)</p> <p><i>Refining Self-Image:</i> The bid for independence extends beyond appearance and into arenas such as political views and philosophical opinions. Teens expressing value systems that differ from those of their family might be distressing to parents, however most (but not all!) youth actually return to the values parents promoted in earlier childhood once they emerge from this phase. Many mid-adolescents start to recognize the ‘gray’ area around morals, politics, etc., but this skill is still undeveloped as well. They might understand that there is a gray area (for example, that people have a variety of religious preferences, and that there can be positive and negative aspects of various religions) but tend to be relatively rigid in their own beliefs (for example, “I am an atheist and cannot go to church with my grandmother because it is against my religion,” even if it would mean a lot to the grandparent)</p> | <p>Late (18 years old–early/mid 20s)</p> <p><i>Time of Transition:</i> This is a time when many teens transition away from their prior family and/or school roles, moving on to college, work, independent living, and/or the military. Many young people are preoccupied with vocation—what will come next?</p> |
| <p>Psychosocial</p> | | <p><i>Importance of Peers:</i> Starting to separate from the family unit is emotionally stressful, but desired. This dissonance is often dealt with by creating very strong connections with a peer group. Youth want to be different and separate from family but still need that comforting sense of fitting in somewhere. Often this is achieved through peers. Adults often joke about kids this age talking about how they want to “be different,” but then looking and acting exactly the same as their peers</p> | <p><i>Clearer Sense of Self:</i> Dependence on peers starts to lessen; many young people are now able to define and pursue independent goals. Strong connections to school, family and/or community indicate less likelihood of participating in risky behaviors</p> |
| <p>Emotional</p> | <p><i>Deeper Peer Relationships and Romance:</i> Most mid-adolescents have fully developed secondary sexual characteristics. This newly developed body often leads to heightened peer and self-awareness. Because their executive functioning is not fully developed, there is often less understanding of consequences. Teens also have less impulse control. In this age group there is often an increase in engaging in physical intimacy. Most teens start to explore sexual relationships at some level. Twenty percent of 15-year-olds, and 48% of 17-year-olds, have had penile-vaginal intercourse (Finer and Philbin 2013)</p> | | |

accompanied by increased myelination and white matter tract organization over time. Additionally, brain activity in certain regions is different between adolescents and adults completing similar tasks. The cause behind this is not yet clear but may relate to the neuroanatomic changes described above; increasing automaticity/decreasing novelty of tasks over the transition toward adulthood; and/or something else altogether. This remains an area of very active study (Blakemore 2012).

It is likely that physiologic, cognitive, psychosocial and emotional changes are inter-connected in ways that are not yet fully understood. We generally encourage providers to keep adolescent developmental concepts in mind when working with teens, and recognize that behaviors that may not “make sense” to an adult often seem reasonable and logical to the youth because of their context and developmental stage. Understanding the youth’s perspective is a key component of promoting adolescent health.

Interviewing the Adolescent Patient

Many issues in adolescent health center around the psychosocial world of the patient. While some of these issues fall into the category of risk behaviors, other health issues, such as mental illness and abuse, may arise due to adverse environments over which the adolescent has little control. Regardless of the reason that an adolescent presents to care, the visit should be viewed as an opportunity to screen for and address common risk behaviors and psychosocial stressors.

There are several different techniques that are used to perform such a screen. Best known is the HEEADSSS mnemonic, which serves as a history-taking tool to cover broad domains of psychosocial assessment (Katzenellenbogen 2005; Goldenring and Rosen 2004). This mnemonic has evolved over time to include more categories and letters. See Table 1.2 for examples of what can be contained in the HEEADSSS assessment.

Confidentiality

The clinician should interview the adolescent patient alone at some point during the visit. Private portions of the visit allow for discussion of topics that adolescents often prefer to keep private from their parents. Adolescents often speak more freely without parents in the room, sometimes making it easier to establish a relationship with the patient. Often, it can also be helpful to meet with the parent alone, as they may be able to provide information about their child’s mental health, school performance, or social stressors that they are not comfortable discussing in front of the adolescent.

Prior to interviewing an adolescent alone, it is helpful to discuss confidentiality with both adolescent patients and their parents. Many providers choose to name the topics that will be discussed confidentially and the specific issues that require breaking confidentiality (Table 1.3). Starting in the early teenage years, providers should counsel parents that adolescents often feel more comfortable talking without their parents, and that these private visits are an important step in their process toward becoming responsible for their own health and wellbeing.

Laws vary by jurisdiction with regard to services that can be provided confidentially to adolescents without parental consent. These services may include contraceptive care (condoms and birth control methods, including long-acting reversible contraception), prenatal care, abortion services, drug and alcohol treatment services, and mental health treatment (including counseling and medications). In the United States (U.S.), all 50 states have laws allowing minors to access confidential STD-related care. The age of consent for these services varies by state. The Guttmacher Institute provides a thorough listing of state-specific minors’ consent laws for reproductive and sexual health: <https://www.guttmacher.org/state-policy/explore/overview-minors-consent-law> (Guttmacher Institute n.d.).

Many jurisdictions also have laws which allow for the general care of adolescents without parental consent in cases where the minor is

Table 1.2 The HEEADSSS assessment: a psychosocial interview tool

| | |
|--|--|
| Home environment | • Who do you live with? |
| | • Do you feel safe at home? |
| | • Who are you closest with? |
| | • Is religion part of your life? |
| Education and employment | • What school and grade are you in? |
| | • <i>Any issues with bullying?</i> |
| | • Do you have friends at school? |
| | • How are you doing in school? Are you failing any classes? |
| | • What are your favorite and least favorite classes? |
| | • Do you have any special circumstances? (504 plan, IEP, special education, tutoring, repeated grades) |
| | • Do you like school? |
| | • What are your plans after high school? |
| | • What are your plans after college? |
| | • Do you have a job currently? |
| Eating | • How do you feel about your body? What do you like and not like about it? |
| | • Are you worried about your weight? |
| | • Has your weight changed recently? |
| | • Tell me what you might eat in a typical day |
| | • Are you trying to lose weight? |
| | • Do you ever starve yourself, skip meals, or make yourself throw up? Ever take diet pills, laxatives, diuretics? |
| | • Do you ever feel like your eating is out of control? Eat so much you feel sick? |
| • <i>Do you have enough food in your home?</i> | |
| Activities | • What do you do for fun? (With friends? With family?) |
| | • How many hours do you spend in front of a screen (not for school/work) per day? |
| | • Tell me about how you get exercise (explore for excessive exercise) |
| Drugs | • Have you ever tried alcohol? Marijuana? Cigarettes? Other drugs such as ecstasy, methamphetamines, cocaine, heroin, prescription medications (pain medicine or ADHD medicine)? |
| | • How do you use (pills, snorting, smoking, injecting)? |
| | • How often and how much do you use? |
| | • Have you been drunk? Blacked out? Vomited? |
| | • Have you ever used alone? |
| | • How many of your close friends use substances? |
| | • Have you ever driven intoxicated or driven with an intoxicated driver? (This includes alcohol, marijuana, and other drugs) |
| | • Have drugs or alcohol ever gotten you into trouble? |
| • What do you think about your drug use? | |

Table 1.2 (continued)

| | |
|--|---|
| Sexuality | • Are you attracted to boys, girls, both, or neither? |
| | • <i>How do you identify? Male, female, both, neither, or neither?</i> |
| | • Have you dated, or had crushes? |
| | • Are you in a relationship? |
| | • Have you ever felt that your boyfriend/girlfriend is jealous or controlling? |
| | • Has your boyfriend/girlfriend ever physically hurt you? |
| | • Have you had any types of physical relationships? Holding hands, hugging, kissing, touching, oral sex, vaginal sex, anal sex? |
| | • <i>Have those experiences been enjoyable?</i> |
| | • Have you ever had any unwanted physical/sexual activity? Have you ever felt pressured into doing something? |
| | • How many partners have you had all together? |
| | • What have you (or your partner) used for protection against pregnancy? STDs? |
| | • Have you ever been pregnant or gotten someone pregnant? |
| | • Have you ever had an STD? Are you concerned about an STD? When were you last tested for STDs? |
| | • <i>How do you talk about sex with a partner before you start doing something physical?</i> |
| • <i>Have you talked with your parents about your sexual orientation, gender, and relationships?</i> | |
| • <i>Have you ever had sex in exchange for drugs, money, or other things you needed?</i> | |
| Suicide and depression | • How do you think your mood is? |
| | • Do you worry you might have depression or anxiety? |
| | • Do you ever think about hurting or killing yourself? |
| | • Have you ever hurt yourself (by cutting or other methods)? |
| | • Have you ever tried to kill yourself? |
| | • For more thorough depression assessment we recommend screening with the PHQ9 |
| • For anxiety assessment, we recommend screening with the GAD7 | |
| Safety | • How often do you wear a bike helmet? |
| | • How often do you wear a seat belt? |
| | • Do you have a driver's license? What are the restrictions? |
| | • Has anyone ever hurt you or touched you inappropriately? |
| | • Is there violence in your home? School? Neighborhood? Relationship? |
| | • Have you ever felt threatened or unsafe? (At home? At school? In your neighborhood? When you are out of your comfort zone?) |
| | • <i>Have you ever felt you had to carry a weapon to be safe?</i> |
| | • Have you ever been in a fight? |
| • Are there guns or other weapons in your home, or anywhere that you could access them? | |

Italicized questions represent concepts that are relatively new parts of the routine HEEADSSS assessment. When assessing safety, the provider may consider the ways that the patient's race, gender expression, and body habitus may impact their perception of safety

Table 1.3 Indications for breaking confidentiality

| Indication for breaking confidentiality | Appropriate course of action |
|--|--|
| Active suicidal ideation with plan of action | Refer to ER (either by EMS or via safe transport if all parties comfortable) Call local crisis line |
| Behaviors that may cause harm to patient (cutting, purging, risky substance use, inadequate or inappropriate prescription use) | Discuss with parent for safety planning Speak with social worker and/or therapist if available |
| Specific plan to harm others | Report to local police Refer patient to ER |
| Report of physical abuse by a caregiver, teacher, or other adult responsible for the child's wellbeing | Call Child Protective Services (CPS) <ul style="list-style-type: none"> • Need as much information as possible including full name and address of perpetrator and details of event • If concern for child's immediate safety, place the call while patient still in office |
| Report of sexual abuse by an adult (or older adolescent, depending on state law) | Call local police <ul style="list-style-type: none"> • Need as much information as possible including full name and address of perpetrator and details of event |

considered “mature” or “emancipated” (Coleman and Rosoff 2013). The criteria for this status as a “mature minor” varies by jurisdiction and may include living separately from parents, having a child, being financially independent, or other criteria. In some states, this status may be determined by a healthcare provider, while in some states this must be determined by a judge or other qualified authority. We suggest that providers familiarize themselves with the laws in their jurisdiction, either through online resources published by their local government or by consulting with social workers or hospital ethics officials.

Adolescent Substance Use and the Changing Legal Environment of Marijuana

Adolescents are very likely to try illicit drugs as they progress into adulthood. In 2015, 44% of high school seniors reported that they had tried marijuana in their lifetime, and 64% reported having ever tried alcohol (Miech et al. 2016). Most people who become addicted to drugs and alcohol begin using in their teen years, making this an important age group to screen for substance use (Chen et al. 2009; Grant and Dawson 1998; Anthony and Petronis 1995). Illicit sub-

stances, if used chronically, can have long-term impacts on brain development (Schepis et al. 2008; Squeglia et al. 2015; Yuan et al. 2015).

Marijuana has become the most commonly used illicit substance amongst U.S. teens (Miech et al. 2016). Jurisdictions vary in their laws on use of marijuana for medical and recreational purposes (Office of National Drug Control Policy n.d.). Despite being legalized only for adults, the legalization of marijuana and other cultural influences have made provider conversations with youth about marijuana more challenging; often, parents and patients are firmly committed to the belief that marijuana use is safe and healthy (Miech et al. 2016). The rest of this section will focus on marijuana use in adolescents, however many of the principles of screening and treatment apply to other drug use as well.

Epidemiology

In 2014, 21.2% of high school seniors reported having used marijuana in the past month via the Monitoring the Future study (Miech et al. 2016). This rate of use has been consistent since 2011. One study of youth who had used marijuana at least five times demonstrated that 46.3% had continued use after 10 years (Perkonig et al. 2008).

Forms of Use

The amount of THC in marijuana products has been increasing over time; The mean concentration of THC in confiscated cannabis products has increased from 3.4% in 1993 to 8.8% in 2008 (Mehmedic et al. 2010).

Inhaled use: Marijuana may be consumed in the form of cigarettes (joint), cigars (blunt), using a small pipe (bowl), or a large water pipe (bong). Marijuana may also be vaporized using vape pens or vape guns. *Dabbing* is the practice of using THC-rich resins extracted from the marijuana plant. The extract can be obtained in the form of oil, wax, or *shatter*, an amber-colored solid (National Institute on Drug Abuse n.d.-a). This form of use is extremely potent and carries high risk for negative experiences. The extracts are prepared for smoking using butane, which has led to several house fires, explosions, and burns (National Institute on Drug Abuse n.d.-a).

Edible marijuana is available in the form of brownies, cookies, candies, and tea. Because the ingested marijuana has to be digested and absorbed into circulation, the effect takes over an hour and users will often ingest more marijuana while waiting to get the desired effect. Because of this risk of overuse, this form of use often results in overdose experiences (National Institute on Drug Abuse n.d.-a). In Washington, where marijuana is legal for adults ages 21 and above, edible marijuana products are being sold in packaging that is increasingly similar in appearance to non-drug products, which may increase the likelihood of accidental ingestion by children.

Synthetic Marijuana is commonly known as K2 or Spice. These substances are chemically related to THC but do not come from the marijuana plant (National Institute on Drug Abuse n.d.-a). These drugs can be smoked or obtained in liquid form and vaporized through e-cigarettes or other vaping devices. They are typically much more potent than smoked marijuana. Adverse effects noted from use of Spice and K2 include anxiety and agitation, nausea and vomiting, high blood pressure, shaking and seizures, hallucinations and paranoia, and violent behavior. These substances may not show up on drug tests (National Institute on Drug Abuse n.d.-a).

Medical Marijuana: At the time of this publication, medical marijuana has been legalized in many jurisdictions, including 23 U.S. states as well as the District of Columbia (Office of National Drug Control Policy n.d.). There is no chemical difference between medical and recreational marijuana. Typical state laws intend medical marijuana use for adults over age 21. In most states where medical marijuana is legal, minors may obtain medical marijuana with parental permission. Some research suggests that marijuana may be effective in treating cancer-related pain and nausea, however data is limited to adults and quality research on this topic is generally lacking (Wilkie et al. 2016; Harrison et al. 2015).

Pharmaceutical cannabinoids: There are two forms of synthetic cannabinoids available in the United States. Neither have been studied in children. Both dronabinol (trade name Marinol, manufactured by Abbvie) and nabilone (trade name Cesamet, manufactured by Meda Pharmaceuticals) are FDA approved for chemotherapy-induced nausea and vomiting.

Adverse Effects

Addiction: An estimated 9% of marijuana users will become addicted to the substance. Among people who begin using as teens, the rate of addiction is 17%. The mechanism for addiction to marijuana is similar to that of other substances, which is via up-regulation of endogenous neurotransmitter receptors due to overstimulation by the exogenous drug (Hasin et al. 2015; Winters and Lee 2008).

Lung disease: Marijuana use is associated with increase risk of pneumonia, bronchitis and chronic cough, and increased sick days due to respiratory illness (Hashibe et al. 2006; Polen et al. 1993). Studies linking marijuana with lung cancer are as yet inconclusive (Hashibe et al. 2006).

Testicular cancer: Two studies have shown an increased risk of testicular germ cell tumors in marijuana users (Lacson et al. 2012; Daling et al. 2009). Marijuana users who began use before age 18 had a 2.8 times higher risk of testicular germ cell tumor.

Driving: Marijuana use has a dose-dependent effect on driving speed, accuracy, and reaction

times. This risk appears to be compounded when marijuana is used in association with alcohol (Lenné et al. 2010; Ramaekers et al. 2004). A review of epidemiologic data showed a twofold increase in risk of a motor vehicle accident after cannabis use (Hartman and Huestis 2013).

Mental Health: While it is difficult to establish causality, marijuana use has been associated with a more than fivefold increase in reporting of depression and anxiety in young adults (Patton et al. 2002). Studies have found links between marijuana use and psychosis as well, though causality is difficult to determine (Caspi et al. 2005; Barkus 2016). Some patients likely use marijuana (and other substances) in attempts to self-medicate mental illness. Because mental illnesses are so frequently present in patients who use drugs, it is important to establish their presence in order to refer the patient for concurrent treatment of both mental illness and substance use.

Cognitive development: Research suggests that marijuana has deleterious effects on cognitive development. Several studies in animals have demonstrated long-term effects on memory and learning which are amplified when marijuana is used in the adolescent period (Gleason et al. 2012; Lisdahl Medina et al. 2007; Meier et al. 2012; Schweinsburg et al. 2008). A New Zealand study found an average decrease in IQ of 8 points in adults who were heavy marijuana users during adolescence. This effect was not seen among marijuana users who began using during adulthood (Meier et al. 2012). Research has also have shown that marijuana users have lower likelihood of graduating high school (Macleod et al. 2004). Marijuana use has been associated with lower income, lower life satisfaction, unemployment, and welfare dependence (Brook et al. 2013; Fergusson and Boden 2008).

Sexual Health

Little research has suggested a relationship between marijuana use and sexually transmitted infection, although one study did demonstrate a correlation between the two in a survey of Black college students (Keen et al. 2016). It is generally felt that substance use may impair judgment, leading to riskier sex behaviors and, subse-

quently, sexually transmitted infections. The relationship between substance use and sexual assault is thought to be bi-directional, in that prior assault increases risk for substance abuse, and substance abuse increases risk for assault (Resnick et al. 2013). One study found that, of women reporting to an emergency room for rape-related medical exam, 54% reported alcohol use and 12% reported marijuana use at the time of assault (Resnick et al. 2012).

Policy and Legal Considerations

Marijuana has been legalized for medical use in 23 U.S. states as well as the District of Columbia and Canada. Four U.S. states (Colorado, Oregon, Washington, and Alaska) have legalized both medical and recreational marijuana use (Office of National Drug Control Policy n.d.). At the time of this publication, the use of recreational marijuana is illegal in Canada (Government of Canada 2016).

The American Academy of Pediatrics (AAP) updated their policy statement on marijuana use in youth in 2015 (Committee on Substance Abuse and Committee on Adolescence 2015). The AAP opposes marijuana use in children and adolescents under age 21 and opposes use of medical marijuana “outside the regulatory process of the U.S. Food and Drug Administration.” The AAP calls for further research into pharmaceutical cannabinoids. They also propose decriminalization of marijuana use, focusing instead on a treatment approach for marijuana use in young people. Lastly, they discourage marijuana use by adults in the presence of young people.

Screening and History

Providers should screen children and teenagers regularly for substance use during clinic visits. This should be done at well child checks as well as intermittently in subspecialty clinic visits. Providers should ask explicitly about use of a variety of substances including alcohol, cigarettes, marijuana, methamphetamines, cocaine, heroin, mushrooms, ecstasy, Molly,

Confidentiality and the Role of the Family

Disclosure of substance use by a minor does not legally require providers to make a report to authorities or parents, unless the patient is at immediate risk of serious harm. In some states, minors have the right to access substance use treatment services without consent from parents. In these cases, the provider may choose to assist the minor in accessing services confidentially. However, most therapy approaches for adolescent substance use rely heavily on family support; for this reason, providers should strongly encourage teen patients to discuss their use with their parents (National Institute on Drug Abuse [n.d.-b](#)). Providers can often help to facilitate this discussion in the clinic. Families can also be key players in motivating the teen patient to engage in treatment. In some states, parents may initiate drug treatment despite the teen's unwillingness to participate.

Treatment

Much of the approach to treatment for marijuana abuse is similar to treatment for abuse of other substances. Many youth who use marijuana have co-morbid use of other substances; treatment can target the use of multiple substances simultaneously. The National Institute of Drug Abuse recommends treatment of substance use even in adolescents with low levels of use due to the high likelihood of substance use impacting adulthood (National Institute on Drug Abuse [n.d.-b](#)).

For assistance in finding available drug treatment resources, we recommend utilizing the Substance Abuse and Mental Health Services Administration Treatment Locator at www.find-treatment.samhsa.gov or by calling 1-800-662-HELP (Substance Abuse and Mental Health Services Administration [n.d.](#)).

Detox/Withdrawal

Users often report symptoms upon quitting such as sleeplessness, irritability, decreased appetite,

Table 1.4 Drug treatment approaches (National Institute on Drug Abuse [n.d.-b](#))

| | |
|-------------------------|--|
| Behavioral approaches | Group therapy—employs CBT techniques |
| | Individual CBT |
| | Adolescent Community Reinforcement Approach (A-CRA) |
| | Contingency management |
| | Motivational enhancement therapy |
| | Twelve-step facilitation therapy |
| Family based approaches | Brief Strategic Family Therapy (BSFT) |
| | Family behavior therapy |
| | Functional family therapy |
| | Multidimensional family therapy |
| Medications | Available for opioid, alcohol and nicotine addiction |

anxiety, and cravings. No medical intervention is typically needed for this process.

Behavioral Treatment

No medications are available for treating marijuana addiction at this time. The mainstay of treatment is behavioral therapy. This typically is provided by a chemical dependency professional (CDP). See [Table 1.4](#) for a list of drug treatment approaches.

Patients with problematic use should undergo a drug and alcohol assessment to determine the appropriate level of treatment ([Table 1.5](#)). Level of treatment is determined by (1) the presence of other behavioral or emotional conditions, (2) motivation to change, (3) risk of relapse or continued drug use, (4) recovery environment (e.g. family, peer, school, community), (5) level of intoxication and potential for withdrawal, (6) presence of other medical conditions.

Support Groups

While not recognized as evidence-based treatment options, Narcotics Anonymous, Marijuana Anonymous, and other support groups offer social support and accountability to people who are undergoing (or have completed) treatment for

Table 1.5 Substance abuse treatment settings (National Institute on Drug Abuse [n.d.-b](#))

| Treatment setting | Description | Indication |
|---------------------------------|--|---|
| Drug/alcohol education | One-time session or limited series, often court ordered | Relatively isolated incident of drug-related infraction (legal, school-related, etc.) |
| Limited outpatient treatment | 1–2 sessions per week, usually individual, may involve family | Less severe addiction, few additional mental health issues, supportive living environment |
| Intensive outpatient treatment | 3+ sessions per week for several hours a day, often involving family | As above, possibly after failure of limited treatment |
| Partial hospitalization | Also known as “day treatment.” 4–6 hours a day, 5 days a week | Severe substance use disorders, safe to reside in home environment |
| Residential/inpatient treatment | 24-hour structured environment | Severe addiction and/or comorbid mental or physical health conditions that require 24 h supervision |

chemical dependency. Youth-specific groups are rare and youth often feel uncomfortable attending general meetings, however they are typically welcome to attend.

Resources for Patients

Providers may refer older adolescent patients or parents to the National Institutes of Drug Abuse (NIDA) website, www.drugabuse.gov, for more information on marijuana and other substances (National Institute on Drug Abuse [n.d.-a](#)). For younger adolescents, <http://kidshealth.org/en/teens/drug-alcohol/> is a site directed toward teenagers that answers drug and alcohol questions (TeensHealth [n.d.](#)).

Contraception

Seventy-one percent of youth have experienced coitarche by the age of 19 (Guttmacher Institute 2014). Although teen pregnancy rates have been declining steadily over the past 20 years, nearly 250,000 infants are born to adolescent mothers each year and over three-quarters of all adolescent pregnancies are described as unintended or occurring “too soon” (Office of Adolescent Health 2016). These rates are significantly higher in the U.S. than most other developed countries. Health care providers working with youth must ensure access to high-quality, reliable contraceptive counseling. Ideally, teens will access contraception prior to becoming sexually active.

Starting the Conversation

Providers can start by initiating a conversation with every teen. It is best to start the conversation by taking a general sexual history, as described in the “Sexuality” section of Table 1.2 in this chapter. If a teen is not sexually active, the provider can initiate a conversation about healthy relationships, providing positive reinforcement that abstinence is a safe and healthy sexual choice. Also remind the teen that if and when they choose to become sexually active, if they are not seeking a pregnancy it is best to initiate contraception prior to their first episode of intercourse. Providers can invite teens to come back and discuss this further at another visit.

If a teen is sexually active, the provider should ask if they are currently trying to get pregnant (for females with any male partner(s)) or currently seeking to become a father (for males with any female partner(s)). If no, the provider should probe further to find out what the patient and their partner(s) are doing to prevent a pregnancy. Assess the teen’s level of knowledge around various contraceptive methods, as well as any contraceptive methods they have used and their satisfaction with these methods.

Understanding Eligibility for Various Methods

Next, assess what options are medically viable for the patient. The Centers for Disease Control publish U.S. Medical Eligibility Criteria for

Contraceptive Use (USMEC), which can easily be accessed free-of-charge online, or downloaded as an app onto a smartphone (Centers for Disease Control and Prevention 2010). The USMEC provides evidence-informed guidance around the use of various contraceptive methods in patients with a variety of medical condi-

tions, lifestyle factors and family history. Some of the most commonly encountered conditions among adolescents that have an impact on contraceptive decision-making are listed in Table 1.6; this is not an exhaustive list so please refer to the full USMEC guidelines for individual patients.

Table 1.6 Commonly encountered conditions among adolescents that have an impact on contraceptive decision-making

| Condition | Special considerations |
|--|--|
| Obesity | Most contraceptive options have not been studied specifically in obese and/or morbidly obese women. It is generally accepted that even if there is a decrease in efficacy for some methods, use of one of these methods will still provide contraceptive benefit. Women with obesity should receive full options counseling (Robinson and Burke 2013; McNicholas et al. 2013) |
| | IUD (copper and levonorgestrel) effectiveness does not vary with BMI category. This may be a particularly good option and is Category 1 per the USMEC (Centers for Disease Control and Prevention 2010; Robinson and Burke 2013; Reifsnider et al. 2013) |
| | Etonorgestrel levels decline with increasing body weight in individuals with the etonorgestrel implant. The implant may need to be replaced sooner than the standard 3 year interval. However, one study found no significant differences in failure rates by body mass (Xu et al. 2012) |
| | Serum medroxyprogesterone levels decline with increasing body mass index in patients using depot medroxyprogesterone acetate (DMPA) (Robinson and Burke 2013). DMPA has been associated with weight gain among obese adolescents (Centers for Disease Control and Prevention 2010) |
| | It remains unclear if there is a difference in efficacy for the combined hormonal patch, ring or pill. The risk of venous thromboembolism (VTE) is increased in women with obesity, but combined methods remain category 2 per the USMEC (Centers for Disease Control and Prevention 2010; Robinson and Burke 2013; Reifsnider et al. 2013) |
| Patients at risk for low bone mineral density (e.g., anorexia nervosa, wheelchair bound) | DMPA use can lead to a loss of bone mineral density (BMD). BMD can be regained after discontinuation, but the full implications of use (especially long term use) are unknown. This is not an absolute contraindication to use of DMPA among adolescents with or at risk for low BMD (Centers for Disease Control and Prevention 2010; American College of Obstetricians and Gynecologists 2006) |
| Smoking | The risk of VTE is increased in smokers using combined hormonal contraceptives. In the adolescent age group, this remains category 2 (Centers for Disease Control and Prevention 2010). Advise smokers to quit; advise non-smokers not to start |
| Hyperlipidemia | Initiation of combined hormonal contraceptives is category 3 (Centers for Disease Control and Prevention 2010) |
| Hypertension | Varies by level of blood pressure control; however, combined hormonal contraceptives are generally considered category 3 or 4, as estrogen may exacerbate hypertension (Centers for Disease Control and Prevention 2010) |
| Known thrombogenic mutation | Combined hormonal contraceptives are category 4 (Centers for Disease Control and Prevention 2010) |
| Depressive disorders | All methods are category 1 (Centers for Disease Control and Prevention 2010) |
| Diabetes mellitus | All methods are category 1 in patients without vascular disease (Centers for Disease Control and Prevention 2010). When vascular disease is present, consult the USMEC directly |

Table 1.6 (continued)

| Condition | Special considerations |
|------------------------|--|
| Anemia | A single, small study showed a potential decrease in bone pain among patients with sickle cell disease using DMPA (Manchikanti Gomez et al. 2007) |
| | The copper IUD may cause heavy menses and worsen anemia. This is category 2 (Centers for Disease Control and Prevention 2010) |
| | Combined hormonal contraceptives are category 2 for patients with sickle cell disease (Centers for Disease Control and Prevention 2010). Some providers and patients avoid these due to the increased risk of VTE |
| Migraine headaches | With aura: Combined hormonal contraceptives are category 4 due to increased risk of stroke (Centers for Disease Control and Prevention 2010) |
| | Without aura: Combined hormonal contraceptives are category 2 for initiation; category 3 to continue if migraines develop or worsen on the method (Centers for Disease Control and Prevention 2010) |
| Use of anticonvulsants | Phenytoin, carbamazepine, barbiturates, primidone, topiramate, and oxcarbazepine decrease efficacy of combined oral contraceptives and progestin only oral contraceptives. Use of these methods is category 3 (Centers for Disease Control and Prevention 2010). If used, contraceptive efficacy may be diminished and a minimum 30 mcg of ethinyl estradiol should be chosen |
| | Lamotrigine levels decrease while on combined oral contraceptives, and can then significantly increase during placebo week. Use of this method is category 3 (Centers for Disease Control and Prevention 2010). If used, consult with the patient's neurologist and consider using continuously to avoid alterations in lamotrigine levels during the placebo week once a steady state is achieved |
| HIV/AIDS | Recommendations vary based on stage of illness and medications. Consult the USMEC |

Category 1 = no restrictions; 2 = benefits generally outweighs risks; 3 = risks generally outweighs benefits; 4 = contraindicated

Describing Contraceptive Options to Teens

Once you have determined what options the patient is eligible for, describe the patient's contraceptive options to her in order of most effective to least effective (Table 1.7). Uptake tends to be higher for the options presented earliest in the conversation. Always recommend that the patient use barrier protection for STI prevention, in addition to any other form of contraceptive the patient chooses.

Long-Acting Reversible Contraception (LARC)

LARC should be the first option that is discussed with most adolescent patients. This recommendation is now supported by the AAP and the American Congress of Obstetricians and Gynecologists (ACOG) (American Academy of Pediatrics Committee on Adolescence 2014; American College of

Obstetricians and Gynecologists 2012). LARC methods include IUDs (copper or levonorgestrel (LNG)-containing) and the implantable levonorgestrel rod. LARC methods are the most effective forms of contraception (other than abstinence) currently available. Return to conception is possible immediately upon device removal.

Despite recommendations to use LARCs as first-line methods among teens, many pediatric and adolescent health providers are less familiar with these methods. A recent review article highlighted a number of barriers that led to limited uptake of these reliable, first-line contraceptive devices, including: provider attitudes, misconceptions and lack of training; cost; concerns around consent and confidentiality; and patient misconceptions and lack of awareness (Kumar and Brown 2016).

Systems are in place to address barriers around cost, consent and confidentiality. Per the Affordable Care Act mandate in the US, contra-

Table 1.7 Effectiveness of contraceptive options

| Most Effective |
|--|
| Abstinence |
| Long-Acting Reversible Contraception (LARC): Intrauterine Devices (IUDs), implantable rods Depot-medroxyprogesterone acetate (DepoProvera®, “the shot”, “depo”) |
| Etonorgestrel-ethinyl estradiol vaginal ring (NuvaRing®, “the ring”); (contains estrogen and a progestin) |
| OrthoEvra® patch (contains estrogen and a progestin) |
| Combined hormonal oral contraceptives (contains estrogen and a progestin) |
| Progestin-only oral contraceptives |
| Barrier protection (most commonly, male condoms) |
| Other (e.g., you can consider discussing natural family planning, withdrawal, etc. depending on patient— these are all better than nothing!) |
| Nothing |
| Least Effective |

Note: permanent sterilization is generally not offered as an option to adolescent patients

ception (including LARC) is now generally covered by insurance with no out-of-pocket cost unless the patient’s insurance company has an exempt status. With regard to confidentiality and consent, we gently encourage teens to involve their caregivers in all health-related decision-making, including reproductive health, when it is feasible and safe for them to do so. Some adolescents will do this on their own, while others will request that their provider help guide the discussion. However, many youth do not wish to discuss their reproductive health with their caregiver(s). Most jurisdictions allow adolescents to consent to their own reproductive healthcare. Providers should familiarize themselves with the minors’ consent laws in their own jurisdiction of practice. These are summarized by the Guttmacher Institute (www.guttmacher.org) and through the Center for Adolescent Health and the Law (<http://www.cahl.org>).

Providers should also be aware that some insurance providers send itemized bills, which may be addressed to the parent, to the home. This can lead to an accidental breach of confidentiality. If this is a concern to your patient, you may need to investigate the policies of their insurance provider and/or understand the billing policies of the clinic where the device will be

placed. Many jurisdictions provide funding to certain clinics where youth may be able to access contraceptive services without using their insurance.

If you are unable to place LARC devices in your office, consider accessing the website www.bedsider.org for a list of providers who place LARCs. First and foremost, it is important that providers understand LARC options and provide accurate, positive messaging around LARC for the teens with whom they are working.

A review of the various LARC options is available in Table 1.8.

Non-LARC Options

The other contraceptive methods mentioned above have been on the market for several decades with relatively high uptake among teens and providers. These methods will not be covered in detail in this update book. If providers or adolescents desire more information on any of the methods available, there are now a number of high-quality, internet based resources that can easily be accessed. www.youngwomenshealth.org is factually accurate and suitable for teens of all ages. www.bedsider.org is another excellent source of reliable information, presented in a teen-friendly format that includes “hooks” such as jokes, videos, infographics, and testimonials. It is a sex-positive site and potentially not developmentally suitable for young adolescents. This site can also be used to get free text reminders sent to patients’ phones for birth control pills, appointments and refills. A portion of the site is geared toward providers.

Emergency Contraception

There are currently four methods of Emergency Contraception (EC) available in the United States: the copper IUD, ulipristal acetate (UPA), levonorgestrel EC (LNG-EC) and the Yuzpe method.

The copper IUD can be placed within 5 days of unprotected intercourse. This is the most effective EC (Cheng et al. 2012). The copper IUD has the added benefit of providing ongoing contra-

Table 1.8 Long-acting reversible contraceptive options

| | Procedure notes | Mechanism of action | Duration of contraceptive effectiveness | | Other |
|--|---|---|---|---------|---|
| Copper IUD (ParaGuard®) | Placement typically is done as an office procedure (though in special circumstances, such as girls with developmental delays, it can be done under anesthesia). Placement is typically well tolerated, though most | Copper ions kill sperm; may disrupt implantation though this is debated | 10 years | | Hormone free Menses continue with same regularity; may be heavier Can be used as emergency contraception if placed within 5 days of unprotected intercourse Can be placed immediately postpartum |
| Levonorgestrel (LNG) IUD (Mirena®, Liletta®, Kyleena®, and Skyla®) | patients experience some cramping at the time of the procedure. While it can vary by provider and patient, the actual procedure usually only takes a few minutes. There is an increased risk of infection during the first approximately 20 days after placement, likely related to introduction of microbes during the procedure. Ongoing increased risk of infection was a concern with a type of IUD that is no longer on the market due to the filaments that were used in the string of the IUD. Current IUDs have monofilament strings and do not promote infection. IUD's are considered safe even in patients with history of prior infection or multiple partners. Patients should be screened for gonorrhea and chlamydia at the time of placement, and treated if infection is present | Thickened cervical mucus diminishes number of sperm passing through cervix LNG causes thinning of endometrium and environment not amenable to sperm survival, fertilization or implantation | Liletta® (19 µg per day) Mirena® (20 µg per day) | 5 years | Very low systemic hormone levels. Also highly effective (more than pill) at treating dysmenorrhea and at treating heavy menstrual bleeding/abnormal uterine bleeding Periods typically become lighter and less frequent over time (approximately 90% of patients). Approximately 40% of patients will develop amenorrhea |
| | | | Skyla® (14 µg per day) | 3 years | Even lower systemic hormone levels than Mirena/Liletta. Most patients continue to have regular periods |
| Etonorgestrel (ENG) implant (Nexplanon®) | Inserted into arm, procedure is very simple with minimal discomfort and is typically done in the office. Training is easy to obtain; needs to be done through the pharmaceutical company | Thickened cervical mucus diminishes number of sperm passing through cervix ENG effects within uterus leads to thinning of endometrium and environment not amenable to sperm survival, fertilization or implantation Inhibition of ovulation | 3 years | | Radio-opaque |

ceptive benefit for up to 10 years. Use of this method requires access to a provider trained to place the copper IUD within 5 days of unprotected intercourse, and willingness/desire of the young woman to undergo the procedure.

Ulipristal acetate (UPA) 30 mg is the most effective oral form of EC (Glasier et al. 2010). UA is a selective progesterone receptor modulator and can prevent or delay ovulation even after luteinizing hormone (LH) starts to peak (Gemzell-Danielsson 2010). UPA is therefore the superior option for use right around the time of ovulation. UPA requires a prescription from a provider in some jurisdictions and can be dispensed directly by the pharmacist in other jurisdictions. UPA is not stocked by all pharmacies. It can be obtained online and shipped overnight through PRJKT RUBY (www.prjkruby.com).

Levonorgestrel (LNG-EC) 1.5 mg is available without a prescription to males and females, and is the most widely used form of EC in the United States. It is less expensive than UPA. LNG-EC is most effective when used within 72 h of unprotected intercourse, but maintains some efficacy out to 5 days (120 h); LNG-EC is not effective once LH starts to peak (Gemzell-Danielsson 2010). LNG-EC is superior to the Yuzpe method, which involves taking multiple combined hormonal contraceptive pills 12 h apart. Dosing regimens by type of OCP can be found at www.bedsider.org, but are not included here because this method is generally no longer utilized due to the wide availability of other, more effective options.

The risk of pregnancy is highest around the time of ovulation; sperm can live for up to 5 days in the reproductive tract. Ovulation occurs 14 days prior to the menstrual period. Predicting the date of the next menstrual period, and therefore determining the expected fertile window, can be more difficult in teens who are not yet regular and are still having anovulatory cycles. However, if the patient is felt to be within her fertile window, we recommend more strongly considering the IUD or UPA even if somewhat more difficult to obtain. The effectiveness of medical EC is also diminished in women with a BMI >25 kg/m²; the copper IUD remains the most effective option, but

among medication options, UPA is preferred (Glasier et al. 2011). For all young women, regardless of fertility timing or weight status, the use of LNG-EC is preferred over nothing. Obtaining a copper IUD or UPA is often more difficult and costly than obtaining LNG-EC, and this must be taken into consideration.

EC is not intended for use as regular contraception. Adolescents seeking EC should be counseled on their options for reliable contraception moving forward, as well as on the benefits of consistent condom use.

Heavy Menstrual Bleeding

The AAP and ACOG have jointly endorsed a statement describing the importance of considering menstruation to be a “vital sign” among adolescent girls, as a means by which to assess development and to identify pregnancy and a number of potentially serious pathologies including nutritional problems, endocrinopathies, and bleeding disorders (American College of Obstetricians and Gynecologists 2015). The median age of menarche for girls in the United States is 12.43; 90% of all US girls have achieved menarche by age 13.75 (Chumlea et al. 2003).

Adolescent bleeding patterns may vary somewhat from adult patterns (Table 1.9). Anovulatory cycles are common in the first 1–5 years following menarche, with prevalence decreasing over time. Up to 85% of cycles may be anovulatory during the first year after menarche, and up to 44% by 4 years after menarche (Holland-Hall 2013). Anovulatory cycles can lead to irregular bleeding; being familiar with the range of adolescent menstrual patterns can help the clinician distinguish between normal and pathological bleeding.

Heavy menstrual bleeding (HMB) is a common presenting gynecologic complaint among adolescents. HMB can significantly impact a teen’s quality of life, including school attendance and sports participation, and can lead to severe anemia. Heavy menstrual bleeding has been defined as prolonged bleeding (more than 7 days) or blood loss greater than 80 mL per cycle among adult women, but these may not be appropriate

Table 1.9 Normal menstrual cycles in adolescent girls (American College of Obstetricians and Gynecologists 2015)

| | |
|--------------------------|-------------------------------------|
| Menarche (median age) | 12.43 years |
| Mean cycle interval | 32.2 days in first gynecologic year |
| Menstrual cycle interval | Typically 21–45 days |
| Menstrual flow length | 7 days or less |
| Menstrual product use | 3–6 pads or tampons per day |

Table 1.10 Warner Criteria-Factors correlated with blood loss >80 mL per cycle

| |
|--|
| 1. Rate of changing sanitary products (>every 1–2 h) |
| 2. Clot size >30 mm |
| 3. High total number of products used |
| 4. Subnormal ferritin level |
| 5. Need to change sanitary protection during the night |

cutoffs for adolescents and are of questionable clinical significance even among adults (Warner et al. 2004a). Regardless, quantifying blood loss can be difficult among both adolescents and adults. The Warner criteria (Table 1.10) list clinical features that are associated with blood loss of >80 mL per cycle (Warner et al. 2004b). The Pictorial Bleeding Assessment Chart (PBAC) is a scoring tool that is widely used for adult women to identify those with clinically significant bleeding (Higham et al. 1990). Both of these assessment tools were developed in adult women and might not be as accurate in teens.

Evaluation

In the absence of any validated screening tool for adolescents, clinicians are called upon to take a careful and detailed history from adolescent patients presenting with a complaint of heavy menstrual bleeding. History should include all of the factors described above in Tables 1.9 and 1.10. Cycle interval is standardly defined as the interval from first day of one menstrual period to the first day of the next menstrual period. It can be helpful to have patients give the date of the

first day of bleeding for their last few cycles, if possible. Many free smart phone apps are available for girls to track their periods.

Clinicians should inquire if the patient perceives their flow to be normal, heavy or light, and further define this by asking how often pads or tampons are changed; absorbency level of pads or tampons that are used (e.g., super plus, super, regular, light, overnight, etc.); level of soiling of the product when changed (this may be aided by use of the PBAC, which is readily available online using any search engine); history of soaking through pad or tampon in 1 hour or less; need for simultaneous use of a pad and a tampon to prevent soaking through onto clothing or bedding; passing clots greater than the size of a quarter or large grape; or flooding or gushing (Holland-Hall 2013). It is also helpful to define if the patient’s bleeding pattern has changed dramatically over time.

If the patient does have a bleeding pattern that is clinically abnormal, the clinician should proceed with a comprehensive evaluation. The differential diagnosis for heavy menstrual bleeding is extensive and a thorough history and examination can help guide further testing. In 2011, the International Federation of Gynecology and Obstetrics proposed use of the PALM-COEIN mnemonic (**p**olyp, **a**denomyosis, **l**eiomyoma, **m**alignancy and hyperplasia, **c**oagulopathy, **o**varian dysfunction, **e**ndometrial, **i**atrogenic and **n**ot yet classified) to classify potential causes of abnormal uterine bleeding and create consistent nomenclature among providers (American College of Obstetricians and Gynecologists 2013). The etiologies included in the “PALM” part of the mnemonic are rare in adolescents, but this may serve as a familiar framework for some clinicians and reminds pediatric and adolescent clinicians to attend to anatomic causes. A more detailed list of causes of abnormal uterine bleeding in adolescent girls is included below (Table 1.11).

History

A careful review of systems can substantially help the clinician narrow down their differential diagnosis. Questions should include screening for

possible complications of heavy bleeding, namely anemia and intravascular depletion. The clinician should also inquire about any other history of heavy bleeding: frequent or prolonged epistaxis (especially if nosebleeds have required medical intervention such as cautery or packing); gum bleeding; prolonged bleeding after cuts; rectal bleeding; ecchymoses, purpura and/or petichiae; and deep tissue bleeding. A comprehensive review of systems that includes inquiry about weight gain or loss; fatigue; constipation or diarrhea; dry skin/hair/nails; development of acne and/or hirsutism; changes in vocal tone; visual field abnormalities; palpitations; level of stress; lymphadenopathy; abdominal masses; abdominal or pelvic pain; vaginal discharge; dyspareunia; urinary symp-

toms; joint hypermobility; and cardiac symptoms can also provide clues toward a potential etiology. Dyspareunia, vaginal pain or pelvic discomfort may point to anatomic or infectious etiologies.

A complete past medical history should be performed. Ask about any chronic illnesses, history of chemotherapy or radiation, and history of hepatic or renal disease. The medical history should also include a pregnancy history and any history of genital trauma. Patients should be specifically asked about any surgical history, including if they experienced abnormal bleeding with surgery. In particular, brisk post-operative bleeding following a tonsillectomy, adenoidectomy, or oral surgery may be a clue to an underlying bleeding disorder, particularly if the patient

Table 1.11 Differential diagnosis for abnormal uterine bleeding in adolescents (American College of Obstetricians and Gynecologists 2015; Emans and Laufer 2012)

| |
|--|
| Anatomic (eg, carcinoma, endometrial hyperplasia, hemangioma, polyp, sarcoma) |
| Anovulatory cycles |
| Immature hypothalamic-pituitary-ovarian axis |
| Hyperandrogenic anovulation (eg, polycystic ovary syndrome, congenital adrenal hyperplasia, androgen-producing tumors) |
| Bleeding disorder (eg, hemophilia, hepatic failure, platelet function disorder, thrombocytopenia, von Willebrand disease) |
| Foreign body or trauma |
| Hypothalamic dysfunction |
| Eating disorder |
| Significant, rapid weight loss |
| Stress-related |
| Idiopathic |
| Iatrogenic |
| Intrauterine device |
| Medication (eg, androgens, anticoagulants, antipsychotics, chemotherapy, hormonal contraceptives, selective serotonin reuptake inhibitors) |
| Radiation |
| Other endocrine disorders |
| Hyperprolactinemia |
| Thyroid disease |
| Cushing syndrome |
| Primary ovarian insufficiency |
| Pregnancy or pregnancy-related complications |
| Sexually transmitted infections |
| Systemic disease |
| Celiac disease |
| Chronic kidney disease |
| Diabetes mellitus |
| Systemic lupus erythematosus |

required a return to the operating room or transfusion. A complete medication list should be obtained, including prescription, over the counter, and herbal preparations. Among adolescents, two commonly encountered classes of medications that can impact bleeding include non-steroidal anti-inflammatory drugs (NSAIDs) and selective serotonin reuptake inhibitors (SSRIs). NSAIDs tend to diminish menstrual bleeding, though may worsen menstrual bleeding in individuals with bleeding disorders.

Social history should include a complete sexual history, including screening for abuse or trauma. Family history should include questions about bleeding disorders and blood clots or clotting disorders, as well as the menstrual and pregnancy histories of female relatives. Providers should ask if any males have had bleeding with circumcision, and if any relatives have had heavy bleeding with surgeries, in particular tonsillectomy and adenoidectomy or dental extractions.

Physical Exam

Similar to the review of systems, the physical exam should be comprehensive. The clinician should carefully attend to any signs of cardiovascular compromise related to the heavy bleeding. Decision of whether or not to pursue a pelvic exam should be guided by history. An external genitourinary exam should be performed in most cases, assessing for general anatomy, including clitoromegaly; lacerations or lesions; and evidence of urethral or rectal source of bleeding. An internal exam can provide helpful information, particularly if you are suspicious for an anatomic or infectious cause, but is neither necessary nor tolerable for all patients. A vaginal exam should not be performed on a patient who does not willingly assent to the procedure. Some virginal patients will tolerate a single-digit vaginal exam to assess for foreign body or any palpable masses. Most sexually active patients and some virginal patients (especially those who use tampons) will tolerate a speculum examination. If a patient is actively bleeding, it is helpful to have multiple long, cotton-tip applicators on hand to remove

blood from the vaginal vault in order to allow visualization of internal structures. If tolerated, a bimanual examination should also be performed to assess for pelvic masses.

Testing

Findings from the history and physical examination should be used to guide laboratory testing (see Table 1.12). In patients complaining of heavy bleeding, but for whom a normal bleeding pattern is described, reassurance without any additional testing may be appropriate. Otherwise, at a minimum, a urine pregnancy test and complete blood count should be obtained in nearly every patient with the complaint of heavy bleeding. If there is concern for significant anemia and/or cardiovascular compromise, a type and screen or type and crossmatch should also be obtained. It is better to obtain additional testing prior to transfusion, but treatment of an acutely unstable patient should never be delayed solely to perform additional testing. Clinicians can consider obtaining a ferritin for patients in whom the history suggests clinically significant bleeding and the clinician is suspicious for a possible bleeding disorder.

Management

The first role of the clinician is to triage the patient to an appropriate level of care. The vast majority of patients with heavy menstrual bleeding can be managed in the outpatient setting, but some will require emergency intervention and/or hospitalization. Patients with ongoing, severe bleeding and moderate anemia are usually stabilized in the hospital. Exact cutoffs vary somewhat by institution and situation, but we recommend consideration of hospitalization for patients with a Hgb <8–10, especially if bleeding is not slowing down; or if the patient has an unstable home situation, lack of clear follow up or inability to comply with medication regimen. For patients with a Hgb of 8–10, providers can consider close follow up and discharge home if bleeding is slowing, patient has transportation to return for follow up, and is easily accessible

Table 1.12 Laboratory and imaging studies for initial evaluation of patients with heavy menstrual bleeding

| | |
|---|---|
| All patients | CBC with differential—obtain in all patients, to assess hematocrit, platelet count, and rule out multi-cell line suppression that would suggest a hematologic malignancy Urine pregnancy test |
| Patients with no clear etiology identified on history or exam, OR with symptoms of thyroid disease | TSH with or without free T4 |
| Personal or family history suspicious for bleeding disorder | von Willebrand Screen (von Willebrand Factor antigen (vWF Ag), Factor VIII, vonWillebrand factor ristocetin cofactor activity)—It is preferable to order these tests before starting treatment, as estrogen can lead to elevation of vWF Ag and Factor VIII. An abnormal test result in the setting of estrogen use is likely a true positive, but a normal result may be a false negative. Test is most sensitive in first 3 days of menses, when estrogen and progesterone levels are at their nadir. In an acutely bleeding patient, treatment should not be significantly delayed to obtain the blood test PT, aPTT, fibrinogen Ferritin- increases sensitivity of screening for “true” heavy bleeding, even in the face of a normal hematocrit and hemoglobin TSH |
| Sexually active patients | Gonorrhea and chlamydia PCR (urine or vaginal) |
| Patients with evidence of hyperandrogenism (acne, hirsutism, clitoromegaly) or family history of PCOS | 17-OH-Progesterone DHEA-S Free and total testosterone |
| Patients with significant anemia and/or signs of cardiovascular compromise | Screen for bleeding disorder, as above Type and Screen or Type and Cross |
| Other considerations | Ultrasound—most providers do not get this first line unless history suggestive of an anatomic abnormality; would consider second line if patient not responding to therapy as expected LH, FSH—can be supportive of a PCOS diagnosis if ratio > 3:1; elevated FSH can suggest primary ovarian insufficiency and should be considered for first-line screening in patients with a history of malignancy, particularly if they had pelvic/abdominal radiation Liver Function Tests- generally second line if coagulation studies abnormal, along with bilirubin to assess synthetic function of the liver; or first line if history suggestive of hepatic disease Prolactin- particularly if periods irregular; more likely to cause hypomenorrhea than heavy menstrual bleeding |

with reliable phone number. Patients who are experiencing severe anemia, Hgb <7, pancytopenia, cardiovascular compromise (significant tachycardia, hypotension, persistently symptomatic orthostasis), or ongoing heavy bleeding should also be hospitalized.

Patients for whom the history reflects a bleeding pattern that actually seems normal can be provided with reassurance. However, if a teen’s bleeding pattern is bothersome and impacting her quality of life—even if within the realm of normal—it is quite reasonable to offer menstrual suppression.

Medical Options for Menstrual Suppression

Patients who report heavy bleeding, but are without significant anemia and/or are not actively bleeding, are candidates for a number of menstrual suppressive options. The 52 mg levonorgestrel-containing IUD is an excellent long-term option for menstrual suppression, leading to lightening of periods in about 90% of users, and amenorrhea for about 40% of users (Hidalgo et al. 2002). It should be noted that the IUD does not provide immediate changes to bleeding patterns, and many women

experience ongoing bleeding and spotting for the first few months after placement. Most women have experienced a reduction in bleeding by about 6 months. It is an effective option for adults, with studies showing that it is more effective than oral medication options (Matteson et al. 2013; Gupta et al. 2013). Although most studies on the use of this method for heavy menstrual bleeding have been done in adults, one small study in adolescents shows this to be a viable option for this age group as well (Adeyemi-Fowode et al. 2017) and we feel that this practice is acceptable and safe in adolescents.

Medication management is generally required to stop acute bleeding, and may be preferred by some patients even if they do not require acute intervention. Combined estrogen-progesterone contraceptive pills have been a mainstay of treatment for HMB for quite some time. For patients without significant, active bleeding, once daily pills usually suffice. Providers can talk with the patient about continuous cycling if the patient wishes to suppress menstruation completely. The pill can be dosed two- to three-times daily in patients who have acute bleeding but are being managed in the outpatient setting. For patients who are hospitalized with heavy bleeding, the combined pills can be given more frequently; however, many patients taking the pill at this frequency require an anti-emetic. OCPs can be given rectally if the patient cannot take the pill orally. We do not recommend intra-vaginal dosing, as the pill is generally expelled in patients who have heavy flow.

Tranexamic acid (oral) or aminocaproic acid (parenteral) are fibrinolysis inhibitors that are being used more frequently in lieu of, or in combination with, oral contraceptive pills. Studies show a reduction in bleeding by 30–55% with these medications (American College of Obstetricians and Gynecologists 2013). Tranexamic acid (trade name Lysteda) is a good option for patients who wish to avoid the use of hormonal medications and do not want an IUD, or for those who do not want daily medication dosing. It is taken only during menses, and does not provide menstrual suppression. For acute bleeding, many providers will combine tranexamic

acid with OCPs. This allows for less frequent and/or lower dosing of estrogen, reducing unpleasant estrogen-related side effects such as nausea. At present, combined use of estrogen and fibrinolysis inhibitors has not been well studied and patients should be counseled about the theoretical increased risk of clots. It is not known how this risk directly compares to the risk of clot with very high-dose estrogen.

Intravenous equine estrogen remains an option for patients who cannot tolerate oral estrogen or have ongoing bleeding even with frequent dosing of oral contraceptive pills. Many institutions are moving away from this in favor of combining fibrinolysis inhibitors with combined oral contraceptives, but this is still an effective, reasonable option that remains part of the standard treatment pathway in many institutions. Patients who cannot take estrogen can use progesterone-only methods such as medroxyprogesterone acetate or depot medroxyprogesterone acetate. As with combined oral contraceptive pills, dosing regimens are readily available (American College of Obstetricians and Gynecologists 2013; Emans and Laufer 2012).

Non-steroidal anti-inflammatory medications (NSAIDs) such as naproxen or ibuprofen can slow menstrual bleeding due to their anti-prostaglandin effects, and may suffice as monotherapy for patients with mild complaints about their bleeding, or in combination with the IUD or a hormonal method. However, NSAIDs may increase bleeding in women with a bleeding disorder so should be avoided in women with known/suspected coagulopathy.

In rare instances, a procedural intervention such as balloon tamponade is required. Surgical intervention such as dilatation and curettage, endometrial ablation or hysterectomy are generally reserved only as a last-resort and are rarely indicated or necessary in the adolescent population. A gynecologist and a hematologist should be involved in cases where bleeding is refractory to medical treatment.

Additional Treatment Considerations

All patients with low hemoglobin and/or low ferritin should be started on iron. Compliance with

prescribed iron regimens is variable; patients should be warned about potential side effects (constipation and GI upset) and offered gentle stool softeners such as docusate, or bulking agents such as polyethylene glycol, if they are prescribed high dose iron supplementation. We recommend menstrual suppression (e.g., continuous cycling of OCP’s) until hemoglobin levels and iron stores are repleted, which may take several months. Some patients may not tolerate continuous cycling due to breakthrough bleeding; if this occurs, patients may stop pills for 3–5 days and then resume.

Patients who are diagnosed with an underlying bleeding disorder may benefit from alternative therapies, such as DDAVP. Many academic pediatric institutions now offer combined hematology-gynecology clinics to streamline management for adolescents with heavy menstrual bleeding and a known or suspected bleeding disorder. If no such clinic is available, providers managing the patient’s gynecologic care are encouraged to partner with a local hematologist to determine the optimal management strategy.

Caring for LGBTQ Teens

Providers who work with adolescents are likely to encounter patients who identify as gay, lesbian, bisexual, or transgender. Development of sexual orientation is often a long process that spans childhood, adolescence and early adulthood. Gender identity begins to develop in early childhood (Weinraub et al. 1984). As part of the HEADSS assessment, discussing gender identity be as simple as asking “do you think of yourself as male, female, both, or neither?”

Terminology

When talking with patients about gender and sexuality, it is important to keep in mind the distinction between biological sex, sexual orientation, gender identity, and gender expression (Fig. 1.2) (Trans Student Educational Resources n.d.).

Sex assigned at birth is the assignment of people as male, female, intersex, or another sex, typically based on chromosome testing or the appearance of external genitalia. People who are born with ambiguous genitalia may be termed as having *differences of sexual development (DSD)*, a topic not discussed in this chapter. People with

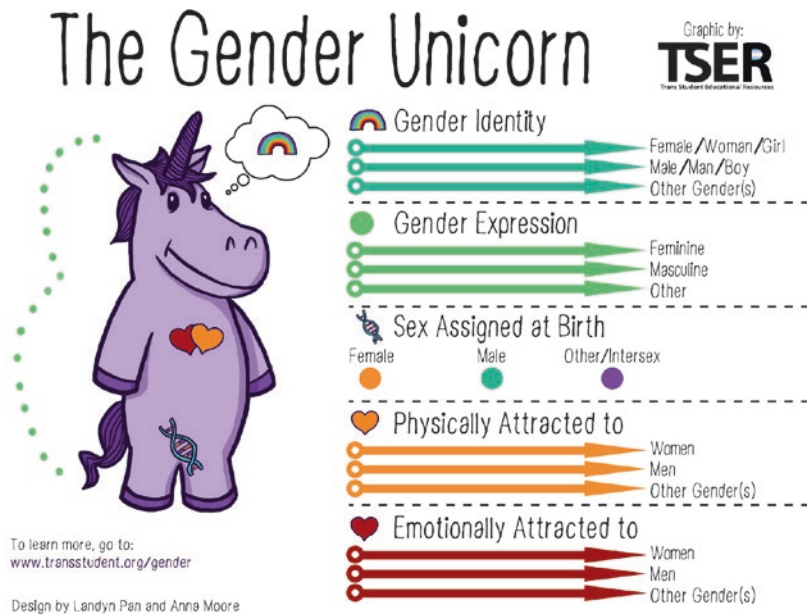


Fig. 1.2 The gender unicorn. Reproduced with permission from Trans Student Educational Resources (TSER) <http://www.transstudent.org/graphics>

DSD are often assigned a sex based on best judgment of their families and providers (McCann-Crosby and Sutton 2015)

Gender identity is the internal feeling of being male, female, neither, both, or another gender. Aside from identifying as male or female, terms that people may use to describe their gender include agender (neither male nor female), *genderqueer*, or non-binary, among others. A person whose gender identity is the same as their biological sex may be referred to as *cis-gender* or *gender conforming*, while a person whose gender identity does not align with biological sex may refer to themselves as *transgender* or *gender non-conforming*. A person who was assigned female sex at birth and identifies as male is referred to as a *transgender male*, while a person who was assigned male sex at birth and identifies as female is a *transgender female*.

Gender expression refers to the external presentation of gender using things such as dress, actions and demeanor. Gender expression does not always align with gender identity. For example, a person may wear masculine clothing but identify as a female.

Sexual attraction or *sexual orientation* are terms that describe which type of person someone is attracted to; this may be men, women, both, or neither. Adolescents may use the term *asexual* to describe having no physical attraction or *pansexual* to describe being attracted to people of all genders. Rather than trying to define a patient's gender and sexuality in the most accurate terms possible, we recommend having open discussions with patients to determine the words they use to identify themselves.

With adolescent patients, it is critical to assess which parts of the patients' gender and sexuality they have shared with family and friends. Patients may prefer to use different names and pronouns with providers than they do with family members.

Gender Dysphoria

The 5th Revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) defines Gender Dysphoria as "discomfort or stress caused

by a discrepancy between a person's gender identity and that person's sex assigned at birth" (American Psychiatric Association 2013). An important distinction should be made between *gender nonconformity* and *gender dysphoria*; not all people who identify as gender non-conforming have discomfort or stress associated with their gender identity. The diagnosis of *Gender Identity Disorder*, listed in the DSM-IV, is no longer utilized.

Research is lacking on the rates that gender dysphoria persists into adulthood. One study found that intensity of gender dysphoria in childhood correlated with persistence of gender dysphoria into adolescence (Steensma et al. 2013). Nearly all people who have gender dysphoria in adolescence have persistence of gender dysphoria into adulthood (de Vries et al. 2011).

Referral and Treatment

Each person with gender dysphoria should be treated with an individualized approach. Pediatric patients with gender dysphoria should be treated by trained providers, typically in the fields of pediatric endocrinology and/or adolescent medicine. In patients who present with gender dysphoria, referral at a young age is preferable. These patients can be followed closely, and when they begin having early signs of puberty, they may choose to pursue use of puberty-blocking medications (Kreukels and Cohen-Kettenis 2011). These medications are analogs of gonadotropin releasing hormone (GnRH) and work by blocking hypothalamic release of GnRH. Medications used include intramuscular leuprolide injections, subcutaneous triptorelin injections, and subcutaneous histrelin implants. These medications block progression of puberty in order to eventually allow an active decision about development of either masculine or feminine secondary sex characteristics.

Based on published guidelines, many providers wait until adolescents reach 16 years of age to begin cross-gender hormones, however some providers are beginning to provide hormone therapy at a younger age in order to allow patients to progress through puberty along with their peers

(World Professional Organization for Transgender Health 2012). In people assigned female sex at birth with gender dysphoria, suppression of menstruation with hormonal contraception may provide some relief of dysphoria. Surgical interventions are usually performed after patients reach adulthood, and patients should be referred specifically to surgical specialists with experience working with transgender patients.

Many people who have significant gender dysphoria can benefit from psychotherapy. Therapists can provide support to patients in navigating relationships with loved ones, man-

aging the stress of gender transition, and making the decision to pursue medical treatments such as cross-gender hormones and surgical interventions (both of which have some level of irreversible effects). It is important that patients understand that the goal of psychotherapy is to manage the stress, stigma and discomfort associated with gender nonconformity, *not* to change or influence the patient’s gender identity.

Not all patients will require all of the management options available, and the order in which these options are pursued may vary (Table 1.13).

Table 1.13 Management of gender dysphoria (World Professional Organization for Transgender Health 2012)

| | |
|----------------------------------|--|
| Psychotherapy | Assistance with social transitions including gender expression and legal name/gender changes |
| | Support in family relationships |
| Hair removal | Waxing |
| | Electrolysis |
| Voice and communication therapy | |
| Pubertal blockers (GnRH analogs) | Leuprolide (Lupron-Depot®) intramuscular injection |
| | Histrelin (Supprelin LA®) implant |
| | Triptorelin (Trelstar®) subcutaneous injection |
| Menstrual suppression | Oral contraceptive pills |
| | Oral medroxyprogesterone |
| | Intrauterine device placement |
| | Vaginal ring (NuvaRing®) |
| | Depot Medroxyprogesterone Injection |
| Masculinizing hormones | Implantable, transdermal or parenteral testosterone |
| Feminizing hormones | Androgen-blocking medications (i.e. spironolactone) |
| | Oral, transdermal, or parenteral estradiol |
| Feminizing surgeries | Facial feminization surgery |
| | Thyroid cartilage reduction |
| | Voice surgery |
| | Breast augmentation |
| | Penectomy |
| | Orchiectomy |
| | Vaginoplasty |
| | Clitoroplasty |
| | Vulvoplasty |
| Masculinizing surgeries | Voice surgery |
| | Mastectomy |
| | Vaginectomy |
| | Hysterectomy |
| | Salpingo-oophorectomy |
| | Phalloplasty |
| Scrotoplasty | |

Sensitive Care

There are a number of measures that providers can take to ensure a safe and comfortable environment for LGBTQ patients (Gridley et al. 2016). Clinics may choose to include open-ended questions on intake forms to allow patients to describe their own gender, rather than offering only a few options to be selected. Clinic staff can ask patients which pronouns they prefer—she/her, he/him, they/them, or another option. Providers can make efforts to assess the patient's gender identity and sexual orientation privately, knowing that a physician may be the first person with whom a youth feels comfortable discussing their sexuality or gender identity. Other measures that providers can take to maintain a welcoming environment for LGBTQ youth and families include providing gender-neutral bathrooms and wearing or posting images that indicate that the clinic is an LGBTQ-friendly space.

Other Health Considerations in LGBTQ Patients

Regardless of whether an LGBTQ patient is referred for specialty care, primary care providers should continue to manage these patients for their general healthcare needs.

One issue of importance is sexual and reproductive healthcare. Girls who identify as lesbians should be offered routine STD screening, and birth control options should be reviewed and encouraged. Teens identifying as lesbian may sometimes have physical relationships with men and have been shown to have higher risk of pregnancy than teen girls identifying as heterosexual (Lindley and Walsemann 2015). Risk of STDs with oral sex should be reviewed and barrier methods such as dental dams should be provided and encouraged.

Men who have sex with men (MSM) are at high risk for STDs and should be screened frequently using the CDC guidelines for STD prevention (Centers for Disease Control and Prevention 2015). This should include anal gonorrhea and chlamydia screening. MSM and transgender people who have sex with men should be

offered PrEP, a medication which can be taken daily to prevent HIV. This is especially important in those who have unprotected anal intercourse, which confers a high risk of HIV.

Transgender males should have regular STD screening, and providers should continue to consider gynecologic etiologies if pelvic symptoms arise. Transgender males should receive ongoing birth control counseling and management, and should have routine pap smears starting at age 21.

LGBTQ youth are at high risk for family conflict and homelessness (Rice et al. 2013). We recommend assessing patients' living situation to ensure they have stable housing and safe relationships with family members. We also recommend assessing whether LGBTQ youth are being sexually exploited. After asking whether the patient is sexually active, providers may ask "have you ever had sex in exchange for drugs, money, or other things you needed?"

LGBTQ youth are also at high risk for substance abuse, depression, and suicidality, especially if their sexuality or gender identity are not supported by friends or family (Puckett et al. 2016; Aitken et al. 2016). While these issues are typically assessed in the HEADS assessment, providers should remain attuned to the fact that LGBTQ youth are at higher risk for complications or escalation of what might be considered mild mental health issues or substance abuse. In transgender patients, psychological well-being is often improved by treating gender dysphoria (through methods listed in Table 1.13), however it is important to diagnose and treat co-morbid mental illness as well (de Vries et al. 2014). Resources for transgender patients and their families include:

- Refuge Restrooms: Smartphone app and website to search for gender-neutral bathrooms
- www.trevorspace.org: Social networking site for LGBTQ youth ages 13–24
- www.thetrevorproject.org: or 866-488-7386: 24 hour crisis line for LGBTQ youth
- www.pflag.org: A national organization with local chapters to support LGBTQ people and their families. Many chapters have support groups.

Media and Adolescents

Technology is pervasive—an unavoidable part of our modern environment. Today's youth have grown up in a world where personal devices, instant information, and virtual connection are the norm. Parents and providers alike may find it difficult to keep up with the nuances of new technologies, particularly in this era of very rapid change. Technological advances over the past few decades have come with new challenges and risks to adolescent health, in addition to creating novel avenues for adolescents' education, social connection, health promotion and civic engagement.

In earlier childhood, parents are encouraged to closely monitor their child's media usage. As young people progress through adolescence, however, this becomes more complicated. Teens often begin to use media more as contributors, rather than just consumers, and to build an individual online presence. As they move toward independence, adolescents make more autonomous media usage decisions. Parents are called upon to support their teen's transition to self-governing media usage, and providers may be asked to give advice on age-appropriate limits around media usage. Understanding the risks and benefits of media usage among teens can help providers and parents support the development of healthy media behaviors.

Risks

Excessive media use has been associated with numerous negative physical consequences, namely obesity and obesity-related metabolic complications, although prospective, longitudinal studies are an ongoing research need as most studies to date have been cross-sectional (van Ekris et al. 2016). There are negative correlations between screen time and sleep (Jacobson et al. 2016; Sayin and Buyukinan 2016), and texting while driving presents a significant threat to physical health related to increased risk of accidents (Jacobson et al. 2016).

An increasing body of international literature identifies problematic media use as an emerging area of concern in regard to social development and mental health, as well. Colloquially, this may be termed media "addiction." The DSM-V included Internet Gaming Disorder as an area for further study, but does not include internet or media addiction as official diagnoses. However, this remains an active area of ongoing research and is a recognized diagnosis in some parts of the world. Regardless, problematic or excessive use has been associated with increased depressive symptoms, higher level of school burnout, and lower measures of well-being (Mei et al. 2016; Chang and Hung 2012; Kawabe et al. 2016; Salmela-Aro et al. 2017).

Cyberbullying is a well-documented phenomenon, and is associated with increased risk of depression, self harm and suicidality (Jacobson et al. 2016; Moreno and Kolb 2012). Cyberbullying can present unique challenges due to the ability for this form of bullying to occur anytime, anywhere; remain anonymous; and rapidly reach large numbers of individuals.

Social media can create an illusion of what is normative, and lead teens to change their own behavior (Moreno and Kolb 2012). For example, exposure to pictures of friends engaging in substance use through social media is associated with higher levels of smoking and alcohol use, particularly among adolescents who do not have high numbers of drinking friends (Huang et al. 2014). Social media is also rife with negative messaging regarding weight and body image, which can promote disordered eating behaviors (Simpson and Mazzeo 2016; Holland and Tiggemann 2016; Sidani et al. 2016; Lydecker et al. 2016).

Current technologies have also created numerous new landmines in regard to sexual health and development of adolescents. The worlds of pornography, solicitation and sex trafficking of minors are rapidly evolving in response to new technologies. Predators have increased access and anonymity to take advantages of youth, who may not fully understand the implications of their online actions. Similarly, youth may be more

prone to engage in risky, inappropriate or even illegal sexual behaviors with and toward other teens, including solicitation, sexting, or photographing/video recording sexual acts.

Benefits

Of course, there are also benefits to the increase in technology. New technologies generate opportunities for social connection, civic engagement, and novel educational applications (Moreno and Kolb 2012). Given the prevalence of smartphones and personal devices, technology can also be used to help teens become more engaged in their health management. Websites (such as bedsider.org) and free phone apps can be used to provide reminders to take birth control or other medications. Numerous studies have employed technology to improve self management among teens with type-1 diabetes (Vaala et al. 2015). Health-related smartphone applications can be used to engage teens in health-related activities such as tracking their menstrual cycle, quantifying their exercise, adhering to a nutritional plan, or even working toward recovery from an eating disorder. A number of high-quality, health-related webpages, blogs and twitter feeds are geared toward improving access for adolescents, a population with notoriously low health care utilization. Some examples include:

- www.youngwomenshealth.org: General information on health for adolescent and young adult females
- www.youngmenshealthsite.org: General information on health for adolescent and young adult males
- <http://teenology101.seattlechildrens.org>: Adolescent health focused blog for parents of teens
- <https://twitter.com/TeenHealthGov>: Twitter feed managed by the Office of Adolescent Health
- <http://www.crisistextline.org/textline>: Web page including information on multiple crisis phone and text contacts

Technology offers many positive ways to interact with teens around their health. As this technology grows, providers must remain mindful of maintaining patient confidentiality. For example, more and more health systems are moving toward granting patients online access to all or part of their health record. Additionally, some clinics are moving toward the use of text for things such as appointment reminders, to follow-up on lab results, or to reinforce behavior change goals set during a visit. While the possibilities for technology-enhanced patient engagement are exciting, they are not always straightforward in this age group. At present, many questions remain unanswered in regard to managing parental and teen access to medical documentation, which may contain confidential information.

Providers' Use of Social Media

Patients have a window into their providers' worlds unlike ever before through the use of social media. Patient-provider relationships can be fractured if the patient or caregiver finds that the provider has created, endorsed or is identified in posts the patient finds inappropriate or offensive. Nonetheless, numerous studies have documented that providers are often using social media in ways that can negatively impact their reputation with patients, often without realizing that what they are posting is either public or potentially inappropriate/offensive (Jain et al. 2014; Langenfeld et al. 2015; Osman et al. 2012; MacDonald et al. 2010). When interacting with teens, we recommend working under the assumption that a patient or their caregiver could potentially discover anything the provider posts. Because adolescent health is so intimately related to risk behavior reduction, the safest policy is not to post or endorse anything that you would not feel confident having a patient or their caregiver view. While the decision on how any individual provider cultivates their online presence is up to the provider's discretion, online postings should never contain patient-related information, even if identifying information has

been removed. Many health care systems have developed their own policies for providers around social media use.

Basic Guidance for Parents and Patients

Providers should have conversations around media usage early and often. At a minimum, the AAP recommends asking the following two questions at every well visit with children and teens (American Academy of Pediatrics Council on Communications and Media 2013):

1. How much recreational screen time does your child or teenager consume daily?
2. Is there a TV set or an Internet-connected electronic device (computer, iPad, cell phone) in the child's or teenager's bedroom?

By opening the door to talking about media, providers can help both parents and teens understand the risks and benefits of media usage. Families should be encouraged to continue the conversation around media usage with each other at home.

We recommend encouraging caregivers to set aside devoted time to sit down with their adolescent to talk about media. Teens and their caregivers should create a set of mutually agreed upon

guidelines around media usage, as well as discuss anticipated consequences of failing to follow the set guidelines. Whenever possible, adolescents and their caregivers should engage in these discussions before expanding an adolescents level of autonomy over their own usage, such as prior to giving a child his or her own smartphone. However, it is never too late. We advise families to have these conversations when everyone is calm—not, for example, immediately after there has been a fight or major negative consequence related to media usage. Some families may prefer to formalize their written conversation with a written contract for certain items (such as a smartphone or a new video game console). Every family situation is different. We suggest giving families some starting questions to consider (Table 1.14).

Expectations will need to change as the teen matures, and because new issues will undoubtedly come up along the way as technology continues to evolve. Families may benefit from setting predetermined times to check in on how things are going and make any necessary adjustments. Some parents may seek guidance from their provider around what the answers to these questions should be, related to their child's developmental stage. The AAP "SafetyNet" website (<http://safetynet.aap.org/>) contains links to a number of high-quality websites for both parents and providers. The AAP's www.healthychildren.org website also has a section on media with useful tips for parents.

Table 1.14 Potential questions to guide discussion with families about media use

| |
|---|
| Where will the teen be allowed to use media devices? Only in public areas of the home? In their bedroom? Elsewhere? |
| When is media usage allowed? Where will the device be kept during times the adolescent is not supposed to be using it? |
| Are certain sites, apps, channels, games off-limits? |
| Are there restrictions on what or where the adolescent may post? |
| With whom may the adolescent engage virtually? Friends, family, friends-of-friends, others? What are family expectations around communication with individuals who are only known virtually? |
| How should the adolescent respond if they encounter something or someone that is inappropriate or threatening? If they experience or witness bullying, solicitation or someone else threatening to harm themselves or others? |
| What aspects of the teen's media usage will the parent have access to? |
| Who will pay any bills or fees associated with the media usage? |
| Are there other non-media related behaviors that could result in the device being taken away or usage restricted? |

Transitioning to Adult Healthcare

Healthcare providers play a critical role in preparing children for adulthood. Just as young children benefit from support and practice to develop motor, verbal and social skills, older children can benefit from support and practice in managing health-related and non-health-related responsibilities. This process must be started early in adolescence and evaluated often (American Academy of Pediatrics et al. 2011).

Development of adult skills in the healthcare setting is referred to by terms such as *transition*, *transfer of care* and *self-management*. The necessary set of skills and behaviors may be very different for adolescents with and without special healthcare needs.

While there are various methods to assess transition readiness and assist in transfer of care, there is currently no agreed-upon “best” tool or program (Chu et al. 2015; Davis et al. 2014).

Developing a Policy for Transition

We recommend developing a clinic-wide practice for addressing transition and transfer of care (American Academy of Pediatrics et al. 2011). www.gottransition.org has an array of resources available to assist with understanding and managing the transition process (Table 1.15) (The National Alliance to Advance Adolescent Health n.d.).

Guiding Transition in Clinical Practice

Clinicians can be involved in several aspects of the transition process for adolescents, including development of health values and health-related skills, finding an adult provider, and planning for future health needs.

Health Values

Beginning in early adolescence, young people begin to develop personal values about their health. These may include things like physical appearance, physical abilities, nutritional priorities, mood, and attitudes about the health impacts

of drug use and sexual activity. Meeting with teens alone beginning in early adolescence gives them an opportunity to express their own health priorities and concerns. In private meetings, providers can use motivational interviewing techniques to help direct adolescents to health topics of importance, including substance use, sexual health, and long term effects of any chronic diseases they may have. A gradual shift from parent-driven health concerns to teen-driven health concerns can help the teen patient to slowly understand that they have control over many aspects of their health. For adolescents with chronic illness, there is conflicting evidence regarding the prevalence of health risk behaviors (e.g. substance use, disordered eating, and sexual risk-taking) as compared to healthy adolescents (Suris and Parera 2005; Surís 2002; Valencia and Cromer 2000). Adolescents with chronic diseases may be particularly vulnerable to the effects of health risk behaviors, and require consistent health surveillance, which requires the coordination of efforts between primary care physicians and subspecialists (Lyons et al. 2014).

Health-Related Skills and Knowledge

Providers and parents/families should work together to assist teens with skill development. Some skills and knowledge, listed in Table 1.16, are important for general participation in the healthcare system (Moynihan et al. 2015). Patients with chronic diseases will have additional disease-related skills and knowledge to master during adolescence.

Transitioning Patients with Chronic Health Conditions

About 500,000 youth with special healthcare needs turn 18 each year (Data Resource Center for Child and Adolescent Health n.d.; <http://www.childhealthdata.org/learn/NS-CSHCN>). For patients with chronic diseases, subspecialty providers often play a key role in assisting teens in developing self-management skills. Often, however, primary care providers are available to meet with patients and families more frequently

Table 1.15 The Six Core Elements of Transition (The National Alliance to Advance Adolescent Health [n.d.](#))

| | |
|------------------------------------|---|
| Transition policy | Develop a transition policy describing the practice's approach to transition with input from youth and families |
| | Educate staff about the practice's policy and the roles of the youth, family, and pediatric and adult health care teams in the transition process |
| | Post policy and share/discuss with youth and families beginning at age 12–14, and review regularly |
| Transition tracking and monitoring | Establish criteria and process for identifying transitioning youth/young adults and enter their data into a registry |
| | Utilize individual flow sheet or registry to track youth's transition progress with the <i>Six Core Elements</i> |
| | Incorporate the <i>Six Core Elements</i> into clinical care process, using EHR if possible |
| Transition readiness | Conduct regular transition readiness assessments, beginning at age 14, to identify and discuss with families their needs and goals in self-care |
| | Jointly develop goals and prioritized actions with youth and parent/caregiver, and document regularly in a plan of care |
| | Identify and list providers interested in caring for adults |
| | <i>For adult providers:</i> establish a process to welcome and orient new young adults into the practice, including online or written information about the practice and a “get-acquainted appointment” |
| Transition planning | Develop and update a plan of care (readiness assessment findings, goals, medical summary, emergency plan) |
| | Prepare youth and parent for adult approach to care (legal changes, privacy and consent, access to information) |
| | Determine level of need for decision-making supports for youth with intellectual challenges |
| | Plan with youth/parent for optimal timing of transfer |
| | Assist youth in identifying an adult provider and communicate with selected provider |
| | Link patient/parent to resources for insurance, self-care management, community support |
| Transfer of care | Complete transfer package, including final transition readiness assessment, plan of care with transition goals, medical summary, emergency care plan |
| | Confirm date of first adult provider appointment |
| | <i>For adult providers:</i> |
| | Clarify adult approach to care (shared decision making, privacy, adherence) |
| | Conduct self-care assessment and discuss needed self-care skills |
| Transfer completion | Review young adult's health priorities |
| | Contact young adult and parent 3–5 months after last visit to confirm transfer to adult practice |
| | Communicate with adult practice to confirm completion of transfer |
| | Elicit feedback from young adult to assess experience with transition process |
| | Build ongoing and collaborative partnerships with adult primary and specialty care providers |

Adapted with permission from [GotTransition.org](#)

or consistently and can provide ongoing support as teens take gradual ownership over their chronic illnesses.

There are several tools available to track an adolescent's progress as they develop the ability to manage their chronic disease (Schwartz et al. 2014; The National Alliance to Advance Adolescent Health [n.d.](#)). Some are “disease-generic” and could apply to any patient with a

chronic health condition, while others are specific to common diseases.

Fewer than half of children with special healthcare needs receive services within a medical home. However, children who do receive care within a medical home are nearly twice as likely to receive transition services (Data Resource Center for Child and Adolescent Health [n.d.](#); Lotstein et al. 2005).

Table 1.16 Key health-related skills and knowledge (Moynihan et al. 2015)

| | |
|-----------|---|
| Skills | Carry health insurance information |
| | Call healthcare provider with questions or concerns |
| | Pick up prescriptions from pharmacy and call for refills |
| | Transport oneself to appointments |
| | Access urgent care resources |
| | Schedule appointments |
| | Attend routine health maintenance visits |
| | Meet with providers alone |
| Knowledge | Prepare questions/concerns for appointments |
| | Know insurance carrier, general coverage plan, and find a covered provider |
| | Understand effects of health risk behaviors (sexual activity, substance use, nutrition) |
| | Understand how to prevent pregnancy and STDs |
| | Understand how to assess risks and benefits of medical treatments |

Medication Adherence

In adolescents with chronic diseases, medication adherence often becomes an issue of contention between patients and their parents or providers. Several considerations may help the teen to improve adherence. Firstly, providers must be confident that a teen fully understands their condition, implications of non-adherence, and what expectations providers have for achieving adequate disease control. It may also be helpful for teens to understand which areas of disease management are negotiable, such as not taking a vitamin every day, and which lapses in self-care may be dangerous, such as not taking insulin (in the case of a type 1 diabetic) or an immunosuppressant medication (in the case of a patient with an organ transplant). Secondly, providers should be attuned to the higher prevalence of mental illness in patients with chronic disease and routinely screen for depression and anxiety, as these may impact the adolescent's ability to adequately manage their illness (Hood et al. 2011; Plener et al. 2015). Thirdly, providers should utilize motivational interviewing in discussing chronic disease management just as they do with other health behaviors. It is common for adolescents to go through periods of time where they wish they did not have an illness and would prefer to ignore it rather than appropriately manage it; a provider may be able to determine this using motivational interviewing and work with the patient to develop shared priorities.

Finding an Adult Healthcare Provider

The process of identifying a new health care provider should begin long before the expected transition of care. This may be an opportunity for adolescents to begin taking over management of their healthcare; however, many teens will require the assistance of their parents in this process. Clinic social workers may also be helpful, if available. Families will need to work with their insurance companies to identify options for new providers, and should feel free to question their new adult provider(s) about their comfort in working with young adults.

References

- Adeyemi-Fowode OA, Santos XM, Dietrich JE, Srivaths L. Levonorgestrel-releasing intra-uterine device use in adolescent females with heavy menstrual bleeding and bleeding disorders: single institution review. *J Pediatr Adolesc Gynecol* [Internet]. 2017;30(4):479–83. <http://www.ncbi.nlm.nih.gov/pubmed/27108228>
- Ahmed SP, Bittencourt-Hewitt A, Sebastian CL. Neurocognitive bases of emotion regulation development in adolescence. *Dev Cogn Neurosci* [Internet]. 2015;15:11–25. <http://www.ncbi.nlm.nih.gov/pubmed/26340451>
- Aitken M, VanderLaan DP, Wasserman L, Stojanovski S, Zucker KJ. Self-harm and suicidality in children referred for gender dysphoria. *J Am Acad Child Adolesc Psychiatry*. 2016;55(6):513–20.
- American Academy of Pediatrics Committee on Adolescence. Contraception for Adolescents. *Pediatrics*. 2014;134:e1244–56.

- American Academy of Pediatrics Section on Endocrinology. Physical changes during puberty [Internet]. 2015. [Cited 5 Jul 2016]. <https://www.healthychildren.org/English/ages-stages/gradeschool/puberty/Pages/Physical-Development-of-School-Age-Children.aspx>
- American Academy of Pediatrics, American Academy of Family Physicians, American College of Physicians, Transitions Clinical Report Authoring Group, Cooley WC, Sagerman PJ. Supporting the health care transition from adolescence to adulthood in the medical home. *Pediatrics* [Internet]. 2011;128(1):182–200. <http://www.ncbi.nlm.nih.gov/pubmed/21708806>
- American Academy of Pediatrics Council on Communications and Media. Children, adolescents, and the media. *Pediatrics* [Internet]. 2013;132(5):958–61. <http://pediatrics.aappublications.org/cgi/doi/10.1542/peds.2013-2656>
- American College of Obstetricians and Gynecologists. Obstetrics and Gynecology. Committee opinion on menstrual manipulation for adolescents with disabilities. 2016;128(2):418–9.
- American College of Obstetricians and Gynecologists. Adolescents and long-acting reversible contraception: implants and intrauterine devices. Committee opinion no. 539. *Obstet Gynecol*. 2012;120:982–8.
- American College of Obstetricians and Gynecologists. ACOG committee opinion no. 557: management of acute abnormal uterine bleeding in nonpregnant reproductive-aged women. *Obstet Gynecol* [Internet]. 2013;121(4):891–6. <http://www.ncbi.nlm.nih.gov/pubmed/23635706>
- American College of Obstetricians and Gynecologists. Committee opinion on menstruation in girls and adolescents: using the menstrual cycle as a vital sign. Committee Opinion No. 651. *Obstet Gynecol*. 2015;126:143–6.
- American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed., Washington D.C: American Psychiatric Association 2013.
- Anthony JC, Petronis KR. Early-onset drug use and risk of later drug problems. *Drug Alcohol Depend* [Internet]. 1995;40(1):9–15. <http://www.ncbi.nlm.nih.gov/pubmed/8746919>
- Barkus E. High-potency cannabis increases the risk of psychosis. *Evid Based Ment Health* [Internet]. 2016;19(2):54. <http://www.ncbi.nlm.nih.gov/pubmed/27036127>
- Blakemore S-J. Imaging brain development: the adolescent brain. *Neuroimage* [Internet]. 2012;61(2):397–406. <http://www.ncbi.nlm.nih.gov/pubmed/22178817>
- Brook JS, Lee JY, Finch SJ, Seltzer N, Brook DW. Adult work commitment, financial stability, and social environment as related to trajectories of marijuana use beginning in adolescence. *Subst Abus* [Internet]. 2013;34(3):298–305. <http://www.ncbi.nlm.nih.gov/pubmed/23844962>
- Caspi A, Moffitt TE, Cannon M, McClay J, Murray R, Harrington H, et al. Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction. *Biol Psychiatry* [Internet]. 2005;57(10):1117–27. <http://www.ncbi.nlm.nih.gov/pubmed/15866551>
- Centers for Disease Control and Prevention. U.S. medical eligibility criteria for contraceptive use, 2010: adapted from the World Health Organization medical eligibility criteria for contraceptive use, 4th edition. *Morb Mortal Wkly Rep*. 2010;59(RR04):1–6.
- Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines. 2015.
- Chang JP-C, Hung C-C. Problematic internet use. In: Rey J, editor. IACAPAP e-textbook of child and adolescent mental health. Geneva: International Association for Child and Adolescent Psychiatry and Allied Professions; 2012.
- Chen C-Y, Storr CL, Anthony JC. Early-onset drug use and risk for drug dependence problems. *Addict Behav* [Internet]. 2009;34(3):319–22. <http://www.ncbi.nlm.nih.gov/pubmed/19022584>
- Cheng L, Che Y, Gülmezoglu AM. Interventions for emergency contraception. *Cochrane Database Syst Rev* [Internet]. 2012;(8):CD001324. <http://www.ncbi.nlm.nih.gov/pubmed/22895920>
- Chick CF, et al. *J Neurosci* [Internet]. 2015;35(40):13539–41. <http://www.ncbi.nlm.nih.gov/pubmed/26446208>
- Christie D, Viner R. Adolescent development. *BMJ* [Internet]. 2005;330(7486):301–4. <http://www.ncbi.nlm.nih.gov/pubmed/15695279>
- Chu PY, Maslow GR, von Isenburg M, Chung RJ. Systematic review of the impact of transition interventions for adolescents with chronic illness on transfer from pediatric to adult healthcare. *J Pediatr Nurs*. 2015;30(5):e19–27.
- Chumlea WC, Schubert CM, Roche AF, Kulin HE, Lee PA, Himes JH, et al. Age at menarche and racial comparisons in US girls. *Pediatrics*. 2003;111(1):110–3.
- Coleman DL, Rosoff PM. The legal authority of mature minors to consent to general medical treatment. *Pediatrics* [Internet]. 2013;131(4):786–93. <http://www.ncbi.nlm.nih.gov/pubmed/23530175>
- Committee on Substance Abuse, Committee on Adolescence. The impact of marijuana policies on youth: clinical, research, and legal update. *Pediatrics* [Internet]. 2015;135(3):584–7. <http://pediatrics.aappublications.org/cgi/doi/10.1542/peds.2014-4146>
- Committee on Substance Abuse, Levy SJL, Kokotailo PK. Substance use screening, brief intervention, and referral to treatment for pediatricians. *Pediatrics* [Internet]. 2011;128(5):e1330–40. <http://www.ncbi.nlm.nih.gov/pubmed/22042818>
- Daling JR, Doody DR, Sun X, Trabert BL, Weiss NS, Chen C, et al. Association of marijuana use and the incidence of testicular germ cell tumors. *Cancer* [Internet]. 2009;115(6):1215–23. <http://www.ncbi.nlm.nih.gov/pubmed/19204904>
- Data Resource Center for Child and Adolescent Health. National survey of children with special health care needs. n.d.
- Davis AM, Brown RF, Taylor JL, Epstein RA, McPheeters ML. Transition care for children with special health care needs. *Pediatrics*. 2014;134(5):900–8.
- de Vries ALC, Steensma TD, Doreleijers TAH, Cohen-Kettenis PT. Puberty suppression in adolescents

- with gender identity disorder: a prospective follow-up study. *J Sex Med* [Internet]. 2011;8(8):2276–83. <http://www.ncbi.nlm.nih.gov/pubmed/20646177>
- de Vries ALC, McGuire JK, Steensma TD, Wagenaar ECF, Doreleijers TAH, Cohen-Kettenis PT. Young adult psychological outcome after puberty suppression and gender reassignment. *Pediatrics* [Internet]. 2014;134(4):696–704. <http://www.ncbi.nlm.nih.gov/pubmed/25201798>
- Dixon SD, Stein MT, editors. *Encounters with children: pediatric behavior and development*. 4th ed. Philadelphia: Mosby Elsevier; 2006.
- Emans SJ, Laufer MR. *Pediatric and adolescent gynecology*. 6th ed. Philadelphia: Lippincott, Williams & Wilkins; 2012.
- Fergusson DM, Boden JM. Cannabis use and later life outcomes. *Addiction* [Internet]. 2008;103(6):969–76; discussion 977–8. <http://www.ncbi.nlm.nih.gov/pubmed/18482420>
- Finer LB, Philbin JM. Sexual initiation, contraceptive use, and pregnancy among young adolescents. *Pediatrics* [Internet]. 2013;131(5):886–91. <http://www.ncbi.nlm.nih.gov/pubmed/23545373>
- Gemzell-Danielsson K. Mechanism of action of emergency contraception. *Contraception* [Internet]. 2010;82(5):404–409. Elsevier Inc. <https://doi.org/10.1016/j.contraception.2010.05.004>.
- Glazier AF, Cameron ST, Fine PM, Logan SJ, Casale W, Van Horn J, et al. Ulipristal acetate versus levonorgestrel for emergency contraception: a randomised non-inferiority trial and meta-analysis. *Lancet* [Internet]. 2010;375(9714):555–62. [https://doi.org/10.1016/S0140-3610\(10\)60101-8](https://doi.org/10.1016/S0140-3610(10)60101-8). Elsevier Ltd.
- Glazier A, Cameron ST, Bliithe D, Scherrer B, Mathe H, Levy D, et al. Can we identify women at risk of pregnancy despite using emergency contraception? Data from randomized trials of ulipristal acetate and levonorgestrel. *Contraception* [Internet]. 2011;84(4):363–7. <https://doi.org/10.1016/j.contraception.2011.02.009>. Elsevier Inc.
- Gleason KA, Birnbaum SG, Shukla A, Ghose S. Susceptibility of the adolescent brain to cannabinoids: long-term hippocampal effects and relevance to schizophrenia. *Transl Psychiatry* [Internet]. 2012;2:e199. <http://www.ncbi.nlm.nih.gov/pubmed/23188199>
- Goldenring J, Rosen D. Getting into adolescent heads: an essential update. *Contemp Pediatr*. 2004;21:76.
- Government of Canada. *Understanding the new access to cannabis for medical purposes regulations* [Internet]. 2016. [Cited 5 Dec 2017]. <https://www.canada.ca/en/healthcanada/services/publications/drugs-health-products/understanding-new-access-to-cannabis-for-medical-purposes-regulations.html>.
- Grant BF, Dawson DA. Age of onset of drug use and its association with DSM-IV drug abuse and dependence: results from the National Longitudinal Alcohol Epidemiologic Survey. *J Subst Abuse* [Internet]. 1998;10(2):163–73. <http://www.ncbi.nlm.nih.gov/pubmed/9854701>
- Gridley SJ, Crouch JM, Evans Y, Eng W, Antoon E, Lyapustina M, et al. Youth and caregiver perspectives on barriers to gender-affirming health care for transgender youth. *J Adolesc Health* [Internet]. 2016;59(3):254–61. <http://www.ncbi.nlm.nih.gov/pubmed/27235374>
- Gupta J, Kai J, Middleton L, Pattison H, Gray R, Daniels J. Levonorgestrel intrauterine system versus medical therapy for menorrhagia. *N Engl J Med* [Internet]. 2013;368(2):128–37. <http://www.ncbi.nlm.nih.gov/pubmed/23301731>
- Guttmacher Institute. *American teens' sexual and reproductive health* [Internet]. Guttmacher Institute; 2014. [Cited 28 Apr 2016]. <https://www.guttmacher.org/fact-sheet/american-teens-sexual-and-reproductive-health#1>
- Guttmacher Institute. *An overview of minors' consent law*. n.d.
- Harrison AM, Heritier F, Childs BG, Bostwick JM, Dziadzko MA. Systematic review of the use of phytochemicals for management of pain in cancer therapy. *Biomed Res Int* [Internet]. 2015;2015:506327. <http://www.ncbi.nlm.nih.gov/pubmed/26576425>
- Hartman RL, Huestis MA. Cannabis effects on driving skills. *Clin Chem* [Internet]. 2013;59(3):478–92. <http://www.ncbi.nlm.nih.gov/pubmed/23220273>
- Hashibe M, Morgenstern H, Cui Y, Tashkin DP, Zhang Z-F, Cozen W, et al. Marijuana use and the risk of lung and upper aerodigestive tract cancers: results of a population-based case-control study. *Cancer Epidemiol Biomarkers Prev* [Internet]. 2006;15(10):1829–34. <http://www.ncbi.nlm.nih.gov/pubmed/17035389>
- Hasin DS, Saha TD, Kerridge BT, Goldstein RB, Chou SP, Zhang H, et al. Prevalence of Marijuana use disorders in the United States between 2001–2002 and 2012–2013. *JAMA Psychiatry* [Internet]. 2015;72(12):1235–42. <http://www.ncbi.nlm.nih.gov/pubmed/26502112>
- Hayford SR, Furstenberg FF. Delayed adulthood, delayed desistance? Trends in the age distribution of problem behaviors. *J Res Adolesc* [Internet]. 2008;18(2):285–304. <http://www.ncbi.nlm.nih.gov/pubmed/19633730>
- Hazen E, Schlozman S, Beresin E. Adolescent psychological development: a review. *Pediatr Rev* [Internet]. 2008;29(5):161–7; quiz 168. <http://www.ncbi.nlm.nih.gov/pubmed/18450837>
- Hidalgo M, Bahamondes L, Perrotti M, Diaz J, Dantas-Monteiro C, Petta C, et al. *Contraception* [Internet]. 2002;65(2):129–32. <http://www.ncbi.nlm.nih.gov/pubmed/11927115>
- Higham JM, O'Brien PM, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. *Br J Obstet Gynaecol* [Internet]. 1990;97(8):734–9. <http://www.ncbi.nlm.nih.gov/pubmed/2400752>
- Holland G, Tiggemann M. A systematic review of the impact of the use of social networking sites on body image and disordered eating outcomes. *Body Image* [Internet]. 2016;17:100–10. <http://www.ncbi.nlm.nih.gov/pubmed/26995158>

- Holland-Hall C. Heavy menstrual bleeding in adolescents: normal variant or a bleeding disorder? *Contemp Ob/Gyn* [Internet]. 2013;58(1):34–47. <http://contemporarypediatrics.modernmedicine.com/contemporary-pediatrics/news/clinical/pediatrics/heavy-menstrual-bleeding-adolescents-normal-variant?page=full>
- Hood KK, Rausch JR, Dolan LM. Depressive symptoms predict change in glycemic control in adolescents with type 1 diabetes: rates, magnitude, and moderators of change. *Pediatr Diabetes*. 2011;12:718–23.
- Huang GC, Unger JB, Soto D, Fujimoto K, Pentz MA, Jordan-Marsh M, et al. Peer influences: the impact of online and offline friendship networks on adolescent smoking and alcohol use. *J Adolesc Health* [Internet]. 2014;54(5):508–14. <http://www.ncbi.nlm.nih.gov/pubmed/24012065>
- Jacobson C, Bailin A, Milanaik R, Adesman A. Adolescent health implications of new age technology. *Pediatr Clin North Am* [Internet]. 2016;63(1):183–94. <http://www.ncbi.nlm.nih.gov/pubmed/26613696>
- Jain A, Petty EM, Jaber RM, Tackett S, Purkiss J, Fitzgerald J, et al. What is appropriate to post on social media? Ratings from students, faculty members and the public. *Med Educ* [Internet]. 2014;48(2):157–69. <http://www.ncbi.nlm.nih.gov/pubmed/24528398>
- Katzenellenbogen R. HEADSS: the “Review of Systems” for Adolescents. *Virtual Mentor* [Internet]. 2005;7(3). <http://www.ncbi.nlm.nih.gov/pubmed/23249491>
- Kawabe K, Horiuchi F, Ochi M, Oka Y, Ueno S-I. Internet addiction: prevalence and relationship with mental states in adolescents. *Psychiatry Clin Neurosci* [Internet]. 2016;70(9):405–12. <http://www.ncbi.nlm.nih.gov/pubmed/27178110>
- Keen L, Blandani G, Rehmani N. Lifetime marijuana use and sexually transmitted infection history in a sample of Black college students. *Addict Behav* [Internet]. 2016;60:203–8. <http://www.ncbi.nlm.nih.gov/pubmed/27161534>
- Kreukels BPC, Cohen-Kettenis PT. Puberty suppression in gender identity disorder: the Amsterdam experience. *Nat Rev Endocrinol*. 2011;7(8):466–72.
- Kumar N, Brown JD. Access barriers to long acting reversible contraceptives for adolescents. *J Adolesc Heal* [Internet]. 2016;1–6. Elsevier Inc. <http://linkinghub.elsevier.com/retrieve/pii/S1054139X1630012X>
- Lacson JCA, Carroll JD, Tuazon E, Castela EJ, Bernstein L, Cortessis VK. Population-based case-control study of recreational drug use and testis cancer risk confirms an association between marijuana use and nonseminoma risk. *Cancer* [Internet]. 2012;118(21):5374–83. <http://www.ncbi.nlm.nih.gov/pubmed/22965656>
- Langenfeld SJ, Sudbeck C, Luers T, Adamson P, Cook G, Schenarts PJ. The glass houses of attending surgeons: an assessment of unprofessional behavior on Facebook among practicing surgeons. *J Surg Educ* [Internet]. 2015;72(6):e280–5. <http://www.ncbi.nlm.nih.gov/pubmed/26276300>
- Lenné MG, Dietze PM, Triggs TJ, Walmsley S, Murphy B, Redman JR. The effects of cannabis and alcohol on simulated arterial driving: influences of driving experience and task demand. *Accid Anal Prev*. 2010;42:857–64.
- Lindley LL, Walsemann KM. Sexual orientation and risk of pregnancy among New York city high-school students. *Am J Public Health*. 2015;105(7):1379–86.
- Lisdahl Medina K, Hanson KL, Schweinsburg AD, Cohen-Zion M, Nagel BJ, Tapert SF. Neuropsychological functioning in adolescent marijuana users: subtle deficits detectable after a month of abstinence. *J Int Neuropsychol Soc*. 2007;13(5):807–20.
- Lotstein DS, McPherson M, Strickland B, Newacheck PW. Transition planning for youth with special health care needs: results from the National Survey of Children with Special Health Care Needs. *Pediatrics*. 2005;115(6):1562–8.
- Lydecker JA, Cotter EW, Palmberg AA, Simpson C, Kwitowski M, White K, et al. Does this Tweet make me look fat? A content analysis of weight stigma on Twitter. *Eat Weight Disord* [Internet]. 2016;21(2):229–35. <http://www.ncbi.nlm.nih.gov/pubmed/27068174>
- Lyons SK, Helgeson VS, Witchel SF, Becker DJ, Korytkowski MT. Physicians’ self-perceptions of care for emerging adults with type 1 diabetes. *Endocr Pract*. 2014;21(8):903–9.
- MacDonald J, Sohn S, Ellis P. Privacy, professionalism and Facebook: a dilemma for young doctors. *Med Educ* [Internet]. 2010;44(8):805–13. <http://www.ncbi.nlm.nih.gov/pubmed/20633220>
- Macleod J, Oakes R, Copello A, Crome I, Egger M, Hickman M, et al. Psychological and social sequelae of cannabis and other illicit drug use by young people: a systematic review of longitudinal, general population studies. *Lancet* (London, England) [Internet]. 2004;363(9421):1579–88. <http://www.ncbi.nlm.nih.gov/pubmed/15145631>
- Manchikanti Gomez A, Grimes DA, Lopez LM, Schulz KF. Steroid hormones for contraception in women with sickle cell disease. In: Manchikanti Gomez A, editor. *Cochrane database of systematic reviews* [Internet]. Chichester: Wiley; 2007. <http://doi.wiley.com/10.1002/14651858.CD006261.pub2>.
- Matteson K, Rahn D, Wheeler T, Casiano E, Siddiqui NY, Harvey HS, et al. *Obstet Gynecol*. 2013;121(3):632–43.
- McCann-Crosby B, Sutton VR. Disorders of sexual development. *Clin Perinatol*. 2015;42(2):395–412, ix–x.
- McNicholas C, Zhao Q, Secura G, Allsworth JE, Madden T, Peipert JF. Contraceptive failures in overweight and obese combined hormonal contraceptive users. *Obstet Gynecol* [Internet]. 2013;121(3):585–92. <http://www.ncbi.nlm.nih.gov/pubmed/23635622>
- Mehmedic Z, Chandra S, Slade D, Denham H, Foster S, Patel AS, et al. Potency trends of Δ^9 -THC and other cannabinoids in confiscated cannabis preparations from 1993 to 2008. *J Forensic Sci* [Internet]. 2010;55(5):1209–17. <http://www.ncbi.nlm.nih.gov/pubmed/20487147>
- Mei S, Yau YHC, Chai J, Guo J, Potenza MN. Problematic Internet use, well-being, self-esteem and self-control:

- data from a high-school survey in China. *Addict Behav* [Internet]. 2016;61:74–9. <http://www.ncbi.nlm.nih.gov/pubmed/27249805>
- Meier MH, Caspi A, Ambler A, Harrington H, Houts R, Keefe RSE, et al. Persistent cannabis users show neuro-psychological decline from childhood to midlife. *Proc Natl Acad Sci U S A* [Internet]. 2012;109(40):E2657–64. <http://www.ncbi.nlm.nih.gov/pubmed/22927402>
- Miech RA, Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE. Monitoring the future national survey results on drug use, 1975–2015. Volume I, Secondary school students. Ann Arbor: Institute for Social Research; 2016.
- Moreno MA, Kolb J. Social networking sites and adolescent health. *Pediatr Clin North Am* [Internet]. 2012;59(3):601–12, vii. <http://www.ncbi.nlm.nih.gov/pubmed/22643167>
- Moynihan M, Saewyc E, Whitehouse S, Paone M, McPherson G. Assessing readiness for transition from paediatric to adult health care: revision and psychometric evaluation of the Am I ON TRAC for Adult Care questionnaire. *J Adv Nurs*. 2015;71(6):1324–35.
- National Institute on Drug Abuse. Marijuana. n.d.-a
- National Institute on Drug Abuse. Principles of adolescent substance use disorder treatment: a research-based guide. n.d.-b
- Office of Adolescent Health. Trends in teen childbearing and pregnancy. 2016.
- Office of National Drug Control Policy. Marijuana Resource Center: state laws related to marijuana. <https://www.whitehouse.gov/ondcp/state-laws-related-to-marijuana>
- Osman A, Wardle A, Caesar R. Online professionalism and Facebook—falling through the generation gap. *Med Teach* [Internet]. 2012;34(8):e549–56. <http://www.ncbi.nlm.nih.gov/pubmed/22494078>
- Papadimitriou A. The evolution of the age at Menarche from prehistorical to modern times. *J Pediatr Adolesc Gynecol* [Internet]. 2016;11–4. doi:10.1016/j.jpag.2015.12.002
- Patton GC, Coffey C, Carlin JB, Degenhardt L, Lynskey M, Hall W. Cannabis use and mental health in young people: cohort study. *BMJ*. 2002;325(7374):1195–8.
- Perkonig A, Goodwin RD, Fiedler A, Behrendt S, Beesdo K, Lieb R, et al. The natural course of cannabis use, abuse and dependence during the first decades of life. *Addiction* [Internet]. 2008;103(3):439–49; discussion 450–1. [Cited 15 Dec 2015]. <http://www.ncbi.nlm.nih.gov/pubmed/18269364>
- Plener P, Molz E, Berger G, Schober E, Oller O, Denzer K, et al. Depression, metabolic control, and antidepressant medication in young patients with type 1 diabetes. *Pediatr Diabetes*. 2015;16:58–66.
- Polen MR, Sidney S, Tekawa IS, Sadler M, Friedman GD. Health care use by frequent marijuana smokers who do not smoke tobacco. *West J Med* [Internet]. 1993;158(6):596–601. <http://www.ncbi.nlm.nih.gov/pubmed/8337854>
- Puckett JA, Horne SG, Surace F, Carter A, Noffsinger-Frazier N, Shulman J, et al. Predictors of sexual minority youth's reported suicide attempts and mental health. *J Homosex*. 2016;64:697–715.
- Ramaekers JG, Berghaus G, Van Laar M, Drummer OH. Dose related risk of motor vehicle crashes after cannabis use. *Drug Alcohol Depend*. 2004;73:109–19.
- Reifsnider E, Mendias N, Davila Y, Bever Babendure J. Contraception and the obese woman. *J Am Assoc Nurse Pract* [Internet]. 2013;25(5):223–33. <http://www.ncbi.nlm.nih.gov/pubmed/24170564>
- Resnick HS, Walsh K, McCauley JL, Schumacher JA, Kilpatrick DG, Acierno RE. Assault related substance use as a predictor of substance use over time within a sample of recent victims of sexual assault. *Addict Behav* [Internet]. 2012;37(8):914–21. <http://www.ncbi.nlm.nih.gov/pubmed/22521363>
- Resnick HS, Walsh K, Schumacher JA, Kilpatrick DG, Acierno R. Prior substance abuse and related treatment history reported by recent victims of sexual assault. *Addict Behav* [Internet]. 2013;38(4):2074–9. <http://www.ncbi.nlm.nih.gov/pubmed/23396174>
- Rice E, Barman-Adhikari A, Rhoades H, Winetrobe H, Fulginiti A, Astor R, et al. Homelessness experiences, sexual orientation, and sexual risk taking among high school students in Los Angeles. *J Adolesc Health*. 2013;52(6):773–8.
- Robinson JA, Burke AE. Obesity and hormonal contraceptive efficacy. *Womens Health (Lond Engl)* [Internet]. 2013;9(5):453–66. <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4079263&tool=pmcentrez&rendertype=abstract>
- Rosen DS. Physiologic growth and development during adolescence. *Pediatr Rev* [Internet]. 2004;25(6):194–200. <http://www.ncbi.nlm.nih.gov/pubmed/15173452>
- Salmela-Aro K, Upadyaya K, Hakkarainen K, Lonka K, Alho K. The dark side of internet use: two longitudinal studies of excessive internet use, depressive symptoms, school burnout and engagement among finnish early and late adolescents. *J Youth Adolesc* [Internet]. 2017;46(2):343–57. <http://www.ncbi.nlm.nih.gov/pubmed/27138172>
- Sanders RA. Adolescent psychosocial, social, and cognitive development. *Pediatr Rev* [Internet]. 2013;34(8):354–8; quiz 358–9. <http://www.ncbi.nlm.nih.gov/pubmed/23908362>
- Sayin FK, Buyukinan M. Sleep duration and media time have a major impact on insulin resistance and metabolic risk factors in obese children and adolescents. *Child Obes* [Internet]. 2016;12(4):272–8. <http://www.ncbi.nlm.nih.gov/pubmed/26978730>
- Schepis TS, Adinoff B, Rao U. Neurobiological processes in adolescent addictive disorders. *Am J Addict*. 2008;17(1):6–23.
- Schwartz LA, Daniel LC, Brumley LD, Barakat LP, Wesley KM, Tuchman LK. Measures of readiness to transition to adult health care for youth with chronic physical health conditions: a systematic review and recommendations for measurement

- testing and development. *J Pediatr Psychol*. 2014;39(6):588–601.
- Schweinsburg AD, Brown SA, Tapert SF. The influence of marijuana use on neurocognitive functioning in adolescents. *Curr Drug Abuse Rev* [Internet]. 2008;1(1):99–111. <http://www.ncbi.nlm.nih.gov/pubmed/19630709>
- Sidani JE, Shensa A, Hoffman B, Hanmer J, Primack BA. The association between social media use and eating concerns among US young adults. *J Acad Nutr Diet* [Internet]. 2016;116(9):1465–72. <http://www.ncbi.nlm.nih.gov/pubmed/27161027>
- Simpson CC, Mazzeo SE. Skinny is not enough: a content analysis of fitspiration on pinterest. *Health Commun* [Internet]. 2016;1–8. <http://www.ncbi.nlm.nih.gov/pubmed/27326747>
- Squeglia LM, Tapert SF, Sullivan EV, Jacobus J, Meloy MJ, Rohlfing T, et al. Brain development in heavy-drinking adolescents. *Am J Psychiatry* [Internet]. 2015;172(6):531–42. <http://www.ncbi.nlm.nih.gov/pubmed/25982660>
- Steensma TD, McGuire JK, Kreukels BPC, Beekman AJ, Cohen-Kettenis PT. Factors associated with desistence and persistence of childhood gender dysphoria: a quantitative follow-up study. *J Am Acad Child Adolesc Psychiatry* [Internet]. 2013;52(6):582–90. <http://www.ncbi.nlm.nih.gov/pubmed/23702447>
- Steinberg L. The case for delayed adulthood. *The New York Times*. New York; 21 Sept 2014;SR12.
- Substance Abuse and Mental Health Services Administration. Behavioral health treatment services locator. n.d.
- Suris JC. Chronically ill but still adolescent. *Minerva Pediatr*. 2002;54(6):507–10.
- Suris J-C, Parera N. Sex, drugs and chronic illness: health behaviours among chronically ill youth. *Eur J Pub Health*. 2005;15(5):484–8.
- TeensHealth. Drugs and alcohol. n.d.
- The Center for Adolescent Substance Abuse Research. The CRAFFT screening tool. n.d. <http://www.ceasar-boston.org/clinicians/crafft.php>
- The National Alliance to Advance Adolescent Health. GotTransition. n.d. www.gottransition.org
- Trans Student Educational Resources. The gender unicorn. n.d.
- Vaala SE, Hood KK, Laffel L, Kumah-Crystal YA, Lybarger CK, Mulvaney SA. Use of commonly available technologies for diabetes information and self-management among adolescents with type 1 diabetes and their parents: a web-based survey study. *Interact J Med Res* [Internet]. 2015;4(4):e24. <http://www.ncbi.nlm.nih.gov/pubmed/26715191>
- Valencia LS, Cromer BA. Sexual activity and other high-risk behaviors in adolescents with chronic illness: a review. *J Pediatr Adolesc Gynecol*. 2000;13(2):53–64.
- van Ekris E, Altenburg TM, Singh A, Proper K, Heymans MW, Chinapaw M. An evidence-update on the prospective relationship between childhood sedentary behaviour and biomedical health indicators: a systematic review and meta-analysis. *Obes Rev* [Internet]. 2016;17(9):833–49. <http://www.ncbi.nlm.nih.gov/pubmed/27256486>
- Walvoord EC. The timing of puberty: is it changing? Does it matter? *J Adolesc Health* [Internet]. 2010;47(5):433–9. [Cited 12 Mar 2013]. <http://www.ncbi.nlm.nih.gov/pubmed/20970077>
- Warner PE, Critchley HOD, Lumsden MA, Campbell-Brown M, Douglas A, Murray GD, Menorrhagia II. Is the 80-mL blood loss criterion useful in management of complaint of menorrhagia? *Am J Obstet Gynecol*. 2004a;190(5):1224–9.
- Warner PE, Critchley HOD, Lumsden MA, Campbell-Brown M, Douglas A, Murray GD, Menorrhagia I. Measured blood loss, clinical features, and outcome in women with heavy periods—a survey with follow-up data. *Am J Obstet Gynecol*. 2004b;190(5):1216–23.
- Weinraub M, Clemens LP, Sockloff A, Ethridge T, Gracely E, Myers B. The development of sex role stereotypes in the third year: relationships to gender labeling, gender identity, sex-typed toy preference, and family characteristics. *Child Dev*. 1984;55(4):1493–503.
- Wilkie G, Sakr B, Rizack T. Medical Marijuana use in oncology: a review. *JAMA Oncol* [Internet]. 17 Mar 2016. <http://www.ncbi.nlm.nih.gov/pubmed/26986677>
- Winters KC, Lee C-YS. Likelihood of developing an alcohol and cannabis use disorder during youth: association with recent use and age. *Drug Alcohol Depend* [Internet]. 2008;92:239–47. www.sciencedirect.com
- World Professional Organization for Transgender Health. Standards of care for the health of transsexual, transgender, and gender-nonconforming people, version 7. 2012.
- Xu H, Wade JA, Peipert JF, Zhao Q, Madden T, Secura GM. Contraceptive failure rates of etonogestrel subdermal implants in overweight and obese women. *Obstet Gynecol* [Internet]. 2012;120(1):21–6. <http://www.ncbi.nlm.nih.gov/pubmed/22678035>
- Yuan M, Cross SJ, Loughlin SE, Leslie FM. Nicotine and the adolescent brain. *J Physiol* [Internet]. 2015;593(16):3397–412. <http://www.ncbi.nlm.nih.gov/pubmed/26018031>



Update in Pediatric Allergy

2

Amanda Ciccolini, Shannon French, Mark Tenn,
and Anne K. Ellis

Food Allergy

Introduction

Food allergy is a reproducible, abnormal immune response to a food. It is broadly categorized into immunoglobulin E (IgE) and non-IgE mediated reactions (Johansson et al. 2004). There are hundreds of food proteins which have been reported as allergens, however, the most common food allergens in the North American population include milk, peanuts, tree nuts, egg, shellfish, fish, wheat, and soy which account for 90% of all food allergies (“The Food Allergy and Anaphylaxis Network 2016”). Food allergy remains one of the main causes of anaphylaxis presenting to the emergency department (Sampson 2004). This section will give an overview of food allergy, with a focus on the new literature that has emerged on the topic.

A. Ciccolini, M.D. • S. French, M.D. • M. Tenn,
B.H.Sc., M.Sc. Candidate
Queen’s University, Kingston, ON, Canada
e-mail: 13ac51@queensu.ca; 14sbf@queensu.ca;
Omwt2@queensu.ca

A.K. Ellis, M.D., M.Sc., F.R.C.P.C. (✉)
Queen’s University, Kingston, ON, Canada

Division of Allergy and Immunology, Department of
Medicine, Queen’s University, Kingston, ON, Canada
e-mail: ellisa@kgh.kari.net

Prevalence

The prevalence of food allergy is a challenging entity to accurately determine because it is calculated based on variable factors, including allergy definitions, methodologies, study populations and more (Sicherer 2011). Many studies gather data based on self-reported food allergy, which is less accurate than confirming an allergy with an oral food challenge in a clinical setting (McGowan and Keet 2013). Recent literature reviews conclude that food allergy affects more than 1–2% but less than 10% of the population, however an increased prevalence in food allergy has not yet been confirmed (Chafen et al. 2010).

In Canada the prevalence of food allergy is estimated to be approximately 7%, based on self-reported data (Soller et al. 2012). Recent data suggests that food allergy is becoming more prevalent. The US Centers for Disease Control and Prevention completed a data brief in 2013 which demonstrated that among children age 0–17 years, there was an increase in the prevalence of food allergies from 3.4% in 1997–1999 to 5.1% in 2009–2011 (Jackson et al. 2013). On a global scale, studies from the UK (Kotz et al. 2011), China (Hu et al. 2010), the US, and Australia (Osborne et al. 2011) have also demonstrated an increase in the prevalence of food allergy (Sicherer 2011).

Pathophysiology

Significant advancements have been made in the past few years to better our understanding of the pathophysiology of food allergy, however there is still much to be discovered. Food allergy reactions are generally categorized into immunoglobulin E (IgE)-mediated or non-IgE-mediated processes, although mixed processes also occur (Burks et al. 2012). IgE mediated food allergic reactions are more common and occur quickly, with the onset usually occurring minutes to two hours after ingestion. Following the initial consumption of the allergenic food, the allergic individual becomes 'sensitized.' The allergenic food protein stimulates IgE antibody production which is specific to the food. These antibodies then bind to basophil and mast cells. When the allergenic food is later consumed, it binds to its specific IgE antibody to activate an immune response involving histamine, leukotriene, and prostaglandin release. This response vasodilation, mucus secretion, and smooth muscle contraction, which causes the clinical signs and symptoms of an IgE mediated allergic reaction, such as urticaria (Sicherer and Sampson 2010). The activated mast cells also release various cytokines which results in further inflammatory cell recruitment. This can also be responsible for late-phase allergic responses (Perry and Pesek 2013).

Non-IgE mediated food allergy is caused by a T cell response to the allergenic food protein, rather than an IgE response. This then results in a cell mediated inflammatory response invoked by the activated T Cells. This reaction type usually results in gastrointestinal and dermatological symptoms of allergy. Examples of non-IgE mediated food allergies include food protein-induced proctocolitis, food protein-induced enterocolitis, and dermatitis herpetiformis. Mixed IgE and non-IgE mediated food allergy can also occur, and an example of this type of entity includes eosinophilic esophagitis (Sicherer and Sampson 2006; Sicherer and Sampson 2010).

Risk Factors

Family history, genetics, ethnicity, sex, geography and lifestyle are all thought to play a role in determining the likelihood of developing food allergy. Children are at a higher risk for developing food allergy if there is a first-degree relative who has an allergic condition such as food allergy, atopic dermatitis, allergic rhinitis or asthma (Muraro et al. 2004). A study done by Hourihane et al. showed that there is a sevenfold increase in the risk of developing peanut allergy for a child with a sibling or parent with peanut allergy (Hourihane et al. 1996). It has also been shown that in monozygotic twins there is a 64% likelihood of one twin developing a peanut allergy if their twin has a peanut allergy (Sicherer et al. 2000). In a National Health and Nutrition Examination Survey study conducted from 2005 to 2006, Liu et al. demonstrated an increased risk of developing food allergy in non-Hispanic black study subjects (Liu et al. 2010). Gupta et al. also completed a study in 2012 which also demonstrated increased risk of food allergy in black and Asian subjects (Gupta et al. 2011).

The Western lifestyle has been associated with an increased risk of food allergies, and this has been demonstrated in North America, Europe, Australia and Asia (Graham-Rowe 2011). Children living in urban areas are more likely to develop food allergy than those living in rural areas (Majkowska-Wojciechowska et al. 2007). Specific food allergies are more likely in certain areas of the world. For example, mustard seed allergy has been reported to be more common in France (Rancé et al. 2000), and royal jelly allergy has been found to be more prevalent in Hong Kong (Leung et al. 1997). Interestingly, peanut allergy has been found to be ten times more prevalent in Jewish children living in the UK than in Jewish children living in Israel (Du Toit et al. 2008).

Several studies have demonstrated a relationship between sex and likelihood of developing food allergy. Research done by Lie et al. looked

at food specific IgE levels from 8203 participants in the National Health and Nutrition Examination Survey and found that males had an increased risk of developing food allergy (Liu et al. 2010). Studies have also shown that risk stratification based on sex varies depending on age. As an example, Sicherer et al. found in their study that male children were nearly five times more likely to develop peanut allergy than female children, however male adults were not more likely than female adults to develop a peanut allergy (Sicherer et al. 2003). Similar patterns have been found for tree nut allergies (Emmett et al. 1999).

Clinical Presentation

Food allergy has a broad and variable clinical presentation. Presentations can range from mild reactions to life threatening depending on the severity. As mentioned above, food allergy can be IgE mediated, non-IgE mediated, or a mix of the two. IgE mediated reactions tend to occur quickly, while non-IgE mediated reactions tend to be delayed or more chronic (Waserman and Watson 2011).

The mildest IgE mediated reaction is called the ‘oral allergy syndrome (a.k.a. pollen food syndrome)’. Individuals with this syndrome are usually pollen allergic and develop itchiness and tingling of the oropharynx after consumption of things like fresh vegetables and fruits. Oral allergy syndrome is caused by IgE antibodies cross reacting to certain pollens with proteins found in fresh vegetables and fruit. The proteins are sensitive to heat, which is why some of these individuals may tolerate these foods if they are cooked, which denatures the protein. Skin testing is typically negative for these foods in these individuals (Connors and Waserman 2010).

IgE mediated allergic reactions can present with cutaneous, respiratory, gastrointestinal, and cardiovascular symptoms, with cutaneous reactions being the most common (Boyce et al. 2010). Non-IgE mediated reactions tend to present with

gastrointestinal and cutaneous symptoms. An example is food protein-induced enterocolitis syndrome (FPIES), which can present with gastrointestinal symptoms; typically profuse vomiting and diarrhea after ingestion of the allergenic food. FPIES usually presents in infancy and is often secondary to a reaction to infant formula or maternal breast milk (Sicherer 2005).

A summary of IgE mediated and non-IgE mediated reaction symptoms is listed by body system in the table below.

| | IgE-mediated (immediate reactions) | Non-IgE-mediated (delayed/chronic reactions) |
|--|------------------------------------|--|
| Skin: | | |
| Urticaria | √ | |
| Angioedema | √ | |
| Erythema | √ | √ |
| Pruritus | √ | √ |
| Eczematous rash/lesions | √ | √ |
| Respiratory: | | |
| Laryngeal edema | √ | |
| Rhinorrhea | √ | |
| Bronchospasm | √ | |
| Nasal congestion | √ | |
| Cough | √ | |
| Chest tightness | √ | |
| Wheezing | √ | |
| Dyspnea | √ | |
| Gastrointestinal: | | |
| Angioedema of the lips, tongue, palate | √ | |
| Oral pruritus | √ | |
| Tongue swelling | √ | |
| Vomiting | √ | √ |
| Diarrhea | √ | √ |
| Pain | √ | √ |
| Cardiovascular: | | |
| Presyncope/syncope | √ | |
| Hypotension | √ | |
| Tachycardia | √ | |

Waserman and Watson (2011), Perry and Pesek (2013)

Diagnosis

It is important to complete a relevant history and clinical examination to aid your diagnosis prior to completing investigations.

Management

The main treatment for food allergy is strict avoidance of the allergenic food (Boyce et al. 2010). All patients diagnosed with a food allergy

The history should include:

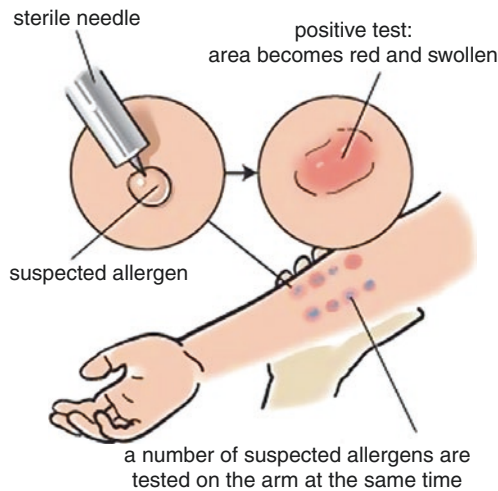
| | |
|---|---|
| <ul style="list-style-type: none"> • Details of suspected foods causing allergy | <ul style="list-style-type: none"> • Family history of allergic and atopic diseases |
| <ul style="list-style-type: none"> • Manner of food preparation (i.e. cooked vs. raw, added spices, oils, or other ingredients) | <ul style="list-style-type: none"> • Description of all symptoms and severity |
| <ul style="list-style-type: none"> • Reproducibility of symptoms with food exposure | <ul style="list-style-type: none"> • Duration of reaction |
| <ul style="list-style-type: none"> • Factors potentiating allergic reactions (i.e. NSAIDs use or exercise) (Sicherer and Sampson 2010) | <ul style="list-style-type: none"> • Occurrence of bimodal or delayed reaction |
| <ul style="list-style-type: none"> • Route of exposure (i.e. ingestion, inhalation, skin contact) | <ul style="list-style-type: none"> • Response to treatment |
| <ul style="list-style-type: none"> • Timing of the onset of reaction | <ul style="list-style-type: none"> • Episodes requiring hospital presentation or admission |

Physical examination:

Physical examination during an allergic reaction can yield many of the signs and symptoms of allergy that were previously described above. However, assessments are not always done while allergic reactions are occurring. The physical examination in these cases is useful in assessing for evidence of atopic and allergic disease, such as atopic dermatitis. It is also important to rule out other conditions which can mimic food allergy. All pediatric physical examinations should also include assessment for overall health, growth and nutrition status

Diagnostic tests

1. Skin prick testing:



- Rapid, safe and sensitive screening method for suspected IgE-mediated food allergy
- Positive SPT appears as a wheal and flare when the food extract is applied to the skin and pricked
- The larger the wheal size the more likely that a clinical allergy exists
- Takes less than 20 min to complete
- Can be done on infants in first few months of life
- Positive SPT has a sensitivity of roughly 90%, although specificity is only approximately 50%
- SPT should only be completed for foods that are relevant to the patient history
- SPT has a negative predictive value of >95% (Sampson 2004; Scurlock et al. 2005; "Allergy Skin Test 2016")

2. Serum-specific IgE testing:

- Specific IgE antibodies to foods can be quantified by in vitro laboratory methods
- Less sensitive and more expensive than SPT
- Predictive value of serum-specific IgE testing may be affected by patient ethnicity, age, and time since last ingestion of food allergen (Celik-Bilgili et al. 2005)
- May be useful where SPT is not possible (i.e. dermatographism or generalized dermatitis) or if SPT is negative and there is a high degree of clinical suspicion of food allergy (Boyce et al. 2010)

3. Oral food challenge

- Considered the gold standard for diagnosis of food allergy
- Time consuming
- May be appropriate if diagnosis is uncertain based on results of SPT and/or serum-specific IgE levels
- Involves ingesting gradually increasing portions of the suspected food
- Must be done under careful physician supervision with frequent assessments for symptoms of allergy
- Should only be done in locations where anaphylaxis can be appropriately treated (i.e. hospitals, clinics)
- Challenge is stopped if symptoms develop and treatment is given if required (Nowak-Wegrzyn et al. 2009)

4. Elimination diet

- Requires strict avoidance of suspected food for a time period (usually 1–2 weeks)
- Patient is then monitored for a decrease in their symptoms
- Limitations include bias, patient compliance and this being a time consuming endeavor (Sicherer and Sampson 2010)

5. Patch testing

- Involve exposing skin to a food allergen for 24 h under occlusion, then assessing skin for signs of allergic reaction (i.e. erythema) in the subsequent 24–72 h
- Routine use for food allergy is not recommended due to lack of evidence and standardization (Bernstein et al. 2008)
- Shown to have value in assessing potential food triggers in pediatric eosinophilic esophagitis (Spergel et al. 2012)

6. Basophil activation test

- Relatively new assessment of basophil response to food allergen
 - Limited to research currently and not recommended for clinical setting (Leysen et al. 2011)
-

should be prescribed an epinephrine autoinjector, which should be dosed according to weight in the pediatric population and kept with the child at all times (Sicherer and Simons 2007). Parents, children, care givers and schools should be trained in epinephrine administration (Sicherer and Sampson 2010). If patients have received emergency epinephrine they must be brought to the hospital for observation and assessment. Epinephrine autoinjectors should be stored at the appropriate temperature and checked regularly for their expiration date. Patients and caregivers must also receive education on food avoidance and label reading, identification and treatment of allergic reactions, and how to obtain medical assistance. Food allergic individuals should also

wear medic alert bracelets (Connors and Wasserman 2010).

Patients with suspected food allergy should be referred to an allergist to confirm the diagnosis and investigate for other potential allergies. The natural history of food allergy is quite variable depending on the allergen and the patient. Some food allergies are commonly outgrown, such as egg (Savage et al. 2007), while others are generally lifelong. Long term management should involve regular assessment and testing for evidence of tolerance to foods that the individual previously developed reactions to, and also for the development of new food allergies (Fleischer et al. 2003; Sicherer 2011).

Prevention and New Research

The American Academy of Pediatrics in the year 2000 recommended delaying the introduction of potential high risk foods for infants at an elevated risk of developing allergy (e.g., cow's milk protein until 1 year of age, peanut until 3 years of age) (Fleischer et al. 2005). This was solely based on expert opinion because, at the time, there was no convincing data to support this. Fortunately, this has now changed. Since 2000, there has been a large amount of new evidence to suggest that delayed introduction of high risk foods has no effect on preventing allergy, and rather it may actually increase the likelihood of developing an allergy to these foods (Nwaru et al. 2013). In 2008 the American Academy of Pediatrics issued a new guideline which confirmed that there was no convincing evidence to show that delaying solid food introduction, including peanuts, fish, and egg, past 4–6 months of age has a significant effect towards preventing allergy (Greer et al. 2008).

Nearly a decade ago the Learning Early About Peanut (LEAP) study was started in the United Kingdom. This study was a prospective trial which aimed to investigate whether early introduction of peanuts to the diet may be protective from the development of peanut allergy. The LEAP trial randomly assigned over 600 high-risk infants age 4–11 months to either an early introduction of peanut protein (at 4–10 months of age) or delayed introduction (at 5 years of age). Infants assigned to the early introduction were fed a minimum of 6 g of peanut protein per week, distributed in at least three meals per week, until the age of 60 months. Infants in the late introduction group were instructed to avoid peanut until the age of 60 months. All participants were assessed at baseline, 12, 30 and 60 months of age. Of the children in the avoidance group, 17% developed a peanut allergy by the age of 60 months. However, in the early introduction group, only 3% developed a peanut allergy by age 60 months. It was concluded that the early introduction of peanuts in high-risk infants decreased the frequency of peanut allergy (Du Toit et al. 2015).

A follow up trial to the LEAP study was done to determine if the rate of peanut allergy remained low after a 12-month period of peanut avoidance in the study group who had an early introduction to peanuts. This was compared with the group who avoided peanuts until age 60 months. This follow up trial, called the LEAP-ON study, followed 556 of the original 640 children who participated in LEAP (both consumer and avoiders) for 12 months of complete peanut avoidance. In the LEAP-ON study there were 274 previous peanut consumers and 282 previous peanut avoiders. All of these individuals were followed for 1 year of peanut avoidance, and at completion it was found that only 4.8% of the original peanut consumers were found to be allergic, compared to 18.6% of the original peanut avoiders. This demonstrates that a 12-month period of peanut avoidance was not associated with an increase in the prevalence of peanut allergy in children who have been introduced to peanuts in the first year of life and continued until age 5. For the most part, the immune system has been shown to sustain its tolerance in these individuals, despite a break in regular exposure to peanuts (Du Toit et al. 2016).

While the LEAP trial showed success with peanuts and high-risk infants, it did not look at whether this method could prevent allergies in children in the general population, and if it could be applied to other common dietary allergens. The Enquiring about Tolerance (EAT) study investigated whether early introduction of common dietary allergens from 3 months of age in exclusively breast-fed infants in the general population would prevent food allergies, compared with infants who only receive breast milk for approximately 6 months. A total of 1303 exclusively breast fed 3 month old infants were recruited from the general population, and randomly assigned to the exclusive breast feeding group until approximately 6 months, or the early introduction of six allergenic foods group. These six foods were cooked egg, peanut, cow's milk, sesame, whitefish, and wheat. They were regularly assessed for food allergy to one or more of these six foods between 1 and 3 years of age.

Results of this study were variable. There was a significant 67% lower relative risk of food allergy overall in the early-introduction group, but only in those that adhered strictly to the study protocol by consuming the recommended amounts of the allergenic foods. As well, in those who adhered strictly to the diet the prevalence of any food allergy was significantly lower in the early introduction group than in the group who was exclusively breast-fed until approximately 6 months of age (2.4% vs. 7.3%, $P = 0.01$) The prevalence of peanut allergy (0% vs. 2.5%, $P = 0.003$) and egg allergy (1.4% vs. 5.5%, $P = 0.009$) was also lower in this group. However, significant effects were not observed with milk, fish, wheat or sesame. Interestingly, higher levels of peanut and egg-white ingestion were associated with lower prevalence of allergies to peanut and egg, compared with lower ingestion levels. This raises the question as to whether preventing food allergies through early introduction of allergenic foods was dose-dependent. It was found that the early introduction of all six foods was safe, however challenging to eat the recommended amounts. Despite the promising findings listed above, overall this trial did not show the efficacy of early introduction of allergenic foods in an intention-to-treat analysis. This study was published in *The New England Journal of Medicine* in May 2016. More research is currently being done in this area of allergy and immunology.

In response to the new evidence found in some of the aforementioned studies, in January 2017 the National Institute of Health issued a new three-part addendum to the current clinical guidelines on the early introduction of peanuts-containing foods to infants. The guidelines are aimed at a variety of health care professionals, and are meant to help clarify peanut introduction for infants at different levels of risk of developing a peanut allergy. Part one of the addendums recommends that infants at high risk of developing peanut allergy should have peanut-containing foods introduced to their diets as early as 4–6 months. Infants were deemed to be high risk if they already had severe eczema, egg allergy or

both. It was also recommended that parents of high risk infants check with their health care providers prior to introducing peanuts. Health care providers may consider doing specific IgE blood testing, skin prick testing and/or an oral food challenge before introducing peanut-containing foods for high risk infants.

The second guideline addendum proposes that peanut-containing foods be introduced to infants who have mild to moderate eczema around 6 months of age in order to reduce their risk of developing a peanut allergy. The expert panel suggests that infants in this category may have peanut-containing foods introduced in their home, however recognizing that some health care professionals may prefer to supervise this in their office. The third addendum suggests that infants who do not have any food allergies or eczema may have peanut-containing foods freely introduced. It is recommended in all cases, however, that other solid foods be introduced prior to peanut-containing foods to ensure that the infant is developmentally ready for solid food introduction.

NIH-sponsored expert panel issues clinical guidelines to prevent peanut allergy [Internet]. National Institutes of Health (NIH). 2017 [cited 6 April 2017]. Available from: <https://www.nih.gov/news-events/news-releases/nih-sponsored-expert-panel-issues-clinical-guidelines-prevent-peanut-allergy>

Atopic Dermatitis

Updates in Atopic Dermatitis

Atopic dermatitis (AD) is the most common chronic inflammatory skin disorder in children, affecting up to 30% of infants, and is characterized by pruritus (itchy skin), enhanced transepidermal water loss (TEWL; outward loss of water), reduced skin barrier function, and increased permeability to environmental allergens (Bieber 2008; Hon et al. 2013). Moreover, 50% of children with AD often demonstrate symptoms within the first 6 months of life, highlighting the need for interventions

targeting the skin barrier in infants early in life to reduce the risk of AD (Bieber 2008, 2010). Currently, the main treatments for AD include topical corticosteroids (TCSs), topical calcineurin inhibitors (TCIs), and topical emollients. The goals of these treatments are to reduce both skin inflammation and pruritus, and maintain skin barrier hydration. TCSs are commonly used to treat severe and chronic cases of AD. However, long-term use of TCSs is often associated with both local (including skin atrophy or “skin thinning”) and systemic adverse events (including hypertension and hyperglycemia), restricting their use on thin-skinned areas such as the eyelids (Silverberg et al. 2016). TCIs have also been available for AD treatment for over a decade. They relieve inflammation by inhibiting the production of pro-inflammatory cytokines from T cells (Kalavala and Dohil 2011). However, physicians may be reluctant to prescribe TCIs to their patients due to the FDA Black Box warning highlighting the theoretical lymphoma risk associated with TCI usage (Siegfried et al. 2013). Topical emollients are mixtures of fats and oils that form an occlusive layer on the skin, preventing water evaporation and maintaining skin hydration (Hon et al. 2013). Emollients may appeal to children of all ages due to the low amount of associated side effects and has been a focus of AD prevention in recent studies.

The efficacy of emollients in reducing the incidence of AD in high-risk neonates (defined as having a parent or sibling with AD, asthma, or allergic rhinitis) was recently investigated in a randomized controlled trial. The investigators observed a significant association between daily full-body emollient therapy and reduced AD incidence at 6 months of age. Forty-three percent of untreated infants developed AD at 6 months of age compared with the 22% observed in the emollient-treated infants, reporting a relative risk reduction of 50% (relative risk, 0.50; 95% confidence interval [CI], 0.28–0.90; $P = .017$) (Simpson et al. 2014). This protective effect was replicated in a separate cohort of high-risk Japanese neonates. Approximately 32% fewer neonates in the intervention (daily emollient application) group developed AD/eczema by week 32 compared to neonates in the control

(emollient used as needed by parents) group ($P = .012$, log-rank test) (Horimukai et al. 2014).

In the same cohort of Japanese high-risk neonates, a retrospective post-hoc analysis was recently performed to evaluate the efficacy of different measurements of neonatal skin barrier function in predicting AD development. The investigators observed a significantly higher incidence of AD in neonates with high TEWL (defined as ≥ 6.5 g_{water}/m²/h) than in neonates with low TEWL (defined as < 6.5 g_{water}/m²/h), reporting a hazard ratio (HR) of 2.00 (95% CI, 1.05–3.80; $P < .05$). Similar findings were observed in the control group (HR, 2.65; 95% CI, 1.16–6.06; $P < .05$), but not for the intervention group (HR, 1.60; 95% CI, 0.57–4.49, $P = .368$). All TEWL measurements were made within the first 7 days of life and were made on the forehead (Horimukai et al. 2016). Moreover, these findings were confirmed in a recent prospective birth cohort study following infants up until 12 months of age. With mean forearm TEWL measured at 2 days and 2 months after birth, infants with day 2 TEWL readings ≥ 9.0 g_{water}/m²/h exhibited an increased odds of developing AD at 12 months compared to infants with day 2 TEWL readings < 9.0 g_{water}/m²/h (odds ratio [OR], 7.1; 95% CI, 1.8–12.9; $P = .001$). Similar results were also seen in infants with 2 month TEWL readings ≥ 12.3 g_{water}/m²/h compared to infants with 2 month TEWL readings < 12.3 g_{water}/m²/h (OR, 7.9; 95% CI, 1.7–25.0; $P = .01$) (Kelleher et al. 2015).

Overall, these studies support the use of emollient therapy as a simple and low-cost intervention that could be used from birth to potentially reduce the risk of AD. The latter two studies also highlight the use of TEWL measurements taken as early as 2 days after birth as an effective tool in identifying neonates at high risk of AD. TEWL measurements are non-invasive, quick to perform, and can identify high risk infants in time to start preventative interventions.

Filaggrin Mutations and Skin Barrier Function

Filaggrin (FLG) is a critical structural protein involved in the maintenance of proper skin barrier

function and is primarily expressed in keratinocytes located in the stratum granulosum. Initially made as profilaggrin polymers, these polymers are dephosphorylated and cleaved to form FLG monomers, which aid in the maintenance of natural moisturizing factors (NMFs; a group of metabolites that help maintain skin hydration and pH) and the transformation of keratinocytes into corneocytes in the skin (Proksch et al. 2008; Sandilands et al. 2009; Thyssen and Kezic 2014). Null mutations in the gene encoding *FLG* produce truncated profilaggrin polymers, leading to abnormal keratinocyte morphology, skin barrier impairment, and increased permeability to environmental allergens (Brown and McLean 2012). While the prevalence of *FLG* null mutations is estimated to be 10% in the normal population, this proportion can largely vary depending on race with prevalence being as low as <1% in the African population (Thyssen and Kezic 2014; Asai et al. 2013). These mutations also represent the strongest genetic risk factor for AD development (McGrath 2012). Initially observed in an Irish cohort of children with dermatologist-diagnosed AD, the strong association between *FLG* null mutations and AD has been confirmed in several meta-analyses, reporting an overall OR of 3.12–4.78 (Palmer et al. 2006; van den Oord and Sheikh 2009; Rodríguez et al. 2009).

Recent studies have also reported an association between *FLG* null mutations and disease severity in pediatric AD. A prospective birth cohort study followed children from 1 month up until 7 years of age and observed that children with *FLG* null mutations had an early age of AD onset (246 vs. 473 days; $P < .0001$) and more widespread dermatitis (10% vs. 6% of body area; $P < .001$) compared to children without mutations (Carson et al. 2012). Moreover, a separate prospective cohort study demonstrated that children with *FLG* null mutations had more persistent AD, and were 50% less likely to have symptom-free skin over a 6-month period compared to children without mutations (OR, 0.54; 95% CI, 0.41–0.71; $P < .0001$) (Margolis et al. 2012). Altogether, these findings highlight the strong association between *FLG* null mutations and both the development and severity of AD in children.

Food Allergy Risk with Atopic Dermatitis

Skin barrier impairment is often shown to precede allergic disease development. This is known as the atopic march, the tendency for infants to progress from AD to other allergic diseases (including food allergy and asthma) in later life (Bantz et al. 2014). An impaired skin barrier brought upon by AD or *FLG* null mutations is thought to enhance the percutaneous penetration of food protein, augmenting the risk of both food sensitization (FS) and food allergy (FA) in children.

The association between AD and both FS and FA in children has been evaluated in a very recent systematic review. In the identified population-based studies, approximately 15% of children with AD developed FA symptoms after a food challenge while up to 60% of children with AD were also reported to be food sensitized. The investigators also observed a significant association between AD and overall FS in 3 month old children (OR, 6.18; 95% CI, 2.94–12.98; $P < .001$). Although the adjusted OR for sensitization to different foods (including peanut, milk, and egg) varied, the reported values remained statistically significant (Tsakok et al. 2016). The relationship between early-life skin barrier impairment and the development of FS and FA at 2 years of age was also examined in a recent prospective birth cohort study. Infants were followed until 2 years of age with mean TEWL measured at 2 days after birth (neonatal), 2 months, and 6 months of age. The investigators observed a significant association between FA development at 2 years of age and having top-quartile neonatal TEWL (defined as $>9 \text{ g}_{\text{water}}/\text{m}^2/\text{h}$) compared to infants with bottom-quartile neonatal TEWL (defined as $\leq 5 \text{ g}_{\text{water}}/\text{m}^2/\text{h}$), reporting an OR of 18.7 (95% CI, 7.13–49.3; $P < .0001$). Even in infants without AD, those with top-quartile neonatal TEWL were more likely to develop FA at 2 years compared to infants with bottom-quartile neonatal TEWL (OR, 3.5; 95% CI, 1.3–11.1; $P = .04$) (Kelleher et al. 2016). Overall, these findings support the strong relationship between AD and FS/FA development in children, and

highlight for the first time the association between changes in skin barrier function at birth and FA development at 2 years of age.

Although *FLG* null mutations can impair the skin barrier, the association with food allergy development has only been recently investigated. In a cross-sectional study involving a mixed cohort of English, Dutch, and Irish children, *FLG* null mutations were significantly associated with peanut allergy, yielding an overall OR of 5.3 (95% CI, 2.8–10.2; $P = 3.0 \times 10^{-6}$). Even after controlling for coexisting AD, the association remained significant (Brown et al. 2011). Another prospective birth cohort study followed children from birth up until 11 years of age and found a significant association between *FLG* null mutations and early-life environmental peanut exposure (EPE). Children with *FLG* null mutations demonstrated a sixfold and threefold increase in the odds of peanut sensitization and peanut allergy to increasing house dust peanut protein levels respectively compared to children without mutations (Brough et al. 2014). Similarly, children with either AD (OR, 1.97; 95% CI, 1.26–3.09, $P < .01$) or severe AD (OR, 2.41; 95% CI, 1.30–4.47, $P < .01$) also had an increased risk of peanut sensitization associated with EPE (Brough et al. 2015). Regarding different types of foods, the odds of being reactive to at least one food (including different types of tree nuts, eggs, soy, and milk) was also increased in children with *FLG* null mutations compared to children without mutations, reporting an OR of 4.9 (95% CI, 1.6–14.7; $P = .005$) (van Ginkel et al. 2015).

In summary, these studies emphasize the importance of the skin barrier in the development of both FS and FA in children. With several studies consistently observing an increased FS and FA risk in children with AD or *FLG* null mutations, early introductions of interventions aimed at repairing the skin barrier may be beneficial in reducing the risk of FA development.

Safety of Calcineurin Inhibitors in Atopic Dermatitis

Since their introduction in 2001, TCIs have been used as alternatives to TCSs for the treatment of

AD in both pediatric and adult patients. TCIs avoid the risk of skin atrophy and percutaneous/systemic absorption through the skin (both commonly associated with TCS usage) and is the only approved drug for the management of chronic pediatric AD (Siegfried et al. 2013). There are currently two approved TCIs available for use: pimecrolimus (available as a 1% cream) and tacrolimus (available as a 0.03 and 0.1% ointment). Both inhibit the actions of calcineurin, a calcium-binding messenger protein, thereby preventing the production and release of pro-inflammatory cytokines and mediators from T cells and mast cells (Kalavala and Dohil 2011). Common side effects associated with TCI usage include site-specific burning and pruritus (itching of the skin). Although several clinical trials have demonstrated the efficacy of both pimecrolimus and tacrolimus over TCS in the management of AD in children (Kalavala and Dohil 2011), a US FDA Black Box warning was implemented in January 2006 highlighting the theoretical association between TCI usage and lymphoma/skin melanoma development, the lack of long-term safety data for both pimecrolimus and tacrolimus, and emphasized its use only in adults and children ≥ 2 years of age. (Segal et al. 2013; Siegfried et al. 2013). Since the warning was issued, several physician groups (including the Canadian Society of Allergy and Clinical Immunology and the American Academy of Dermatology) have raised concerns regarding the validity and need of the warning due to the apparent lack of evidence from human studies (Segal et al. 2013; Berger et al. 2006).

To date, several studies have been conducted to evaluate lymphoma risk associated with both pimecrolimus and tacrolimus in the management of pediatric AD. In a longitudinal cohort study of the Pediatric Eczema Elective Registry cohort, no association was found between increased lymphoma risk and topical pimecrolimus use in patients 2–17 years old, yielding standardized incidence ratios of 1.2 (95% CI, 0.5–2.8), 2.0 (95% CI, 0.5–8.2), and 2.9 (95% CI, 0.7–11.7) for all reported malignancies, leukemia, and lymphoma cases respectively. None of these findings reached statistical significance (Margolis et al. 2015). Similar results were also observed in a recent retrospective cohort study of patients with atopic and endogenous eczema, reporting

adjusted HRs for overall malignancy of 1.30 (95% CI, 0.59–2.45, $P = .460$) and 0.82 (95% CI, 0.44–1.39, $P = .508$) for pimecrolimus-exposed and tacrolimus-exposed respectively when compared to the unexposed group (Cai et al. 2016). Furthermore, two recent meta-analyses observed no significant association between lymphoma and malignancy risk and use of TCIs in the management of AD (Legendre et al. 2015; Broeders et al. 2016). These findings together suggest that in both children and adults with AD, pimecrolimus and tacrolimus are not significantly associated with increased lymphoma risk.

Two recent clinical studies have evaluated the long-term safety associated with tacrolimus and pimecrolimus use for AD management in a 4 and 5 year follow-up study respectively (Reitamo et al. 2008; Sigurgeirsson et al. 2015). Although both studies reported adverse events, these events were minor and included skin infection, skin burning, and pruritus. Of note, nine malignancy and carcinoma cases (out of 690 patients aged 2 years and older) were reported in the 4 year study. However, an independent monitoring board did not find an association between the cases and tacrolimus use (Reitamo et al. 2008). Both follow-up studies demonstrated that tacrolimus and pimecrolimus have excellent long-term safety profiles when used to treat AD. Moreover, not only was pimecrolimus well-tolerated after 5 years of follow up, the study population was comprised of infants aged 3–12 months, suggesting that pimecrolimus can be used to treat infants ≤ 2 years of age with mild-to-moderate AD. Within the 5 year open-label study, $>85\%$ of infants achieved overall treatment success with minimal side-effects on the immune system (Sigurgeirsson et al. 2015).

Despite the FDA Black Box warning, these studies suggest that there is no significant association between TCIs and increased lymphoma risk. Long-term safety profiles have been demonstrated for both pimecrolimus and tacrolimus in children, and pimecrolimus has been established as a potential non-TCS alternative for young infants (≤ 2 years of age) with mild-to-moderate AD, associated with TCS-sparing effects and excellent treatment success.

Allergic Rhinitis

Allergic rhinitis is estimated to affect 20–25% of the Canadian population and has a significant impact on quality of life, with many patients reporting inadequate control of their symptoms (Keith et al. 2012). Mainstays of treatment for allergic rhinitis include avoidance, intranasal steroids, oral antihistamines and leukotriene receptor antagonists (Small and Kim 2011). Specific immunotherapy offers the advantage of disease-modifying treatment for those uncontrolled by, intolerant or adverse to pharmacotherapy (Moote and Kim 2011).

Currently two types of allergen immunotherapy are used clinically: subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). SLIT was first accepted as an alternative to SCIT by the WHO in 1998, and then incorporated into the ARIA guidelines (Canonica et al. 2009; Bousquet et al. 2008). While SLIT has been available in Europe for decades, Canada first approved a sublingual grass immunotherapy tablet in 2012. At present there are three sublingual tablet immunotherapy products on the market in Canada (Table 2.1), two of which are approved for use in the pediatric population

Table 2.1 Health Canada approved sublingual immunotherapy tablets

| | Extract composition | Age indication | Dose initiation | Timing of initiation before pollen season | Daily dose |
|-----------|----------------------|----------------|------------------|---|--------------|
| Oralair® | 5 grass pollen | 5–50 years | 3 day escalation | 8–16 weeks | 300IR |
| Grastek® | Timothy grass pollen | 5–65 years | Full dose | At least 8 weeks | 2800 BAU |
| Ragwitek® | Short ragweed pollen | 18–65 years | Full dose | At least 12 weeks | 12 Amb a 1-U |

Merck Canada Inc. (2013), Merck Canada Inc. (2014), Paladin Labs Inc. (2012)

(Oralair[®] and Grastek[®]). The sublingual route of immunotherapy offers several potential benefits over the subcutaneous route including: the comfort of avoiding injections, convenience of home administration and a favourable side effect profile (Hankin and Cox 2014; Dranitsaris and Ellis 2014).

How Effective Is SLIT?

Strength of evidence is seen to support use of SLIT in children in a 2013 systematic review by Lin et al. (2013). This evidence was based on nine studies with 471 participants, and was deemed moderately strong to support SLIT use for treatment of rhinoconjunctivitis in this population.

SLIT has been shown to have a sustained benefit once treatment has been discontinued, supporting its disease modifying properties. One 2013 study demonstrated sustained efficacy in the year post-treatment after 3 years of pre and co-seasonal treatment with a 5 grass pollen sublingual tablet (Didier et al. 2013). Durham et al. (2012) also demonstrated sustained efficacy 2 years after completion of 3 years of pre-seasonal Grastek[®] treatment. Most studies of SLIT have looked at treatment for a single allergen. Very little data is available regarding multiallergen SLIT in polysensitized individuals (Calderon et al. 2012). While there are few studies directly comparing the efficacy of SLIT and SCIT, a 2013 meta-analysis indirectly compared systematic reviews. As expected from prior studies, both had significant benefits over placebo, however one modality could not conclusively be deemed superior to the other (Dretzke et al. 2013).

How Safe Is SLIT?

To date, all studies have shown a common occurrence of local side effects with SLIT, with no reports of severe systemic reactions, anaphylaxis or epinephrine use. While only 15 studies reported drop-out due to adverse reactions, this was seen in 5% of the SLIT group compared to

1% of the placebo group (Radulovic et al. 2011). In an extensive 2013 systematic review the authors comment on the lack of a standardized grading system for adverse events among studies, and the inconsistent reporting of adverse events as a whole. They deem the evidence insufficient to comment on safety, but do note that while local reactions were common, severe systemic reactions were rare with no reported cases of anaphylaxis (Lin et al. 2013).

Clinical trials of Grastek[®] estimated the rate of severe adverse events at 2.9% versus 1% of the placebo population. The most common local reactions were oral pruritus (26.7%), throat irritation (22.6%) and ear pruritus (12.5%) (Hankin and Cox 2014). In two randomized, double-blind, placebo controlled studies of grass tablet immunotherapy published in 2011 including 439 and 345 patients, each reported one use of epinephrine for treatment-related adverse reactions. The former study reported one non-treatment related use in the placebo group, while the latter reported one non-treatment related use in both the placebo and treatment arms (Nelson et al. 2011; Blaiss et al. 2011). To date there have been no reported deaths attributed to sublingual immunotherapy. Insufficient evidence is available to make recommendations regarding the safety of SLIT in pregnancy, severe autoimmune disease and immune deficiency.

When Should SLIT Be Prescribed?

Sublingual immunotherapy is indicated for those with rhinitis or rhinoconjunctivitis in the context of allergen exposure, who have not responded to or tolerated, or are adverse to use of conventional pharmacotherapy. Failure of treatment with traditional pharmacotherapy is not an absolute requirement for use of SLIT. Patients require evidence of sensitization to the relevant pollen via skin prick or in vitro testing. While SLIT has been shown to be safe and effective in children as young as 5, currently only the grass extract products have been approved for use in children (Merck Canada Inc. 2013, 2014; Paladin Labs Inc. 2012; Lin et al. 2013).

Sublingual immunotherapy is contraindicated in patients with severe, unstable or uncontrolled asthma, and it should not be used in patients on beta-blocker therapy or in those with active oral inflammation or sores (Merck Canada Inc. 2013, 2014; Paladin Labs Inc. 2012; Canonica et al. 2014).

Treatment should be initiated 8–16 weeks prior to and through to the end of the pollen season (Table 2.1). For all available SLIT products the first dose should be observed in the prescribing physician's office with subsequent doses self-administered at home. The patient should be monitored for 30 min after the first dose with no food or drink for 5 min after. The current available SLIT products in Canada are initiated at full dose or with a short 3-day escalation depending on the product (Merck Canada Inc. 2013, 2014; Paladin Labs Inc. 2012).

Continuation of therapy relies on patient compliance to the home regimen. Currently all available product monographs advise returning to the prescribing physician for re-initiation should more than 7 days of therapy be missed. Clear instructions should be given to the patient not to take extra doses if a dose is missed (Merck Canada Inc. 2013, 2014; Paladin Labs Inc. 2012). While some physicians may choose to equip those at increased risk for reaction with an epinephrine auto-injector, this is not an absolute requirement for SLIT administration, but should be left to the discretion of the individual allergist.

In summary, SLIT is an effective modality of treatment for allergic rhinitis and rhinoconjunctivitis. Similar to SCIT in efficacy, it can provide long-term benefit with a potentially more favourable side effect profile and increase patient acceptance in the pediatric population.

Anaphylaxis

Introduction

Anaphylaxis is a severe and potentially life-threatening systemic allergic reaction. It remains a substantial health problem and its incidence appears to be rising. In most cases it is mediated

by an immunologic mechanism involving immunoglobulin E (IgE), which leads to the release of chemical mediators from mast cells and basophils. Signs and symptoms can be quite variable involving multiple organ systems and occur within minutes, or up to a few hours, after exposure to a known or likely trigger. Diagnosis is based primarily on clinical signs and symptoms, as well as a detailed description of the acute episode including preceding events and exposures. Prompt administration of intramuscular epinephrine remains the first-line therapy. Other second-line therapies including H1 and H2 antihistamines, bronchodilators and glucocorticoids, are often used as adjunctive agents but should never be used as the initial or sole treatment. A period of observation following acute treatment is recommended because of the risk of biphasic reactions. Long-term management for children who have experienced an anaphylactic episode includes the prescription of an epinephrine auto-injector, education around allergen avoidance (if known), development of an emergency action plan and referral to an allergist for further evaluation.

Definition

Anaphylaxis is defined as a serious allergic reaction that is rapid in onset and may cause death (Sampson et al. 2006). Most cases of anaphylaxis are mediated through an immunologic mechanism involving IgE. This classic form involves the cross-linking of cell-bound allergen-specific IgE upon exposure to a sensitizing allergen with subsequent activation of mast cells and basophils. Upon activation, these cells rapidly release inflammatory mediators such as histamine, tryptase, leukotrienes, and prostaglandins, which produce the clinical effects seen in anaphylaxis (Simons 2010). Other mechanisms of anaphylaxis include immunologic IgE-independent reactions (immune complex complement-mediated and IgG-dependent), nonimmunologic reactions (direct activation of mast cells and basophils in the absence of immunoglobulins) and idiopathic reactions (Simons 2010). Despite having different underlying mechanisms, these

reactions are clinically indistinguishable and have the same acute management (Lieberman et al. 2005).

In the pediatric population, food continues to be the most common trigger of anaphylaxis (Simons et al. 2011). Any food can potentially trigger anaphylaxis, but the predominant foods include peanuts, tree nuts, cow's milk, egg, fish, shellfish and soy (Lieberman et al. 2010). Other triggers include venom from stinging insects (such as bees, wasps, yellow jacket, hornets), medications (most commonly penicillins, other antibiotics and nonsteroidal anti-inflammatory drugs) and natural rubber latex. Less common causes include physical factors (exercise, cold, heat, sunlight/UV radiation), food additives (such as spices and monosodium glutamate) and hormonal changes (menstrual factors) (Simons 2016). In certain cases, the trigger is unknown; this is referred to as idiopathic anaphylaxis (Simons et al. 2011). The aforementioned triggering agents can induce anaphylaxis through immunologic or nonimmunologic mechanisms. Foods, medications and insect stings, the most common triggers of anaphylaxis in children, are mediated through an IgE-dependent immunological mechanism (Simons 2016).

Epidemiology

The prevalence of anaphylaxis from all triggers is estimated to be 0.05–2% (Lieberman et al. 2006); however, the rate of occurrence appears to be increasing (Wood et al. 2014). This observation is supported by various studies, including a recently published Canadian study by Hockstadter et al. (2016). The data for the study was collected from the Cross-Canada Anaphylaxis Registry (C-CARE), which is an initiative that aims to assess the rate, triggers, management and temporal trends of anaphylaxis. The findings show that the percentage of pediatric emergency department (ED) visits due to anaphylaxis doubled over a 4-year period (2011 to 2015), from 0.20 to 0.41%, with the largest increase seen in the final 2 years of the study period. The authors also reported that the majority (80.2%) of anaphylaxis

cases were triggered by food, with peanut and tree nut being the most predominant. Even though these results were limited to one pediatric centre, they are consistent with previous literature outlining an overall increase in anaphylaxis rates (Hockstadter et al. 2016). Furthermore, a report by the Canadian Institute for Health Information (CIHI) released in 2015 found similar increases in anaphylaxis rates based on Canadian ED visits. The data revealed that while the number of visits to Canadian EDs for all allergic reactions remained stable over a 7-year period, the number of visits per 100,000 population specifically for anaphylaxis significantly increased by 95%. Specifically, the rate of anaphylaxis visits in Ontario and Alberta (for which complete data was available) nearly doubled over the study period for children less than 18 years of age. Adolescents (ages 13–17) experienced the highest increase. The study also reported that there was a 64% increase in the rate of individuals prescribed an epinephrine auto-injector (CIHI 2015). The exact reasons for the increasing rates are not clear but increasing awareness is thought to be one of the contributing factors.

Clinical Presentation

Anaphylaxis can present with a wide variety of signs and symptoms depending on the body systems affected. Typically, at least two or more target organs are involved, which can include the cutaneous, respiratory, gastrointestinal, cardiovascular and central nervous systems. Skin involvement (urticaria, angioedema, itching, flushing) is the most common clinical manifestation and is reported in up to 80–90% of patients (Simons et al. 2011). In the absence of skin involvement, the diagnosis of anaphylaxis may be difficult to make but cannot be excluded (Lieberman et al. 2010). Respiratory tract and cardiovascular involvement are of the more concerning signs and symptoms, which present in 60–70% and up to 45% of individuals, respectively (Simons 2010).

Signs and symptoms of anaphylaxis are usually sudden in onset and occur within minutes, or

up to a few hours, after exposure to the offending antigen. The majority of children have uniphasic reactions. Some children, however, experience a biphasic reaction, which is defined as the return of symptoms within 1–72 h (usually 8–10 h) after the initial symptoms have resolved without any further exposure to the trigger (Simons et al. 2011). The reported incidence of biphasic reactions in the literature ranges between 1 and 23% (Alqurashi et al. 2015). A recent Canadian study by Alqurashi et al. (2015) found the incidence of biphasic reactions to be 15% in their pediatric cohort, which was not significantly different from previously reported pediatric studies. The study also found that approximately 75% of these reactions occurred within 6 h of the onset of the initial reaction. Given the risk of a biphasic reaction, it is recommended that children be observed for a certain period of time following an anaphylactic episode. There is no consensus regarding the optimal duration of observation given that there are no validated and widely accepted clinical predictors of biphasic reactions (Sampson et al. 2006; Alqurashi et al. 2015). As one of the main objectives of their study, Alqurashi et al. (2015) identified five independent predictive factors, which included: delay in presentation to the ED longer than 90 min after the onset of the initial reaction, children age 6–9 years, wide pulse pressure at triage, treatment of the initial reaction with more than one dose of epinephrine and administration of inhaled beta-agonists in the ED. Overall, they found that the severity of the initial reaction appears to be associated with an increased risk of biphasic reactions. Children presenting with severe initial anaphylactic episodes would therefore benefit from a prolonged observation period. Furthermore, those with mild anaphylaxis who do not have any of the above risk factors could be considered for possible early discharge from the ED (defined as less than 6 h from the onset of reaction). The authors recommended that these clinical predictors be used with caution prior to being validated in a large prospective study (Alqurashi et al. 2015). The majority of literature and current guidelines recommend that observation periods be individualized. A 4–8 h observation period is reasonable in

most patients, with a prolonged length of time for those with severe or protracted symptoms (Sampson et al. 2006; Lieberman et al. 2015).

Anaphylaxis can range in severity from milder episodes to very severe reactions, progressing within minutes to respiratory or cardiovascular compromise and death (Simons and Sheikh 2013). It is important to recognize that the clinical manifestations, as well as the severity of anaphylaxis, are unpredictable and may differ from one patient to another and from one episode to another in the same patient (Simons et al. 2011). In infants and young children, anaphylaxis may be difficult to recognize and diagnose for a number of reasons. Many of the signs and symptoms of anaphylaxis (itching, throat and chest tightness and other subjective symptoms) cannot be described by infants. In addition, various signs are nonspecific and are also seen in healthy children for other reasons; examples include flushing and dysphonia after crying, spitting up after feeding, behavioural changes, such as irritability, inconsolable crying, clinging to a caregiver and incontinence (Rudders et al. 2011; Simons and Sampson 2015; Simons et al. 2011). A high index of suspicion is therefore often needed to make the diagnosis in infants and younger children.

Diagnosis

The diagnosis of anaphylaxis is primarily based upon clinical signs and symptoms, as well as a careful and detailed description of the acute episode, including the preceding events and any potential exposures (Simons et al. 2011). Specific diagnostic criteria for anaphylaxis have been established by a multidisciplinary panel of experts and continue to be widely used. Anaphylaxis is highly likely when any one of the three following criteria are fulfilled: acute skin and/or mucosal involvement and at least one of the following: respiratory compromise or reduced blood pressure or symptoms of end-organ dysfunction; two or more of the following that occur rapidly after exposure to a likely allergen: skin/mucosal involvement, respiratory compromise, reduced blood pressure, gastrointestinal symptoms; reduced blood pressure after

exposure to a known allergen (Sampson et al. 2006). Because the majority of anaphylactic reactions have cutaneous involvement, a large number of them can be identified by the first criterion. The criteria have been shown to have excellent specificity and good sensitivity, and are believed to identify more than 90% of cases of anaphylaxis (Sampson et al. 2006; Campbell et al. 2012).

The patient's history is an essential tool to help establish the cause of anaphylaxis. It should focus on the following key elements: recall of exposure to potential triggering agents (such as foods, medications, insect stings) and events in the hours preceding the onset of symptoms; the time elapsed between exposure and symptom onset; description of clinical manifestations (such as flushing, urticaria, airway involvement, gastrointestinal symptoms); progression of signs and symptoms; and enquiry into any previous reactions (Lieberman et al. 2005; Wasserman et al. 2010).

Laboratory tests can be used to support a diagnosis of anaphylaxis, but they are generally not required because anaphylaxis is primarily a clinical diagnosis. Increased levels of serum total tryptase and plasma histamine can be observed during or shortly after an acute anaphylactic episode (Lieberman et al. 2010). Normal levels, however, cannot be used to rule out anaphylaxis (Simons et al. 2010). Measurements of these chemical mediators are often normal in children and in food-triggered reactions (Simons 2016; Simons et al. 2010). They may be useful, however, if the diagnosis is unclear, or to distinguish anaphylaxis from other disorders that have overlapping clinical features, such as severe asthma. Obtaining a tryptase level after an acute event once symptoms have resolved can be useful as a screening test for systemic mastocytosis, where levels will remain elevated (Lieberman et al. 2010). Additional investigations may include skin prick tests and/or *in vitro* IgE tests to identify the specific cause of anaphylaxis. These tests can determine the presence of specific IgE antibodies to foods, certain medications (such as penicillin) and stinging insects. Skin testing is more sensitive and is generally the preferred diagnostic method (Lieberman et al. 2010).

Other conditions present with similar clinical features to anaphylaxis and should be considered in the differential diagnosis. The most common entities in children include acute generalized urticaria associated with a viral infection, foreign body aspiration, acute asthma, vasovagal syncope and panic attacks or anxiety (Simons 2016). In infants, an apparent life-threatening event, congenital abnormalities of the respiratory or gastrointestinal tracts and food protein-induced enterocolitis syndrome are important to consider (Simons and Sampson 2015). Less common conditions include excess histamine syndromes, postprandial syndromes, seizures and nonorganic diseases such as vocal cord dysfunction (Simons 2016).

Management

The treatment of suspected anaphylaxis begins with a rapid assessment of the airway, breathing, circulation, and skin examination, with simultaneous administration of epinephrine (Wasserman et al. 2010). Epinephrine remains the cornerstone of management (Lieberman et al. 2005). It should be given by intramuscular injection in the mid-antrolateral thigh, as this route and location has been shown to have superior absorption in comparison to deltoid and subcutaneous injections (Simons et al. 1998, 2001). In children, the recommended dose is 0.01 mg/kg of a 1:1000 dilution, to a maximum of 0.15 mg in infants, 0.3 mg in children and 0.5 mg in adolescents (and adults) (Simons 2016). The dose can be repeated every 5–15 min as needed, depending on the patient's clinical response. Intravenous epinephrine is rarely used, however may be necessary in those with uncompensated shock or cardiac arrest (Lieberman et al. 2005). There are no absolute contraindications to epinephrine and it should be given without any hesitation or delay to any individual where anaphylaxis is diagnosed or strongly suspected (Wasserman et al. 2010).

Additional treatment measures should include: removal of the offending trigger (if relevant, for example, discontinuation of an intravenous medication); administration of supplemental oxygen and maintenance of an adequate airway;

placement of the child in a supine position with their legs elevated to optimize venous return to the heart and perfusion of vital organs; and establishment of intravenous access, preferably two large bore IVs in the anticipation of the need for aggressive fluid resuscitation (Lieberman et al. 2010). Intravenous fluids should be administered since massive fluid shifts may occur due to increased vascular permeability associated with anaphylaxis (Lieberman et al. 2005). Patients with hypotension and poor perfusion that are unresponsive to epinephrine and positioning may require multiple fluid boluses of a crystalloid solution, typically 20 mL/kg of normal saline (Lieberman et al. 2005; Cheng 2011).

Adjunctive agents that may be considered in the management of anaphylaxis include antihistamines (H1 and H2 antagonists), corticosteroids and bronchodilators. These therapies continue to be used as second-line treatments since they do not have the same life saving effects compared with epinephrine, and should therefore never be used in place of epinephrine (Simons et al. 2011). Antihistamines can be used to control the cutaneous symptoms of anaphylaxis, however they do not prevent or relieve upper airway obstruction or hypotension (Sampson et al. 2006; Simons et al. 2011). There is a lack of evidence in the literature to support the use of H1 and H2 antihistamines in the overall management of anaphylaxis (Lieberman et al. 2010). Corticosteroids have a slow onset of action, and do not play a role in the acute management of anaphylaxis (Simons et al. 2011). They have been thought to help prevent or minimize prolonged or biphasic reactions, although there is not strong evidence to support this (Choo et al. 2010). Inhaled bronchodilators may be used in individuals who present with bronchospasm that have not responded to epinephrine, however they do not prevent or treat upper airway obstruction or laryngeal edema (Lieberman et al. 2015).

Children should be observed and monitored for a period of time following an acute anaphylactic episode due to the risk of biphasic reactions. The duration should be individualized and based on various factors including the severity of the initial reaction, response to treatment, history of previous biphasic reactions, medical

comorbidities (such as asthma) and access to care. The recommended observation period for most patients is a minimum of 4–8 h following the reaction (Simons et al. 2011; Lieberman et al. 2015). Prolonged observation periods or hospital admission may be necessary for those with severe or refractory symptoms (Waserman et al. 2010).

The principles of long-term management for patients who have experienced anaphylaxis include: prescription of an epinephrine auto-injector and instructions on how and when to use it; education on avoidance of precipitating triggers; development of an anaphylaxis action plan; and referral to an allergist for further assessment and ongoing management (Simons et al. 2011).

References

- Allergy Skin Test [Internet]. Medbroadcast. 2016. [Cited 25 May 2016]. <http://www.medbroadcast.com/procedure/getprocedure/Allergy-Skin-Test>
- Alqurashi W, Stiell I, Chan K, Neto G, Alsadoon A, Wells G. Epidemiology and clinical predictors of biphasic reactions in children. *Ann Allergy Asthma Immunol.* 2015;115:217–23.
- Asai Y, Greenwood C, Hull PR, Alizadehfar R, Ben-Shoshan M, Brown SJ, et al. Filaggrin gene mutation associations with peanut allergy persist despite variations in peanut allergy diagnostic criteria or asthma status. *J Allergy Clin Immunol.* 2013;132:239–42.
- Bantz SK, Zhu Z, Zheng T. The atopic march: progression from atopic dermatitis to allergic rhinitis and asthma. *J Clin Cell Immunol.* 2014;5:202.
- Berger TG, Duvic M, Van Voorhees AS, MJ VB, Frieden IJ, American Academy of Dermatology Association Task Force. The use of topical calcineurin inhibitors in dermatology: safety concerns. Report of the American Academy of Dermatology Association Task Force. *J Am Acad Dermatol.* 2006;54:818–23.
- Bernstein IL, Li JT, Bernstein DI, Hamilton R, Spector SL, Tan R, et al. Allergy diagnostic testing: an updated practice parameter. *Ann Allergy Asthma Immunol.* 2008;100(3 Suppl 3):S1–148.
- Bieber T. Atopic dermatitis. *N Engl J Med.* 2008;358(14):1483–94.
- Bieber T. Atopic dermatitis. *Ann Dermatol.* 2010;22:125–37.
- Blaiss M, Maloney J, Nolte H, Gawchik S, Yao R, Skoner DP. Efficacy and safety of timothy grass allergy immunotherapy tablets in North American children and adolescents. *J Allergy Clin Immunol.* 2011;127:64–71.

- Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy*. 2008;63(Suppl 86):8–160.
- Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol*. 2010;126(6 Suppl):S1–58.
- Broeders JA, Ahmed Ali U, Fischer G. Systematic review and meta-analysis of randomized clinical trials (RCTs) comparing topical calcineurin inhibitors with topical corticosteroids for atopic dermatitis: a 15-year experience. *J Am Acad Dermatol*. 2016;75(2):410–9. e3. doi:10.1016/j.jaad.2016.02.1228.
- Brough HA, Simpson A, Makinson K, Hankinson J, Brown S, Douiri A, et al. Peanut allergy: effect of environmental peanut exposure in children with filaggrin loss-of-function mutations. *J Allergy Clin Immunol*. 2014;134:867–875.e1.
- Brough HA, Liu AH, Sicherer S, Makinson K, Douiri A, Brown SJ, et al. Atopic dermatitis increases the effect of exposure to peanut antigen in dust on peanut sensitization and likely peanut allergy. *J Allergy Clin Immunol*. 2015;135:164–70.
- Brown SJ, McLean WHI. One remarkable molecule: filaggrin. *J Invest Dermatol*. 2012;132(3 Pt 2):751–62.
- Brown SJ, Asai Y, Cordell HJ, Campbell LE, Zhao Y, Liao H, et al. Loss-of-function variants in the filaggrin gene are a significant risk factor for peanut allergy. *J Allergy Clin Immunol*. 2011;127:661–7.
- Burks AW, Tang M, Sicherer S, Muraro A, Eigenmann PA, Ebisawa M, et al. ICON: food allergy. *J Allergy Clin Immunol*. 2012;129:906–20.
- Cai SCS, Li W, Tian EAL, Allen JC, Tey HL. Topical calcineurin inhibitors in eczema and cancer association: a cohort study. *J Dermatolog Treat*. 2016;27(6):531–7.
- Calderon M, Cox L, Casale TB, Moingeon P, Demoly P. Multiple allergen and single allergen strategies in polysensitized patients: looking at the published evidence. *J Allergy Clin Immunol*. 2012;129:929–34.
- Campbell RL, Hagan JB, Manivannan V, Decker WW, Kanthala AR, Bellolio MF, et al. Evaluation of national institute of allergy and infectious diseases/food allergy and anaphylaxis network criteria for the diagnosis of anaphylaxis in emergency department patients. *J Allergy Clin Immunol*. 2012;129:748–52.
- Canadian Institute for Health Information (CIHI). Visits to the ED for anaphylaxis nearly doubled in 7 years. 2015. [Cited 10 Sept 2015]. <https://www.cihi.ca/en/types-of-care/hospital-care/visits-to-the-ed-for-anaphylaxis-nearly-doubled-in-7-years>
- Canonica GW, Bousquet J, Casale T, Lockey RF, Baena-Cagnani CE, Pawankar R, et al. Sub-lingual immunotherapy: World Allergy Organization position paper 2009. *World Allergy Organ J*. 2009;2:233–81.
- Canonica GW, Cox L, Pawankar R, Baena-Cagnani CE, Blaiss M, Bonini S, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. *World Allergy Organ J*. 2014;7:6.
- Carson CG, Rasmussen MA, Thyssen JP, Menné T, Bisgaard H. Clinical presentation of atopic dermatitis by filaggrin gene mutation status during the first 7 years of life in a prospective cohort study. *PLoS One*. 2012;7:e48678.
- Celik-Bilgili S, Mehl A, Verstege A, Staden U, Nocon M, Beyer K, et al. The predictive value of specific immunoglobulin E levels in serum for the outcome of oral food challenges. *Clin Exp Allergy*. 2005;35:268–73.
- Chafen JJS, Newberry SJ, Riedl MA, Bravata DM, Maglione M, Suttrop MJ, et al. Diagnosing and managing common food allergies: a systematic review. *JAMA*. 2010;303:1848–56.
- Cheng A. Emergency treatment of anaphylaxis in infants and children. *Paediatr Child Health*. 2011;16:35–40.
- Choo KJ, Simons E, Sheikh A. Glucocorticoids for the treatment of anaphylaxis: Cochrane systematic review. *Allergy*. 2010;65:1205–11.
- Connors L, Waserman S. Food allergy—the nuts and bolts [Internet]. Parkhurst Exchange 2010. 2010. [Cited 25 May 2016]. <http://www.parkhurstexchange.com/clinical-reviews/apr10/food-allergy>
- Didier A, Malling HJ, Worm M, Horak F, Sussman G, Melac M, et al. Post-treatment efficacy of discontinuous treatment with 300 IR 5 grass pollen sublingual tablet in adults with grass pollen induced allergic rhinoconjunctivitis. *Clin Exp Allergy*. 2013;43:568–77.
- Dranitsaris G, Ellis AK. Sublingual or subcutaneous immunotherapy for seasonal allergic rhinitis: an indirect analysis of efficacy, safety and cost. *J Eval Clin Pract*. 2014;20:225–38.
- Dretzke J, Meadows A, Novielli N, Huissoon A, Fry-Smith A, Meads C. Subcutaneous and sublingual immunotherapy for seasonal allergic rhinitis: a systematic review and indirect comparison. *J Allergy Clin Immunol*. 2013;131:1361–6.
- Du Toit G, Katz Y, Sasieni P, Meshor D, Maleki SJ, Fisher HR, et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol*. 2008;122:984–91.
- Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med*. 2015;372:803–13.
- Du Toit G, Sayre PH, Roberts G, Sever ML, Lawson K, Bahnson HT, et al. Effect of avoidance on peanut allergy after early peanut consumption. *N Engl J Med*. 2016;374:1435–43.
- Durham SR, Emminger W, Kapp A, de Monchy JG, Rak S, Scadding GK, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. *J Allergy Clin Immunol*. 2012;129:717–25.
- Emmett SE, Angus FJ, Fry JS, Lee PN. Perceived prevalence of peanut allergy in Great Britain and its association with other atopic conditions and with peanut allergy in other household members. *Allergy*. 1999;54:380–5.
- Fleischer DM, Conover-Walker MK, Christie L, Burks AW, Wood RA. The natural progression of peanut allergy: resolution and the possibility of recurrence. *J Allergy Clin Immunol*. 2003;112:183–9.

- Fleischer DM, Conover-Walker MK, Matsui EC, Wood RA. The natural history of tree nut allergy. *J Allergy Clin Immunol*. 2005;116:1087–93.
- Graham-Rowe D. Lifestyle: when allergies go west. *Nature*. 2011;479:S2–4.
- Greer FR, Sicherer SH, Burks AW, American Academy of Pediatrics Committee on Nutrition, American Academy of Pediatrics Section on Allergy and Immunology. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics*. 2008;121:183–91.
- Gupta RS, Springston EE, Warriar MR, Smith B, Kumar R, Pongracic J, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics*. 2011;128:e9–17.
- Hankin CS, Cox L. Allergy immunotherapy: what is the evidence for cost saving? *Curr Opin Allergy Clin Immunol*. 2014;14(4):363–70.
- Hockstadter E, Clarke A, De Schryver S, LaVieille S, Alizadehfah R, Joseph L, et al. Increasing visits for anaphylaxis and the benefits of early epinephrine administration: a 4-year study at a pediatric emergency department in Montreal, Canada. *J Allergy Clin Immunol*. 2016;137:1888–90.e4. doi:10.1016/j.jaci.2016.02.016.
- Hon KL, Leung AKC, Barankin B. Barrier repair therapy in atopic dermatitis: an overview. *Am J Clin Dermatol*. 2013;14:389–99.
- Horimukai K, Morita K, Narita M, Kondo M, Kitazawa H, Nozaki M, et al. Application of moisturizer to neonates prevents development of atopic dermatitis. *J Allergy Clin Immunol*. 2014;13:824–30.e6.
- Horimukai K, Morita K, Narita M, Kondo M, Kabashima S, Inoue E, et al. Transepidermal water loss measurement during infancy can predict the subsequent development of atopic dermatitis regardless of filaggrin mutations. *Allergol Int*. 2016;65:103–8.
- Hourihane JO, Dean TP, Warner JO. Peanut allergy in relation to heredity, maternal diet, and other atopic diseases: results of a questionnaire survey, skin prick testing, and food challenges. *BMJ*. 1996;313:518–21.
- Hu Y, Chen J, Li H. Comparison of food allergy prevalence among Chinese infants in Chongqing, 2009 versus 1999. *Pediatr Int*. 2010;52:820–4.
- Jackson KD, Howie LD, Akinbami LJ. Trends in allergic conditions among children: United States, 1997–2011. *NCHS Data Brief*. 2013;(121):1–8.
- Johansson SGO, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol*. 2004;113:832–6.
- Kalavala M, Dohil MA. Calcineurin inhibitors in pediatric atopic dermatitis: a review of current evidence. *Am J Clin Dermatol*. 2011;12:15–24.
- Keith P, Desrosiers M, Laister T, Schellenberg RR, Wasserman S. The burden of allergic rhinitis (AR) in Canada: perspectives of physicians and patients. *Allergy Asthma Clin Immunol*. 2012;8:7.
- Kelleher M, Dunn-Galvin A, Hourihane JO, Murray D, Campbell LE, McLean WHI, et al. Skin barrier dysfunction measured by transepidermal water loss at 2 days and 2 months predates and predicts atopic dermatitis at 1 year. *J Allergy Clin Immunol*. 2015;135:930–5.e1.
- Kelleher MM, Dunn-Galvin A, Gray C, Murray DM, Kiely M, Kenny L, et al. Skin barrier impairment at birth predicts food allergy at 2 years of age. *J Allergy Clin Immunol*. 2016;137:1111–6.e8.
- Kotz D, Simpson CR, Sheikh A. Incidence, prevalence, and trends of general practitioner-recorded diagnosis of peanut allergy in England, 2001 to 2005. *J Allergy Clin Immunol*. 2011;127:623–30.e1.
- Legendre L, Barnette T, Mazereeuw-Hautier J, Meyer N, Murrell D, Paul C. Risk of lymphoma in patients with atopic dermatitis and the role of topical treatment: a systematic review and meta-analysis. *J Am Acad Dermatol*. 2015;72:992–1002.
- Leung R, Ho A, Chan J, Choy D, Lai CK. Royal jelly consumption and hypersensitivity in the community. *Clin Exp Allergy*. 1997;27:333–6.
- Leysen J, Sabato V, Verweij MM, De Knop KJ, Bridts CH, De Clerck LS, et al. The basophil activation test in the diagnosis of immediate drug hypersensitivity. *Expert Rev Clin Immunol*. 2011;7:349–55.
- Lieberman P, Kemp SF, Oppenheimer JJ, Land I, Bernstein IL, Nicklas RA, et al. The diagnosis and management of anaphylaxis: an updated practice parameter. *J Allergy Clin Immunol*. 2005;115:483–523.
- Lieberman P, Camargo CA Jr, Bohlke K, Jick H, Miller RL, Sheikh A, et al. Epidemiology of anaphylaxis: findings of the American college of allergy, asthma and immunology epidemiology of anaphylaxis working group. *Ann Allergy Asthma Immunol*. 2006;97:596–602.
- Lieberman P, Nicklas RA, Oppenheimer J, Kemp SF, Lang DM. The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol*. 2010;126:477–80.
- Lieberman P, Nicklas RA, Randolph C, Oppenheimer J, Bernstein D, Bernstein J, et al. Anaphylaxis—a practice parameter update 2015. *Ann Allergy Asthma Immunol*. 2015;115:341–84.
- Lin ST, Erekosima N, Kim JM, Ramanathan M, Suarez-Cuervo C, Chelladurai Y, et al. Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. *J Am Med Assoc*. 2013;309:1278–88.
- Liu AH, Jaramillo R, Sicherer SH, Wood RA, Bock SA, Burks AW, et al. National prevalence and risk factors for food allergy and relationship to asthma: results from the National Health and Nutrition Examination Survey 2005–2006. *J Allergy Clin Immunol*. 2010;126:798–806.e13.
- Majkowska-Wojciechowska B, Pełka J, Korzon L, Kozłowska A, Kaczała M, Jarzebska M, et al. Prevalence of allergy, patterns of allergic sensitization and allergy risk factors in rural and urban children. *Allergy*. 2007;62:1044–50.
- Margolis DJ, Apter AJ, Gupta J, Hoffstad O, Papadopoulos M, Campbell LE, et al. The persistence of atopic der-

- matitis and filaggrin (FLG) mutations in a US longitudinal cohort. *J Allergy Clin Immunol.* 2012;130:912–7.
- Margolis DJ, Abuabara K, Hoffstad OJ, Wan J, Raimondo D, Bilker WB. Association between malignancy and topical use of pimecrolimus. *JAMA Dermatol.* 2015;151:594–9.
- McGowan EC, Keet CA. Prevalence of self-reported food allergy in the National Health and Nutrition Examination Survey (NHANES) 2007–2010. *J Allergy Clin Immunol.* 2013;132(5):1216–1219.e5.
- McGrath JA. Profilaggrin, dry skin, and atopic dermatitis risk: size matters. *J Invest Dermatol.* 2012;132:10–1.
- Merck Canada Inc. Grastek product monograph 2013. Kirkland, Quebec; 2013.
- Merck Canada Inc. Ragwitek product monograph 2014. Kirkland, Quebec; 2014.
- Moote W, Kim H. Allergen-specific immunotherapy. *Allergy Asthma Clin Immunol.* 2011;7(Suppl 1):S5.
- Muraro A, Dreborg S, Halken S, Høst A, Niggemann B, Aalberse R, et al. Dietary prevention of allergic diseases in infants and small children. Part II. Evaluation of methods in allergy prevention studies and sensitization markers. Definitions and diagnostic criteria of allergic diseases. *Pediatr Allergy Immunol.* 2004;15:196–205.
- Nelson HS, Nolte H, Creticos P, Maloney J, Wu J, Bernstein DI. Efficacy and safety of timothy grass allergy immunotherapy tablet treatment in North American adults. *J Allergy Clin Immunol.* 2011;127:72–80.
- Nowak-Węgrzyn A, Assa'ad AH, Bahna SL, Bock SA, Sicherer SH, Teuber SS, et al. Work Group report: oral food challenge testing. *J Allergy Clin Immunol.* 2009;123(6 Suppl):S365–83.
- Nwaru BI, Takkinen H-M, Niemelä O, Kaila M, Erkkola M, Ahonen S, et al. Introduction of complementary foods in infancy and atopic sensitization at the age of 5 years: timing and food diversity in a Finnish birth cohort. *Allergy.* 2013;68:507–16.
- Osborne NJ, Koplin JJ, Martin PE, Gurrin LC, Lowe AJ, Matheson MC, et al. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. *J Allergy Clin Immunol.* 2011;127:668–76.e1-2.
- Paladin Labs Inc. Oralair product monograph 2012. Montreal, Quebec; 2012.
- Palmer CNA, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet.* 2006;38:441–6.
- Perry TT, Pesek RD. Clinical manifestations of food allergy. *Pediatr Ann.* 2013;42:e106–11.
- Proksch E, Brandner JM, Jensen J-M. The skin: an indispensable barrier. *Exp Dermatol.* 2008;17:1063–72.
- Radulovic S, Wilson D, Calderon M, Durham S. Systematic reviews of sublingual immunotherapy (SLIT). *Allergy.* 2011;66:740–52.
- Rancé F, Dutau G, Abbal MM. Mustard allergy in children. *Allergy.* 2000;55:496–500.
- Reitamo S, Rustin M, Harper J, Kalimo K, Rubins A, Cambazard F, et al. A 4-year follow-up study of atopic dermatitis therapy with 0.1% tacrolimus ointment in children and adult patients. *Br J Dermatol.* 2008;159:942–51.
- Rodríguez E, Baurecht H, Herberich E, Wagenpfeil S, Brown SJ, Cordell HJ, et al. Meta-analysis of filaggrin polymorphisms in eczema and asthma: robust risk factors in atopic disease. *J Allergy Clin Immunol.* 2009;123:1361–70.e7.
- Rudders SA, Banerji A, Clark S, Camargo CA Jr. Age-related differences in the clinical presentation of food-induced anaphylaxis. *J Pediatr.* 2011;158:326–8.
- Sampson HA. Update on food allergy. *J Allergy Clin Immunol.* 2004;113:805–819; quiz 820.
- Sampson HA, Munoz-Furlon A, Campbell RL, Adkinson NF Jr, Bock A, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report—second national institute of allergy and infectious disease/food allergy and anaphylaxis network symposium. *J Allergy Clin Immunol.* 2006;117:391–7.
- Sandilands A, Sutherland C, Irvine AD, McLean WHI. Filaggrin in the frontline: role in skin barrier function and disease. *J Cell Sci.* 2009;122(Pt 9):1285–94.
- Savage JH, Matsui EC, Skripak JM, Wood RA. The natural history of egg allergy. *J Allergy Clin Immunol.* 2007;120:1413–7.
- Scurlock AM, Lee LA, Burks AW. Food allergy in children. *Immunol Allergy Clin North Am.* 2005;25:369–388, vii–viii.
- Segal AO, Ellis AK, Kim HL. CSACI position statement: safety of topical calcineurin inhibitors in the management of atopic dermatitis in children and adults. *Allergy Asthma Clin Immunol.* 2013;9:24.
- Sicherer SH. Food protein-induced enterocolitis syndrome: case presentations and management lessons. *J Allergy Clin Immunol.* 2005;115:149–56.
- Sicherer SH. Epidemiology of food allergy. *J Allergy Clin Immunol.* 2011;127:594–602.
- Sicherer SH, Sampson HA. 9. Food allergy. *J Allergy Clin Immunol.* 2006;117(2 Suppl Mini-Primer):S470–5.
- Sicherer SH, Sampson HA. Food allergy. *J Allergy Clin Immunol.* 2010;125(2 Suppl 2):S116–25.
- Sicherer SH, Simons FER. Section on Allergy and Immunology, American Academy of Pediatrics. Self-injectable epinephrine for first-aid management of anaphylaxis. *Pediatrics.* 2007;119:638–46.
- Sicherer SH, Furlong TJ, Maes HH, Desnick RJ, Sampson HA, Gelb BD. Genetics of peanut allergy: a twin study. *J Allergy Clin Immunol.* 2000;106(1 Pt 1): 53–6.
- Sicherer SH, Muñoz-Furlong A, Sampson HA. Prevalence of peanut and tree nut allergy in the United States determined by means of a random digit dial telephone survey: a 5-year follow-up study. *J Allergy Clin Immunol.* 2003;112:1203–7.
- Siegfried EC, Jaworski JC, Hebert AA. Topical calcineurin inhibitors and lymphoma risk: evidence

- update with implications for daily practice. *Am J Clin Dermatol.* 2013;14:163–78.
- Sigurgeirsson B, Boznanski A, Todd G, Vertruyen A, Schuttelaar M-LA, Zhu X, et al. Safety and efficacy of pimecrolimus in atopic dermatitis: a 5-year randomized trial. *Pediatrics.* 2015;135:597–606.
- Silverberg JI, Nelson DB, Yosipovitch G. Addressing treatment challenges in atopic dermatitis with novel topical therapies. *J Dermatolog Treat.* 2016;11:1–9.
- Simons FER. Anaphylaxis. *J Allergy Clin Immunol.* 2010;125:S163–81.
- Simons FER. Anaphylaxis: assessment and management. In: Leung DYM, Szefer SJ, Bonilla FA, Akdis CA, Sampson HA, Heim A, editors. *Pediatric allergy: principles and practice.* 3rd ed. Edinburgh: Elsevier; 2016. p. 524–36.
- Simons FER, Sampson HA. Anaphylaxis: unique aspects of clinical diagnosis and management in infants (birth to age 2 years). *J Allergy Clin Immunol.* 2015;135:1125–31.
- Simons FER, Sheikh A. Anaphylaxis: the acute episode and beyond. *BMJ.* 2013;346:1–10.
- Simons FER, Roberts JR, Gu X, Simons KJ. Epinephrine absorption in children with a history of anaphylaxis. *J Allergy Clin Immunol.* 1998;101:33–7.
- Simons FER, Gu X, Simons KJ. Epinephrine absorption in adults: intramuscular versus subcutaneous injection. *J Allergy Clin Immunol.* 2001;108:871–3.
- Simons FER, Arduzzo LRF, Beatrice Bilò M, El-Gamal YM, Ledford DK, Ring J, Sanchez-Borges M, Senna GE, Sheikh A, Thong BY. World Allergy Organization Guidelines for the Assessment and Management of Anaphylaxis. *World Allergy Organ J.* 2011;4(2):13–37.
- Simpson EL, Chalmers JR, Hanifin JM, Thomas KS, Cork MJ, McLean WHI, et al. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *J Allergy Clin Immunol.* 2014;134:818–23.
- Small P, Kim H. Allergic rhinitis. *Allergy Asthma Clin Immunol.* 2011;7(Suppl 1):S3.
- Soller L, Ben-Shoshan M, Harrington DW, Fragapane J, Joseph L, St Pierre Y, et al. Overall prevalence of self-reported food allergy in Canada. *J Allergy Clin Immunol.* 2012;130:986–8.
- Spergel JM, Brown-Whitehorn TF, Cianferoni A, Shuker M, Wang M-L, Verma R, et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. *J Allergy Clin Immunol.* 2012;130:461–7.e5.
- The Food Allergy & Anaphylaxis Network [Internet]. 2016. <http://www.foodallergy.org>. Accessed 23 May 2016.
- Thyssen JP, Kezic S. Causes of epidermal filaggrin reduction and their role in the pathogenesis of atopic dermatitis. *J Allergy Clin Immunol.* 2014;134:792–9.
- Tsakok T, Marrs T, Mohsin M, Baron S, du Toit G, Till S, et al. Does atopic dermatitis cause food allergy? A systematic review. *J Allergy Clin Immunol.* 2016;137:1071–8.
- van den Oord RAHM, Sheikh A. Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: systematic review and meta-analysis. *BMJ.* 2009;339:b2433.
- van Ginkel CD, Flokstra-de Blok BMJ, Kollen BJ, Kukler J, Koppelman GH, Dubois AEJ. Loss-of-function variants of the filaggrin gene are associated with clinical reactivity to foods. *Allergy.* 2015;70:461–4.
- Waserman S, Watson W. Food allergy. *Allergy Asthma Clin Immunol.* 2011;7(Suppl 1):S7.
- Waserman S, Chad Z, Francoeur MJ, Small P, Stark D, Vander Leek TK, et al. Management of anaphylaxis in primary care: Canadian expert consensus recommendations. *Allergy.* 2010;65:1082–92.
- Wood RA, Camargo CA Jr, Lieberman P, Sampson HA, Schwartz LB, Zitt M, et al. Anaphylaxis in America: the prevalence and characteristics of anaphylaxis in the United States. *J Allergy Clin Immunol.* 2014;133:461–7.



Jane Lougheed and Jenna Ashkanase

Congenital Heart Disease: Current Changes in Epidemiology

With ongoing advancements in prenatal screening, medical interventions, and surgical techniques, the epidemiology of congenital heart disease (CHD) in society has experienced several key transitions in recent years. Canada has experienced a 21% decrease in the birth prevalence of CHD from 1998 to 2009, from 10.7 to 8.5 per 1000 total births (Moore and Rouleau 2013). Variations in rates amongst provinces and territories do exist, with the remote territory of Nunavut consistently having more than double the national rate at approximately 22.9 per 1000 births (Moore and Rouleau 2013; Arbour et al. 2004). Worldwide, the incidence is approximately 9.1 per 1000 live births as of 2011 (Van Der Linde et al. 2011). This international estimate almost certainly underestimates the true total, as it is restricted to live births and both diagnostic and reporting capabilities in developing nations can be limited. Mortality rates also vary internationally with estimates of 20% in developing nations to 3–7% in developed nations (Bernier et al.

2010). Again, the different rates are likely multifactorial, reflecting imbalances in access to prenatal screening and health care between developed and developing nations (Moore and Rouleau 2013; Bernier et al. 2010). In Canada, mortality rates associated with CHD in the pediatric population have declined by 59% over the past two decades (Khairy et al. 2010).

Although overall mortality rates have decreased, fetal deaths at an early gestational age have increased (Moore and Rouleau 2013). Conversely, mortality rates are lower in late gestation and in infancy (Moore and Rouleau 2013). This trend may be due to earlier prenatal diagnoses and subsequent pregnancy termination, combined with improved outcomes for CHD live births when current post-natal management strategies are employed. Termination rates currently range from an estimated 44–57% with a 1.4-fold increased probability of termination following prenatal diagnosis of CHD, most likely to occur when other congenital anomalies and/or genetic syndromes are identified (Moore and Rouleau 2013; Tegnander et al. 2006; Tomek et al. 2009; Germanakis and Sifakis 2006).

Overall survival rates for CHD in the North American population are now well over 90% (Marelli et al. 2007). The median age of patients living with severe CHD has increased, from 11 to 17 years from 1985 to 2000 (Marelli et al. 2007). The median age at death for patients with any form of CHD has increased from 60 to 75 years

J. Lougheed (✉) • J. Ashkanase
Division of Pediatric Cardiology,
Department of Pediatrics,
Children's Hospital of Eastern Ontario,
University of Ottawa, Ottawa, ON, Canada
e-mail: jlougheed@cheo.on.ca

within the last few decades (Khairy et al. 2010). For the subset of patients with severe CHD, the median age at death also increased, from 2 to 23 years. The most common types of CHD afflicting both the adult and pediatric populations are unchanged, with atrial septal defects (ASDs) and ventricular septal defects (VSDs) accounting for over 80% of diagnoses in Canada (Moore and Rouleau 2013). In terms of severe lesions, conotruncal anomalies such as Tetralogy of Fallot and atrioventricular septal (canal) defects (AVSDs) still account for the majority of severe CHD.

In summary, the recent epidemiologic data reflect that CHD is becoming a chronic condition with high survival rates, resulting in a greater proportion of adults living with CHD than children. This heralds a new era of management for CHD patients in which late outcomes, including complications of CHD and/or surgical interventions, neurodevelopment outcomes, and quality of life outcomes become more significant, and thus merit further scrutiny and research.

Late Outcomes of CHD

Pediatric CHD patients will undergo life-long monitoring by their primary care providers and cardiologists for complications of their underlying lesions and cardiac interventions. In order to determine the most appropriate screening measures, it is necessary to have an understanding of the most common complications that contribute to morbidity and mortality.

In a Finnish study of late causes of death following cardiac surgery, 592/6024 (9%) patients died during the 45-year follow-up period. The majority of deaths with a cause identified (67%) were related to CHD, most often due to heart failure (40%) (Nieminen et al. 2007). Perioperative death (within 30 days of a second, third, or fourth operation), sudden death, and cardiovascular complications (most prominently, stroke) were also common causes of mortality. For patients with tetralogy of Fallot (TOF), surgery was the most frequently recorded cause of death, while sudden death was more common amongst

patients with coarctation of the aorta (CoA), presumed to be secondary to arrhythmia. Of note, this population also had a high rate of non-CHD-related deaths with a significant proportion of respiratory (17%) and neurological (14%) pathology, highlighting the importance of monitoring CHD patients for general health concerns.

As heart failure is frequently encountered as a complication in the CHD population, increasing efforts to promptly identify and efficiently manage this condition have been initiated. For patients with CHD, making a diagnosis can be challenging due to the complexity of the underlying condition(s) contributing to heart failure and the evolving symptomatology that accompanies further growth and aging (Kantor et al. 2013a). Scoring indices are often not applicable across age groups and are not validated to predict prognosis for patients with complex congenital lesions (Kantor et al. 2013b). Guidelines for heart failure in the pediatric population have been developed by the Children's Heart Failure Study Group in collaboration with the Canadian Pediatric Cardiology Association (Kantor et al. 2013a). These guidelines assert that while the New York Heart Association (NYHA)/Ross classification can be used to stratify pediatric patients with established chronic heart failure, it is not necessary for diagnosis or prognostication (Kantor et al. 2013a). Instead, clinical findings according to patient age and investigations including electrolytes, chest radiography (CXR), electrocardiograms (ECGs), and echocardiograms are recommended. Brain natriuretic peptide (BNP) or amino terminal (NT)-proBNP can be utilized as confirmatory tests if needed, with elevated levels indicative of heart failure. Current medications utilized in the pediatric population for heart failure mirror many of those used in the adult population, including diuretics, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and aldosterone antagonists. Algorithms for a step-wise approach to initiating these medical therapies have been developed based on currently available evidence (Kantor et al. 2013a) and patients should undergo continual, individualized assessment as treatment progresses. Further randomized trials for heart failure man-

agement in the pediatric population are pending, and will be critical to developing a comprehensive understanding of the risks and benefits of currently available and new treatments.

Heart transplantation will become a necessity for a growing number of CHD patients as the prevalence of heart failure in this population increases (Attenhofer Jost et al. 2013). Of patients requiring heart and lung transplantation, CHD was the leading underlying condition worldwide between January 2000 and June 2012 (Yusen et al. 2013). Typically, CHD patients spend a longer time on the transplantation waiting list, potentially due to early identification of mild stages of heart failure as these patients undergo serial monitoring by health care professionals. Higher perioperative mortality also plagues this population of patients due to the complexity created by previous procedures and increased bleeding risks from prior sternotomy-related adhesions (Attenhofer Jost et al. 2013). However, internationally, post-transplantation outcomes for patients with CHD have improved annually during the past two decades (Chen et al. 2004; Stehlik et al. 2012). In a retrospective review from a single centre, a decrease in mortality was associated with later year of transplantation with mortality rates of 62.5% prior to 1990 decreasing to 12.5% after the year 2000 (Chen et al. 2004). Older age at transplantation was associated with better outcomes, with the highest mortality rates observed in neonates (57.1%) and the lowest rates in adults (23%). The mortality rate was constant amongst infants and children at 40%. The increasing use of mechanical ventricular assist devices may further change (decrease) mortality rates for patients on the transplantation waiting list in the years to come.

Neurodevelopmental Outcomes in CHD

Parents in cardiology clinics often inquire about the impact on intelligence and development for their infant or child following a new diagnosis of CHD. Indeed, as more patients with CHD are enrolled in daycare and progress through the

school system, there has been an increasing awareness of neurodevelopmental impairments in this population. As a result, further analysis from both an imaging and a clinical perspective has been undertaken. We will review current findings broadly but urge readers to keep in mind that prognostication must be individualized, as findings can vary based on the cardiac lesion, type of repair, the mode of assessment, and the patient's age at time of diagnosis and follow-up (Massaro et al. 2008).

Differences in central nervous system development have been documented in CHD patients via magnetic resonance imaging (MRI) in both the fetal and postnatal period, prior to surgical interventions (Ortinou et al. 2012; Limperopoulos et al. 2010). Overall, brain size in CHD patients has been observed to be smaller than that seen in the general population, particularly in the frontal and brainstem regions (Ortinou et al. 2012; Limperopoulos et al. 2010). These changes have been observed in the third trimester of pregnancy with associated impairments in neuroaxonal metabolism (Limperopoulos et al. 2010). Focal white matter signal abnormalities, usually of a mild nature, can occur in up to 42% of patients (Ortinou et al. 2012). Brain structures are also more premature, by approximately 1 month at baseline, in patients with hypoplastic left heart syndrome (HLHS) and transposition of the great arteries (TGA) (Licht et al. 2009). Small studies have shown that in some populations, predominantly patients with TGA, brain volume can improve over time, particularly if cyanotic cardiac lesions have resolved (Ibuki et al. 2012). However, it is possible for structural differences to persist through adolescence, particularly white matter injuries and significant volume loss (von Rhein et al. 2011). If chronic changes remain on imaging, they are commonly seen in association with neurodevelopmental deficits.

As patients with CHD proceed to further interventions and surgery, there are further risks for neurological injury posed by the potential for thromboembolism causing cerebral infarction and ischemia-reperfusion injury resulting from hypothermic cardiopulmonary bypass and/or total circulatory arrest (Su and Üндar 2010; Beca

et al. 2013). Post-operatively, transient risk factors such as hypotension, hypercarbia, and inflammatory responses can also be detrimental to neurodevelopmental outcomes (Bassan et al. 2005; Gressens and Hagberg 2012).

With increasing data to support structural abnormalities of the central nervous system, it becomes necessary to accurately evaluate clinically meaningful, functional outcomes for CHD patients. The International Cardiac Collaborative on Neurodevelopment (ICCON) recently provided a 14-year pooled analysis of outcomes following cardiac surgery in infancy for 1770 patients at the age of 14.5 ± 3.7 months using the Bayley Scales of Infant Development (Gaynor et al. 2015). This scoring system incorporates gross and fine motor skills through the Psychomotor Development Index (PDI) and parameters such as memory, problem solving, language, and social skills through the Mental Development Index (MDI). Scores for both indices in CHD patients were significantly lower than those seen in the general population ($p < 0.001$), but both slightly improved (by 5–6 points) during the study period. For patients with more complex CHD, PDI but not MDI was lower. Several factors were identified as being associated with poor neurodevelopmental outcomes including Caucasian race, male gender, low birth weight, genetic syndromes, complex CHD, and low maternal education level. In addition, increased length of stay in hospital following cardiac surgery has been associated with neurodevelopmental delays evident by the age of 8 years, including lower IQ with reduced verbal IQ and math achievement (Newburger et al. 2003). These effects persisted even when outcomes were adjusted for perioperative events and perfusion times.

Several forms of CHD are commonly associated with genetic syndromes, including Down syndrome, 22q11 microdeletion syndrome (DiGeorge syndrome), Williams syndrome, and Noonan syndrome (Gaynor et al. 2015). Neurodevelopmental delays are more prominent in patients with genetic syndromes (Fuller et al. 2009), but imaging abnormalities and impaired developmental progress have also been identified as increased within this population for patients

who also have CHD. Smaller brain volumes have been noted in patients with 22q11 microdeletion syndrome and CHD as compared to those with 22q11 microdeletion *without* CHD (reduced by 16.9% vs. 6.9% compared to controls, respectively) (Schaer et al. 2010). In pediatric CHD patients with Down syndrome, small studies have documented language delays (Alsaied et al. 2016) and/or motor delays (Visootsak et al. 2011) compared to patients with Down syndrome and no CHD in infancy and as toddlers. However, by the time of preschool entry and extending into school age, differences in development have not been observed to be significantly different (Alsaied et al. 2016). These early delays coincide with the usual timing of surgical interventions, and may reflect interruptions in developmental progress during medical care with subsequent recovery.

The risk of neurodevelopmental disability is closely linked to the type of CHD, with mild lesions such as ASDs or VSDs having a low prevalence of neurodevelopmental disabilities. In this particular subgroup of CHD patients, over 80% have no disabilities whatsoever (Marino et al. 2012). In contrast, patients with moderate (eg. AVSDs or TOF) or severe lesions (eg. TGA or single-ventricle lesions) have progressively increasing rates of disabilities that correlate with the degree of CHD severity. Less than 50% of those with severe CHD lesions experience normal developmental progress (Marino et al. 2012). The vast majority of patients with genetic syndromes will experience impairments, to a severe extent in over 25% of patients. Following identification of these trends, the American Heart Association has issued a scientific statement (Marino et al. 2012) regarding the evaluation and management of CHD patients at risk for neurodevelopmental delays. These guidelines state that patients should be risk-stratified with ongoing surveillance for developmental issues via age-appropriate screening tools. For high-risk patients, ie. those with CHD and other comorbidities, cyanotic lesions, and neonates requiring open heart surgery, referral for a full developmental assessment at baseline should be initiated. Low-risk patients will require ongoing periodic

screening with referral for developmental assessment only if concerns are identified.

With increasing numbers of CHD patients surviving into adulthood, it is likely that a larger population of adult patients requiring additional supportive resources will emerge. Further data regarding long-term neurodevelopmental outcomes will be needed as the epidemiology of CHD continues to change.

Quality of Life in CHD

Quality of life (QOL) measures in the pediatric CHD population have also been scrutinized, with more data accumulating annually. Across all age groups, up to 1 in 5 patients with CHD perceive a lower QOL and detriment in psychosocial functioning, even in those with mild cardiac conditions (Uzark et al. 2008). Lower QOL scores have also been associated with having cyanotic CHD and a history of cardiac surgeries, with an inverse relationship between the number of surgeries and QOL scores (Areias et al. 2013). Children with CHD indicate lower scores for physical well-being, financial resources, peer relationships, and autonomy than their healthy age- and gender-matched peers (Amedro et al. 2015). Self-perception was significantly influenced by the severity of the cardiac condition, and parental perception of QOL was also lower in CHD patients. However, in a study of 59 post-operative adolescents with CHD, lower peer-relationship scores were noted but overall QOL was not significantly lower than that of the general population (Schaefer et al. 2013). A larger, multicenter cross-sectional study demonstrated lower health-related QOL for patients with either biventricular or univentricular CHD compared with healthy peers, with scores that paralleled those of patients with other chronic diseases (Mellion et al. 2014). Recent scoring systems (Marino et al. 2012; Uzark et al. 2008) to evaluate QOL specifically in cardiac patients will enhance the current understanding of the challenges faced by this growing patient population.

Behavioural and psychiatric issues can have a profound impact on QOL and are also common

in CHD patients. Based on parental report alone, there are perceived psychosocial issues in 15–25% (Marino et al. 2012). A study conducted in Portugal evaluating diagnostic outcomes in a cohort of 110 adolescents and young adults with various forms of CHD similarly found a lifetime prevalence of psychopathology in 21.8%, higher in female patients (Freitas et al. 2013). Externalization (eg. aggression), internalization (eg. social withdrawal), and symptoms of depression or anxiety were the most commonly diagnosed disorders based on self-report. A meta-analysis examining psychological and cognitive functioning in CHD patients found that risks were higher only in older children and adolescents (mean age > 10 years) for internalizing more so than externalizing behaviours (Karsdorp 2007). Symptoms of depression, anxiety, and disruptive behaviour have been self-reported frequently in adolescents with d-TGA, who also have an increased risk of attention-deficit/hyperactivity disorder (19% vs. 7% in the general population) (Demaso et al. 2014). The effect of disease severity on psychosocial scores varies in the literature, with some groups correlating more severe disease with higher rates of depressed mood and lower self-esteem (Cohen et al. 2007) and others demonstrating no correlation (Uzark et al. 2008; Karsdorp 2007). Patients with certain genetic syndromes may also be at risk for psychosocial impairments with a known association between 22q11 microdeletion syndrome and attention-deficit hyperactivity disorder, autism spectrum disorder, and schizophrenia or schizoaffective disorders (Niklasson et al. 2002). Awareness of the increased risk of behavioural and psychiatric problems for older children and adolescents with CHD, particularly those with pre-existing risk factors, will be helpful in promoting early screening for disorders.

Exercise in CHD

Exercise recommendations for CHD patients may differ depending on the specific cardiac condition. Overall, most patients with minor, uncomplicated cardiac lesions should be able to tolerate

60 min of at least moderate physical activity daily with an increase to 70% of maximal heart rate (Brothers et al. 2016). Prior to initiating a new exercise regimen it is ideal for patients to engage in a discussion with their cardiologist to review their history and clinical findings and, in cases of more complex CHD, undergo any individualized screening investigations such as electrocardiogram (ECG), echocardiogram, or exercise testing, if indicated. Studies have demonstrated that the perceived severity of heart disease by patients and parents is correlated with lower participation in exercise and sports (Cohen et al. 2007). Thus, it is beneficial to ensure that CHD patients are aware of their current health status and given reasonable expectations for their involvement in physical activity.

For patients with more complex forms of CHD, functional limitations may be imposed not only by the underlying pathology, but also by surgical repairs, medications, or arrhythmias. In particular, patients with the conditions listed in Table 3.1 commonly require specific restrictions to physical activity (Brothers et al. 2016). However, alternate forms of mild to moderate physical activity can be safely initiated if the patient is motivated and aware that this is possible. The Task Force for Congenital Heart Disease from the 36th Bethesda Conference has provided

recommendations for involvement in highly competitive sports primarily for adult patients with a variety of forms of CHD, which can serve as a basic outline for patient counseling (Maron et al. 2011).

Increasing awareness of sedentary lifestyles in the adult CHD population (Chaix et al. 2015) in combination with increased obesity rates in the pediatric population have prompted initiatives to improve physical activity levels for these patients. In 2013, the American Heart Association published a scientific statement promoting physical activity for both pediatric and adult patients with CHD (Longmuir et al. 2013). These guidelines state that discussion of appropriate forms of physical activity should occur at each clinical assessment and provide a wide range of suggestions to improve counseling for patients. Adult recommendations for exercise training in CHD, categorized by the type of cardiac lesion, associated conditions, and the type of activity, were published earlier this year (Chaix et al. 2015). The authors readily acknowledge, however, that further research will be crucial in further delineating which regimens are the most effective. Undoubtedly, further research in the pediatric population is needed to provide further data on which to base patient counseling.

An accurate depiction of each patient's cardiovascular health status and exercise potential should be obtained. For the overwhelming majority of CHD patients, there are no restrictions to physical activity. Patients with more complex lesions should be counseled to focus on individualized activity adjustment, rather than avoidance, to maintain a healthy, active lifestyle.

Table 3.1 Cardiac conditions commonly requiring exercise restriction (adapted from Moss and Adams 2016)

| Category | Condition |
|--------------------------------|---|
| Left-sided obstructive lesions | • Severe/critical aortic stenosis |
| | • Severe aortic insufficiency |
| | • Clinically significant bicuspid aortic valve |
| Pulmonary vascular disease | • Pulmonary hypertension |
| | • Eisenmenger Syndrome |
| Genetic syndromes | • Marfan syndrome with aortic root dilatation |
| Coronary artery abnormalities | • Anomalous origin of the left coronary artery from the right sinus of Valsalva |
| | • Intramural coronary artery |
| Arrhythmias | • Uncontrolled |
| | • Implantable cardioverter defibrillator |

Pregnancy in CHD

With improved longevity and survival, patients with CHD now face decisions regarding family planning. CHD has been emerging as the most common form of cardiac disease impacting pregnancies as documented by the Canadian Cardiac Disease in Pregnancy (CARPREG) registry and the European Registry on Pregnancy and Cardiac Disease (ROPAC) registry, with a prevalence of

74% and 66%, respectively (Siu et al. 2001; Roos-Hesselink et al. 2013). In order to meet the needs of this patient population, an understanding of the physiology and risks involved during pregnancy must be created.

A series of hemodynamic changes occur during pregnancy, including an increase in heart rate and stroke volume with a decrease in peripheral vascular resistance. The net effect is an increase in cardiac output to support growth of the placenta and fetus. Patients with CHD may have difficulties achieving sufficient cardiac output, especially patients with the Fontan circulation or following insertion of conduits or baffles (Greutmann and Pieper 2015). Arrhythmias can interfere with coordinated intracardiac blood flow and pacemakers may require new heart rate thresholds as the physiologic changes accompanying pregnancy develop. Furthermore, obstetrical complications such as gestational diabetes, pre-eclampsia, and multiple gestations can further challenge hemodynamic recalibration (Siu et al. 2001).

Significant risks are presented at both the maternal and fetal level for patients with CHD. In a prospective Canadian study of pregnant women with CHD, primary cardiac events occurred in 13% (80/599), with pulmonary edema, arrhythmias, and thromboembolic events being the most common complications (Siu et al. 2001). The same risks have been seen to persist even in lower-risk maternal populations (Balci et al. 2014). When these conditions necessitate medical or surgical interventions, the risks for both mother and baby increase even further. Events for offspring are seen in 20–30% of births (Siu et al. 2001; Balci et al. 2014), most commonly related to growth restriction or premature birth and associated complications, such as respiratory distress syndrome or intraventricular hemorrhage. Recurrence rates for CHD in offspring are estimated to be between 3 and 8%, which can vary depending on conditions with gender predilections or genetic associations (Brickner 2014). The risk of fetal or neonatal death is also increased in patients with CHD at approximately 2% (Siu et al. 2001), especially for those with more severe lesions and the related detriment in uteroplacental blood flow.

Discussions surrounding reproduction should ideally be initiated with CHD patients well prior to pregnancy, in late childhood or adolescence (Brickner 2014), especially since adolescents with CHD often demonstrate a limited understanding of their own health status (Greutmann and Pieper 2015). Advice regarding contraception should be individualized, as combined contraceptives may be inappropriate for certain CHD patients at higher risk of thromboembolic events (Thorne 2006). When initiating discussions surrounding future pregnancies, any potential need to optimize clinical status, such as updating cardiac investigations or weaning medications should be outlined. In addition, in some forms of severe CHD, vaginal delivery may be contraindicated, and these patients should be counseled accordingly when formulating a birth plan (Greutmann and Pieper 2015). It is also important to include male patients with CHD in discussions regarding contraception and family planning as there can be an increased risk of CHD in the offspring of some male patients as well.

Accurate characterization of risk level for adverse maternal outcomes during pregnancy is necessary. The most widely accepted guidelines for pregnancy risk classification in CHD are the modified WHO criteria (Balci et al. 2014). Risk level ranges from WHO Class I, in which there are no detectable increased risks of maternal morbidity or mortality (ie. for patients with repaired simple lesions) to WHO Class IV, in which the risks are so high that pregnancy is considered contraindicated (ie. for patients with pulmonary hypertension or severe aortic stenosis). Individuals at a significantly high risk of severe complications can be promptly identified using these guidelines and counseled early regarding elective pregnancy termination if desired, which is generally considered to be safest in the first trimester (Regitz-Zagrosek et al. 2011). Guidelines for the overall management of adult CHD patients are available from several groups worldwide including the Canadian Cardiovascular Society (CCS), the American College of Cardiology and American Heart Association (ACC/AHA), and the European Society of Cardiology (ESC)

(Regitz-Zagrosek et al. 2011; Silversides et al. 2010a, b, c; Warnes et al. 2008).

With more CHD patients progressing into adulthood, pregnancy-related concerns will undoubtedly become more common. A multidisciplinary approach involving obstetricians, cardiologists, family physicians, and genetic counselors, as applicable, will be crucial to ensuring comprehensive care for this patient population.

Neonatal Oximetry Screening

Congenital heart disease is the most common congenital malformation, with a prevalence of 6–9/1000 births worldwide (Van Der Linde et al. 2011). About 1/3 of these newborns will have critical congenital heart disease (CCHD), defined as severe heart disease requiring neonatal diagnosis and correction for optimal outcome.

Many of these lesions are ductal dependent, and may only become apparent as the ductus arteriosus closes, usually in the first 24–28 h of life (Table 3.2). With routine earlier discharge of newborns, there is a concern that more of these lesions will clinically present after a baby is at home. Studies in the US and UK estimate that 25–30% of these lesions will present after discharge or after 3 days of age (Wren et al. 2008; Peterson et al. 2014a). Neonates with missed CCHD have increased morbidity and mortality, related to their degree of decompensation at the

time of presentation (Brown et al. 2006). Pulse oximetry has been studied as a screening method to improve detection of CCHD. This screening method has been endorsed by experts in the US and Europe to become part of routine practice, with other countries including Canada following suit (Mahle et al. 2012).

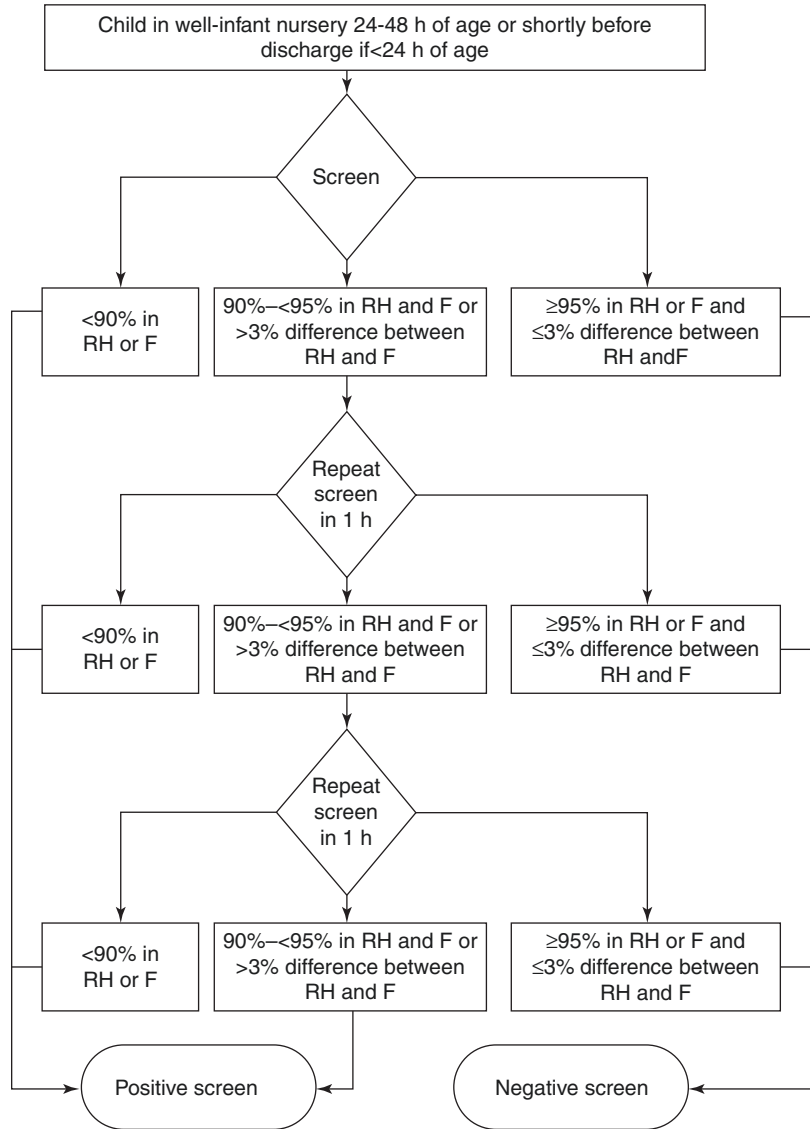
Although prenatal ultrasound is capable of detecting most CCHD, the reality is that less than 50% of CCHD is diagnosed prenatally (Trines et al. 2013; Quartermain et al. 2015). This number is very region specific, with higher rates of diagnosis in larger, tertiary care level centres. The routine newborn physical examination (in the absence of oximetry) may detect CCHD, but this is dependent on clinical expertise and experience. There are higher rates of detection in centres with higher care level nurseries, but also a high false positive detection rate compared to oximetry (Dawson et al. 2013). Pulse oximetry using a cut off saturation of 95% has a high specificity of 99.9% and a moderately high specificity of 76.5% for CCHD, in a recent systematic review including over 225,000 newborns (Thangaratinam et al. 2012). Optimal timing for screening is between 24 and 48 h of age, with higher false positives when screening is performed before 24 h. Most current recommendations advocate for screening after 24 h of age, with saturations being checked in the right hand and one foot (Kemper et al. 2011) (Fig. 3.1). A failed screen results in a full physical examination for evidence of congenital heart disease or other causes for low saturations such as sepsis or respiratory disease. If this does not clarify the situation, then referral to pediatric cardiology and/or echocardiography is required to exclude CCHD. The anticipated screen positive rate is around 0.2% using this algorithm, with a cost of under \$5 US per newborn screened when reusable probes are used (Peterson et al. 2014b).

Implementation of screening involves developing a protocol, training of personnel, tracking of abnormal results, and a plan for potential transfer of newborns to a site providing pediatric echocardiography—however, the burden and cost of this is justified by not having these infants present back in critical condition.

Table 3.2 Critical congenital heart disease lesions detectable with oximetry screening

| Usually cyanotic | May be cyanotic |
|---|--|
| Transposition of the great arteries | Coarctation of the aorta |
| Hypoplastic left heart syndrome | Ebstein's anomaly of the tricuspid valve |
| Tetralogy of Fallot | Single ventricles |
| Pulmonary atresia with intact septum | Double outlet right ventricle |
| Total anomalous pulmonary venous return | Interruption of the aortic arch |
| Tricuspid atresia | |
| Truncus arteriosus | |

Fig. 3.1 Algorithm for pulse oximetry screening. With permission from Kemper et al., Strategies for Implementing Screening for Critical Congenital Heart Disease, Pediatrics 2011 (Kemper et al. 2011)



Cardiac Imaging

The Growing Role of Cardiac MRI

In the past decade, cardiac MRI has emerged as a reliable, non-invasive form of assessment to further detail cardiac anatomy, function, and hemodynamics in more precise detail. One major advantage is the further assessment of right ventricular volumes, which can be challenging on standard echocardiographic views due to the geometry of the chamber (Nies and Sekar 2013).

Cardiac MRI is now considered the ‘gold standard’ for both right and left ventricular volumetric quantification and has excellent inter-user reproducibility (Mertens et al. 2008). In addition, extracardiac structures, particularly pulmonary and systemic vascular structures and the aortic arch, can be further delineated. These improvements in the imaging of key anatomic areas have multiple applications in the pediatric population, most significantly in evaluations for cardiomyopathy, pulmonary and systemic vein abnormalities, and aortic rings and slings (Nies and Sekar

2013). Both pre-operative planning and post-operative monitoring for complications associated with TOF, TGA, and single ventricle repairs can be supplemented with further anatomic details (Nies and Sekar 2013; Han et al. 2013). Cardiac MRI is also beneficial in adolescents, who can often have unclear echocardiogram imaging associated with changes in body habitus (Krishnamurthy 2008). Myocardial viability can also be analyzed in cases of myocarditis or ischemia with techniques such as delayed contrast enhancement (Nies and Sekar 2013). From a hemodynamic standpoint, estimations of the ratio

of pulmonary to systemic blood flow and pulmonary vascular reactivity can be obtained, similar to findings traditionally gained from diagnostic catheterization studies (Nies and Sekar 2013).

The three-dimensional (3D) imaging capabilities of cardiac MRI have made complex visual reconstructions (Fig. 3.2) and 3D-printed anatomic models possible (Mertens et al. 2008; Costello et al. 2015). These innovative models can provide further details to cardiovascular surgeons for pre-operative planning and enhance the understanding of complex anatomy (Costello et al. 2015). 3D-printed models have the potential

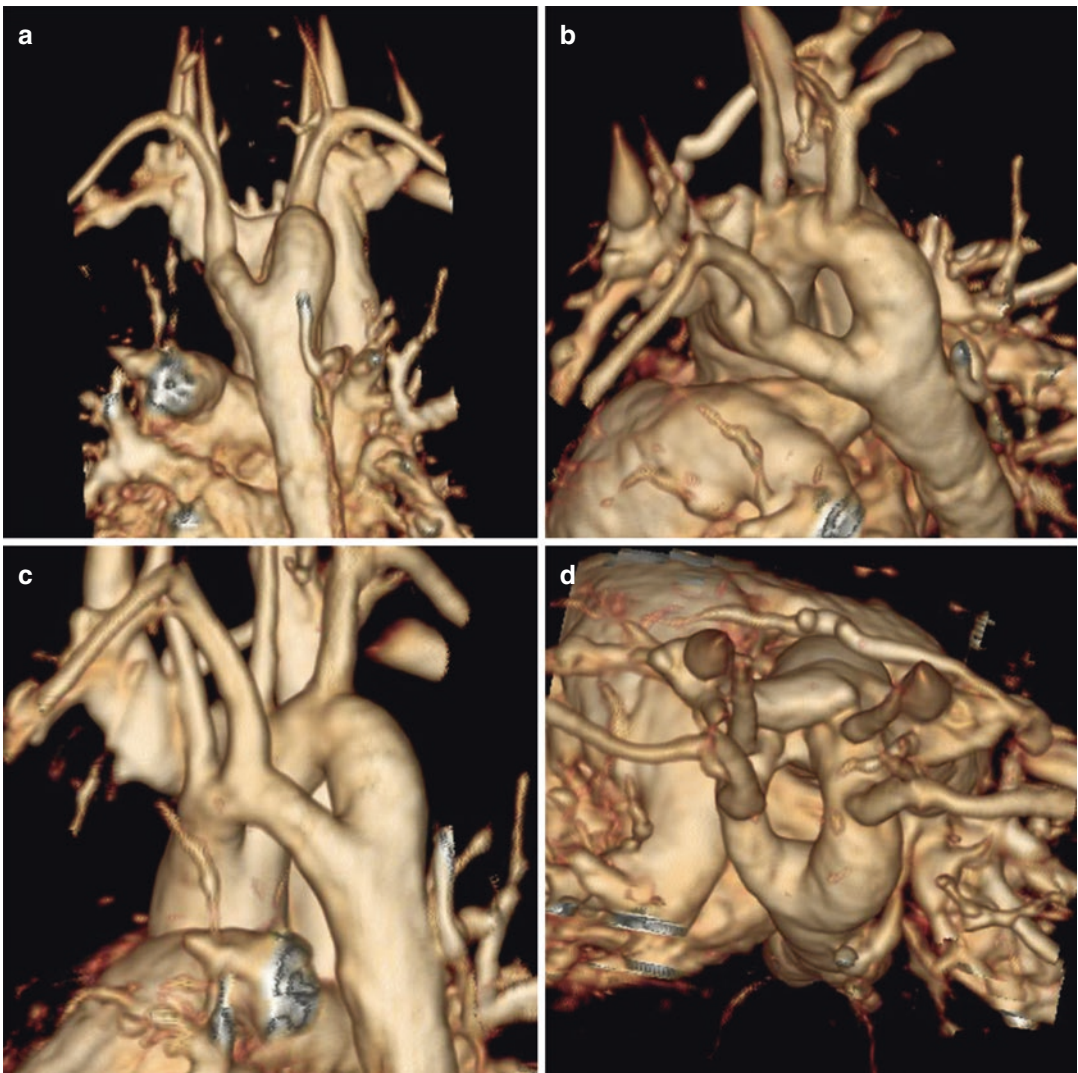


Fig. 3.2 3D Echo images of the tricuspid valve (left) and mitral valve (right) arch

to give the opportunity to rehearse surgical techniques prior to entering the operating room, which carries an enormous potential to hone surgical techniques in a risk-free environment and ultimately, improve patient care.

Although the imaging advantages and lack of radiation make cardiac MRI a very attractive alternative to catheterization, there are some limitations (Han et al. 2013). For optimal results, breath-holding may be required, which is not always realistic in patients under the age of 6 years or for patients with developmental or behavioural concerns. Sedation or general anaesthetic may be required to obtain optimal imaging. As well, both obtaining and processing the imaging can be a time-consuming process requiring expert interpretation, which is not available at all cardiac centres (Krishnamurthy 2008). Full anatomic details may not be possible depending on tissue imaging planes and the limitations of current technology, such that further imaging such as cardiac catheterization may still be required.

The use of cardiac MRI in the pediatric population is projected to play an increasingly important role in characterizing anatomy, function, and hemodynamics as imaging technology continues to improve. Guidelines and protocols for specific cardiac conditions are now under development for both adults and children with CHD (Fratz et al. 2013).

Updates in Echocardiography

Echocardiography remains the workhorse of cardiac imaging and has undergone further enhancements in recent years. With high frequency pediatric 3D transducers, it is now possible to go beyond the standard two-dimensional (2D) images and create 3D reconstructions from volumetric echocardiogram datasets that can be manipulated in multiple planes (Fig. 3.3) (Mertens et al. 2008). An increasing amount of detail regarding the myocardial surface contour,

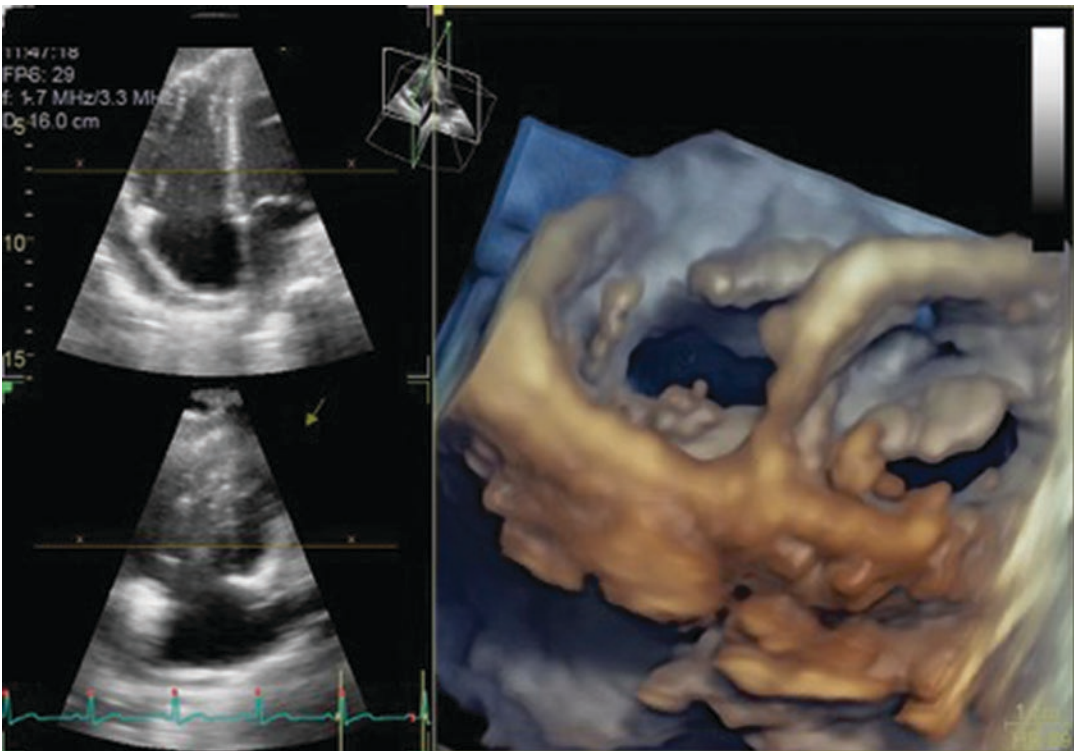


Fig. 3.3 Three-dimensional echocardiogram images of the tricuspid valve and mitral valve

valve morphology, and chamber volumes can bolster pre-operative knowledge and is becoming more routine practice (Mertens et al. 2008). However, as with any imaging modality, the quality of the information gained is directly related to operator technique and experience with this technology is still developing. Optimizing the 3D images can also be a very time-consuming process and standard protocols for specific forms of CHD have not yet been finalized (Mertens et al. 2008).

Ventricular functional analysis has also expanded in echocardiography due to techniques such as tissue Doppler, strain, and strain rate imaging (Mertens et al. 2008). These methods are able to describe the velocity of movement within the myocardium as well as both the percentage and rate of deformation of myocardial segments, respectively, to better characterize regional myocardial function. These methods are highly applicable to patients with cardiomyopathies, anthracycline-induced cardiotoxicity, or post-operative myocardial dysfunction (Mertens et al. 2008).

Criteria for the appropriate use of transthoracic echocardiography in the outpatient setting have been developed in recent years in response to a growing demand for high-quality studies with a limited number of trained pediatric sonographers to perform them (Campbell et al. 2014). Recommendations are grouped by indications for the study, which focus on common patient presentations such as chest pain and syncope. By applying these guidelines, resources and more specialized studies can be directed towards the patients with the highest risk of pathology.

The Role of Cardiac Computed Tomography (CT)

With advancements in echocardiography and the expanding role of cardiac MRI, understanding the applications for cardiac CT merits a brief discussion. Overall, one of the main benefits for this imaging modality comes in the form of improved coronary artery assessment, in some cases above that offered by cardiac MRI (Mertens et al. 2008).

Extracardiac vascular structures including aortic rings and slings can also be well visualized using this modality. CT studies are typically much shorter in duration than echocardiograms or MRI's, and due to this, in some instances the need for sedation can be eliminated. However, the risks inherent to the radiation involved in CT imaging must balance the potential benefits. Weight-based protocols can help to ensure that the lowest possible dose of radiation is used and techniques such as prospectively-gated ECG CT imaging can decrease the amount of radiation administered by at least 64% (Young et al. 2011). Young children with elevated heart rates and/or patients with arrhythmias can also present challenges to the acquisition of ECG-gated CT imaging, and thus specialized adjustments may be required to ensure accurate data capture (Young et al. 2011).

As modern technology continues to advance, new applications of these standard cardiac imaging techniques will undoubtedly progress even further. Uncovering an increasing amount of information regarding cardiac structure and function in multiple forms of CHD will prompt new standards for cardiac measurements and imaging protocols to keep pace with this expanding body of knowledge.

Catheter Based Interventions

The treatment of congenital heart disease has changed significantly over the past two decades with the rapid growth of interventional cardiology and catheter based therapy. Congenital heart diseases that are now frequently treated non-surgically with interventional cardiac catheterization include secundum atrial septal defect (ASD), patent ductus arteriosus (PDA), coarctation of the aorta, pulmonary and aortic valve stenosis, pulmonary artery stenosis and pulmonary regurgitation. Avoiding sternotomy and cardiopulmonary bypass in these cases often results in lower morbidity, shorter hospital stays and lower health care costs.

Catheter repair of secundum ASD (Fig. 3.4a) began in the 1990s, with changes in device

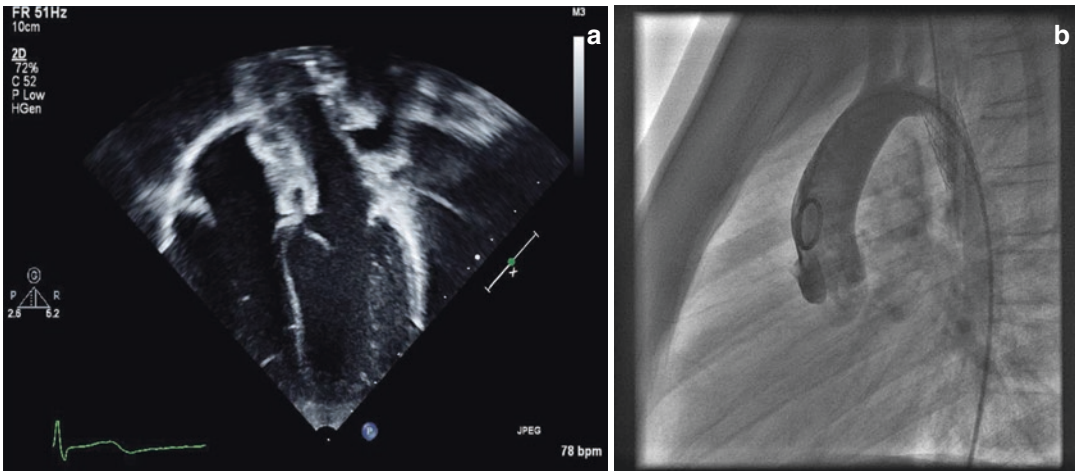


Fig. 3.4 (a) Secundum ASD device closure, (b) stent placement for coarctation of the aorta

construction taking place in the last decade to improve device stability. The earlier ASD devices had some complications of structure fracture which are improved with the new design of devices. The most commonly used devices are the Amplatzer device and the Gore Septal Occluder device, although there are other devices in development for pediatric use. The successful implantation rate is over 98%, including long-term freedom from re-intervention (Du et al. 2002). The age and size of child suitable for device closure depends on the anatomy and size of the ASD, but the majority of secundum ASD's can be closed by the age of 3–5 years or weight of 15 kg. Longterm follow-up reveals rare but potentially serious complications, including erosion with cardiac perforation (0.1%), endocarditis, thrombosis and arrhythmia, the highest risk of which is in the first year after implantation (Moore et al. 2013). This highlights the need for continued longterm surveillance of patient outcomes. Compared to surgical closure, there is equal efficacy of both procedures with lower complication rates, shorter hospital stays and lower cost with device closure, making this a safe and effective alternative to surgical therapy for secundum ASD (Du et al. 2002; Butera et al. 2011).

Closure of hemodynamically significant PDA by transcatheter approach may be performed using either vascular coils or a device. The

success rate of this procedure is near 100% with very low complication rates (El-Said et al. 2013). Closure by this technique is standard in the non-neonatal population. However new devices and techniques are now allowing for the possible extension of this procedure into the premature neonate population (Francis et al. 2010). Although there is continuing debate regarding the indications for PDA closure in the premature neonate population, the ability to non-surgically close this lesion avoids the possible post-operative complications of vocal cord palsy (9%), pneumothorax, chylothorax and need for transfusion. With further experience and studies, it may become standard to offer this as an interventional procedure rather than surgery in this newborn population.

Coarctation of the aorta is also a lesion which is amenable to catheter intervention (Fig. 3.4b). Primary treatment of non-neonatal coarctation (over 6 months of age) by interventional catheterization is standard for many anatomical forms of coarctation. The effectiveness of angioplasty of native coarctation and recurrent post-operative coarctation is high, with the main complication being need for eventual repeat dilation in up to 25% of patients (Tynan et al. 1990; Yetman et al. 1997). Stent placement decreases the rate of recoarctation, however in growing children, care needs to be taken to ensure that an adequate sized stent is placed to allow for repeat balloon dilation

with growth (Forbes et al. 2011). Neonatal primary coarctation catheter intervention is not as universally performed compared to surgery, due to concerns regarding higher recoarctation rates and higher rates of vascular injury (Fiore et al. 2005). Anatomy of the coarctation site, presence of aortic arch hypoplasia and other associated congenital heart lesions influence choice of balloon dilation, with or without stent placement, versus surgery.

The most recent interventional catheterization procedure to become available to a significant number of congenital heart patients is percutaneous implantation of the pulmonary valve. Surgical repair or revision of Tetralogy of Fallot and other repairs involving the right ventricular outflow tract often involve placing a valved conduit in the pulmonary valve position. These valves are prone to progressive stenosis and regurgitation, resulting in the need for recurrent surgical replacements. Since the mid 2000s there has been significant progress in the development of percutaneously placed pulmonary valves, implanted over a balloon and in the framework of a stent. Current technology allows successful placement of these valves in larger children (over 20 kg) with pre-existing medium to large conduits (over 16 mm) (Lurz et al. 2009; Vezmar et al. 2010). There is ongoing research to develop a percutaneous valve procedure suitable for post-operative Tetralogy of Fallot patients with dilated outflow tracts who have not yet had their first valve replacement (Boudjemline et al. 2012; Momenah et al. 2009; Wilson et al. 2015). This represents a large group of patients and involves techniques to downsize the outflow tract to be able to anchor a percutaneous valve. Current clinical trials continue to refine this technique.

Genetic Testing in Pediatric Cardiology

Over the last 5–10 years, there has been an explosion in the knowledge and available testing for heritable causes of cardiac disease. Diseases that were previously labelled as idiopathic or of

unknown etiology are increasingly being attributed to genetic mutations. As this is a rapidly advancing field, it is important to periodically re-evaluate patients with prior negative genetic testing, as they may subsequently test positive for a newly discovered mutation. While most of cardiac screening and genetic testing remains in the realm of pediatric cardiologists and geneticists, it is important for referring physicians and caregivers to be aware of these advances, so that evaluation and screening of appropriate individuals may occur.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) has long been recognized as having inheritance patterns suggestive of a genetic cause. It is now recognized as being the most common of the genetic cardiac diseases (Maron et al. 1995; Zou et al. 2004). Mutations in at least 11 genes encoding proteins of the cardiac sarcomere have been identified, with varied clinical expressions of these mutations (Maron et al. 2012). HCM may present from infancy through adulthood, although the majority of cases present in adolescence to early adulthood. Causes presenting in infancy and childhood tend to represent metabolic causes including glycogen storage disease (Pompe's disease) and mitochondrial myopathies, as well as Noonan syndrome. Most other forms are latent until adolescence or adulthood. HCM is the most common cause of sudden death in young people and is often silent, with the typical murmur, indicating outflow tract obstruction, or any other signs absent in up to 2/3 (Members et al. 2011).

Genetic inheritance of HCM follows an autosomal dominant pattern. Seventy percent of identified mutations are for components of beta-myosin heavy chain or myosin binding protein C. The majority of patients with disease-causing mutations will develop HCM by early adulthood. The challenge is that with current testing panels, only 1/3 will have disease-causing mutations, with the remaining 2/3 negative or

with ambiguous results. This will remain a challenge for diagnosis until all genes for HCM are identified. To add to this challenge, thus far there is minimal data to allow prediction of clinical course and sudden death risk based upon genetic test results (Maron et al. 2012).

Given this information, it is important that first degree family members of patients with HCM be aware of the genetic link, and be considered for referral to specialist assessment regarding cardiac screening and/or genetic testing.

Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) is the most common cardiomyopathy in children (Towbin et al. 2006). This diagnosis carries a high risk of morbidity and mortality, with a significant number of patients requiring advanced heart failure support including mechanical support and heart transplantation. DCM in the pediatric population has been traditionally described as idiopathic in the majority of patients (Towbin et al. 2006). This is in contrast to adult patients, in whom ischemic and hypertensive causes are common. Other causes of DCM in infants and children include inflammatory causes (myocarditis), neuromuscular diseases, anthracycline chemotherapy, metabolic and mitochondrial diseases. Forty percent of patients are diagnosed in the first year of life, and the majority at all ages present with clinical congestive heart failure at diagnosis (Towbin et al. 2006). Age at diagnosis of 6 years or older is associated with a higher risk of death or transplant compared to infants (Alvarez et al. 2011).

Increasingly, a genetic basis to DCM is being identified. At present, sarcomeric or cytoskeletal gene mutations can be identified in an increasing number (20–35%) of patients with DCM (Kindel et al. 2012; Møller et al. 2009). Genetic testing panels for DCM have become commercially available and have over 40–50% diagnostic yield (Kindel et al. 2012). Identification of a disease-causing mutation will guide management of the family. Current recommendations are for yearly

cardiology screening throughout childhood if genetic testing is positive, versus screening every 3–5 years in the absence of testing.

Inherited Arrhythmias, Including Sudden Cardiac Death

Sudden death in a young person is infrequent, occurring in about 1 in 10,000 of those between 1 and 18 years of age. A cause for the sudden death is found on autopsy in up to 50% of these, with most common diagnoses being hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, congenital coronary anomalies and myocarditis (Puranik et al. 2005; Libershon 1996). There is no identifiable abnormality found at autopsy in the remainder (sudden unexplained death or SUD), and these are presumed to be arrhythmia syndromes (Van Der Werf et al. 2010; Chugh et al. 2000). Causes of SUD not identifiable on standard autopsy include long QT syndrome and other cardiac channelopathies. After clinical evaluation of first degree family members, a diagnosis can be made in about one third of these. A further 20% may be diagnosed by genetic evaluation of the deceased (molecular autopsy). While beyond the scope of this chapter to fully discuss these disorders, it is important that referring physicians be aware of the presentation of, inheritance patterns and availability of genetic testing for these channelopathies. The younger the patient who has died is, the more likely it is that the autopsy is negative (Van Der Werf et al. 2010). There is often a positive family history of young SUD or a history of prior syncope in the deceased patient (Van Der Werf et al. 2010).

Cardiac channelopathies describe a number of disorders affecting the ion channels of the heart. These include long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT) and Brugada syndrome. The presenting symptoms of these disorders are most commonly syncope, seizures or sudden death. There is often overlap both in the presenting symptoms, clinical findings and genetic testing

for many of these disorders. CPVT is usually caused by an abnormality in calcium movement within the cardiac cell through the ryanodine receptor. Most of these have autosomal dominant inheritance (Laitinen et al. 2001; Priori et al. 2001), and present as exercise or stress induced ventricular arrhythmias, often manifest as syncope or sudden death *during* exercise. For LQTS, 16 genes have been implicated to date, with hundreds of mutations involving mostly the sodium and potassium cardiac channels (Splawski et al. 2000; Tester et al. 2016; Tester and Ackerman 2011). The majority (>90%) are caused by just three of these—LQTS 1–3. Most have autosomal dominant inheritance. Genetic testing has a yield of over 70–80% if the diagnosis is suspected clinically (Tester et al. 2006). However, expertise in interpretation of both clinical and genetic testing is critical, to avoid false labelling of the patient or family member with or without disease. Treatment for channelopathies is available with significant reduction in symptoms and mortality. Therapeutic choices include medication (frequently beta-blockers), pacemaker therapy and implantable defibrillators. In some situations, the genetic testing result may help guide the therapeutic approach.

It is important to remember that the vast majority of syncopal episodes in the pediatric age range are benign vasovagal syncope. Classic features of vasovagal syncope are syncope occurring in an upright position or with exposure to pain or stress, with prodromal symptoms of diaphoresis, warmth, visual change, and pallor, followed by fatigue following the episode. Less than 5% of pediatric syncope cases have cardiac pathology, and the most useful way to differentiate these cases from benign vasovagal syncope is by careful history taking (Ritter et al. 2000; Steinberg and Knilans 2005). *The details of the episode are crucial.* Features more suggestive of cardiac syncope are sudden episodes with no or minimal prodrome, symptoms of palpitations prior to the episode, and syncope that occurs *during* (not after) exercise. Although vasovagal syncope may occur during exercise, cardiac causes must be excluded prior to making this diagnosis. Features of cardiac syncope should prompt referral to a

pediatric cardiologist for further evaluation, as this may be the only warning of a significant cardiac diagnosis.

Pediatric Chest Pain: Cardiac Features

Chest pain is a common complaint in children and adolescents, prompting many Emergency Room visits. The vast majority of pediatric chest pain symptoms are secondary to non-cardiac causes, which is very distinct from the causes of chest pain in adults. However, the majority of patient, caregiver and health care provider *anxiety* surrounding pediatric chest pain is related to potential cardiac causes. *History and physical examination are key* in determining the cause of chest pain. In large studies evaluating pediatric patients presenting with chest pain, a cardiac etiology was determined in only 1–4%, with most cases attributable to musculoskeletal, gastrointestinal, respiratory or idiopathic causes (Lin et al. 2008; Saleeb et al. 2011; Angoff et al. 2013). Cardiac chest pain is more likely with gradually increasing chest pain with exertion, or chest pain associated with fever, palpitations, syncope or pre-syncope. Although cardiac troponin levels are important in screening and diagnosing ischemia in adults, *the use of troponin screening in children with chest pain is of minimal benefit* unless associated with fever (perimyocarditis) or ECG changes (Liesemer et al. 2012). Pediatric chest pain is usually not an indication for referral to a pediatric cardiologist or for echocardiography unless cardiac features are present (Campbell et al. 2014).

References

- Alsaied T, Marino BS, Esbensen AJ, Anixt JS, Epstein JN, Cnota JF. Does congenital heart disease affect neurodevelopmental outcomes in children with down syndrome? *Congenit Heart Dis.* 2016;11(1):26–33.
- Alvarez JA, Orav EJ, Wilkinson JD, Fleming LE, Lee DJ, Sleeper LA, et al. Competing risks for death and cardiac transplantation in children with dilated cardiomyopathy: results from the pediatric cardiomyopathy registry. *Circulation.* 2011;124(7):814–23.

- Amedro P, Dorka R, Moniotte S, Guillaumont S, Fraise A, Kreitmann B, et al. Quality of life of children with congenital heart diseases: a multicenter controlled cross-sectional study. *Pediatr Cardiol*. 2015;36(8):1588–601. Springer.
- Angoff GH, Kane DA, Giddins N, Paris YM, Moran AM, Tantengco V, et al. Regional implementation of a pediatric cardiology chest pain guideline using SCAMPs methodology. *Pediatrics*. 2013;132(4):e1010–7.
- Arbour L, Gilpin C, Millor-Roy V, Platt R, Pekeles G, Egeland GM, et al. Heart defects and other malformations in the Inuit in Canada: a baseline study. *Int J Circumpolar Health*. 2004;63(3):251–66.
- Areias ME, Pinto CI, Vieira PF, Teixeira F, Coelho R, Freitas I, et al. [Long term psychosocial outcomes of congenital heart disease in adolescents and young adults]. *Zhongguo Dang Dai Er Ke Za Zhi*. 2013;15(10):810–6.
- Attenhofer Jost CH, Schmidt D, Huebler M, Balmer C, Noll G, Caduff R, et al. Heart transplantation in congenital heart disease: in whom to consider and when? *J Transp Secur*. 2013;2013:376027.
- Balci A, Sollie-Szarynska KM, van der Bijl AGL, Ruys TPE, Mulder BJM, Roos-Hesselink JW, et al. Prospective validation and assessment of cardiovascular and offspring risk models for pregnant women with congenital heart disease. *Heart*. 2014;100(17):1373–81.
- Bassan H, Gauvreau K, Newburger JW, Tsuji M, Limperopoulos C, Soul JS, et al. Identification of pressure passive cerebral perfusion and its mediators after infant cardiac surgery. *Pediatr Res*. 2005;57(1):35–41.
- Beca J, Gunn JK, Coleman L, Hope A, Reed PW, Hunt RW, et al. New White matter brain injury after infant heart surgery is associated with diagnostic group and the use of circulatory arrest. *Circulation*. 2013;127(9):971–9.
- Bernier PL, Stefanescu A, Samoukovic G, Tchervenkovic CI. The challenge of congenital heart disease worldwide: epidemiologic and demographic facts. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu*. 2010;13(1):26–34. Elsevier Inc.
- Boudjemline Y, Brugada G, Van-Aerschot I, Patel M, Basquin A, Bonnet C, et al. Outcomes and safety of transcatheter pulmonary valve replacement in patients with large patched right ventricular outflow tracts. *Arch Cardiovasc Dis*. 2012;105(8–9):404–13. Elsevier Masson SAS.
- Brickner ME. Cardiovascular management in pregnancy: congenital heart disease. *Circulation*. 2014;130(3):273–82.
- Brothers JA, Stephens P Jr, Paridon SM. Chapter 10: Exercise screening and sports participation. In: Allen HD, Shaddy RE, Penny DJ, Cetta F, Feltes TM, editors. *Moss and Adams heart disease in infants, children, and adolescents: including the fetus and young adult*. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2016. p. 267–85.
- Brown KL, Ridout DA, Hoskote A, Verhulst L, Ricci M, Bull C. Delayed diagnosis of congenital heart disease worsens preoperative condition and outcome of surgery in neonates. *Heart*. 2006;92(9):1298–302.
- Butera G, Biondi-Zoccai G, Sangiorgi G, Abella R, Giamberti A, Bussadori C, et al. Percutaneous versus surgical closure of secundum atrial septal defects: a systematic review and meta-analysis of currently available clinical evidence. *EuroIntervention*. Europa Digital & Publishing SE - Expert review. 2011;7(3):377–85.
- Campbell RM, Douglas PS, Eidem BW, Lai WW, Lopez L, Sachdeva R. ACC/AAP/AHA/ASE/HRS/SCAI/SCCT/SCMR/SOPE 2014 appropriate use criteria for initial transthoracic echocardiography in outpatient pediatric cardiology. *J Am Coll Cardiol*. 2014;64(19):2039–60. American College of Cardiology Foundation.
- Chaix M-A, Marcotte F, Dore A, Mongeon F-P, Mondésert B, Mercier L-A, et al. Risks and benefits of exercise training in adults with congenital heart disease. *Can J Cardiol*. 2015;32:459–66.
- Chen JM, Davies RR, Mital SR, Mercado ML, Addonizio LJ, Pinney SP, et al. Trends and outcomes in transplantation for complex congenital heart disease: 1984 to 2004. *Ann Thorac Surg*. 2004;78(4):1352–61.
- Chugh SS, Kelly KL, Titus JL. Sudden cardiac death with apparently normal heart. *Circulation*. 2000;102(6):649–54.
- Cohen M, Mansoor D, Langut H, Lorber A. Quality of life, depressed mood, and self-esteem in adolescents with heart disease. *Psychosom Med*. 2007;69(4):313–8.
- Costello JP, Olivieri LJ, Su L, Krieger A, Alfares F, Thabit O, et al. Incorporating three-dimensional printing into a simulation-based congenital heart disease and critical care training curriculum for resident physicians. *Congenit Heart Dis*. 2015;10(2):185–90.
- Dawson AL, Cassell CH, Riehle-Colarusso T, Grosse SD, Tanner JP, Kirby RS, et al. Factors associated with late detection of critical congenital heart disease in newborns. *Pediatrics*. 2013;132(3):e604–11.
- Demaso DR, Labella M, Taylor GA, Forbes PW, Stopp C, Bellinger DC, et al. Psychiatric disorders and function in adolescents with d-transposition of the great arteries. *J Pediatr*. 2014;165(4):760–6. Elsevier Inc.
- Du ZD, Hijazi ZM, Kleinman CS, Silverman NH, Larntz K. Comparison between transcatheter and surgical closure of secundum atrial septal defect in children and adults: results of a multicenter nonrandomized trial. *J Am Coll Cardiol*. 2002;39(11):1836–44.
- El-Said HG, Bratincsak A, Foerster SR, Murphy JJ, Vincent J, Holzer R, et al. Safety of percutaneous patent ductus arteriosus closure: an unselected multicenter population experience. *J Am Heart Assoc*. 2013;2(6):e000424.
- Fiore AC, Fischer LK, Schwartz T, Jureidini S, Balfour I, Carpenter D, et al. Comparison of angioplasty and surgery for neonatal aortic coarctation. *Ann Thorac Surg*. 2005;80(5):1659–65.
- Forbes TJ, Kim DW, Du W, Turner DR, Holzer R, Amin Z, et al. Comparison of surgical, stent, and balloon angioplasty treatment of native coarctation of the aorta: an observational study by the CCISC (Congenital cardiovascular interventional study consortium). *J Am Coll Cardiol*. 2011;58(25):2664–74.

- Francis E, Singhi AK, Lakshmvienkateshaiah S, Kumar RK. Transcatheter occlusion of patent ductus arteriosus in pre-term infants. *JACC Cardiovasc Interv*. 2010;3(5):550–5.
- Fratz S, Chung T, Greil GF, Samyn MM, Taylor AM, Valsangiaco Buechel ER, et al. Guidelines and protocols for cardiovascular magnetic resonance in children and adults with congenital heart disease: SCMR expert consensus group on congenital heart disease. *J Cardiovasc Magn Reson*. 2013;15(1):51.
- Freitas IR, Castro M, Sarmiento SL, Moura C, Viana V, Areias JC, et al. A cohort study on psychosocial adjustment and psychopathology in adolescents and young adults with congenital heart disease. *BMJ Open*. 2013;3(1):1–8.
- Fuller S, Nord AS, Gerdes M, Wernovsky G, Jarvik GP, Bernbaum J, et al. Predictors of impaired neurodevelopmental outcomes at one year of age after infant cardiac surgery. *Eur J Cardiothorac Surg*. 2009;36(1):40–8.
- Gaynor JW, Stopp C, Wypij D, Andropoulos DB, Atallah J, Atz AM, et al. Neurodevelopmental outcomes after cardiac surgery in infancy. *Pediatrics*. 2015;135(5):816–25.
- Germanakis I, Sifakis S. The impact of fetal echocardiography on the prevalence of liveborn congenital heart disease. *Pediatr Cardiol*. 2006;27(4):465–72.
- Gressens P, Hagberg H. Perinatal brain damage: mechanisms and neuroprotective strategies. *J Indian Inst Sci*. 2012;92(4):465–83.
- Greutmann M, Pieper PG. Pregnancy in women with congenital heart disease. *Eur Heart J*. 2015;36(37):2491–9.
- Han BK, Lesser AM, Vezmar M, Rosenthal K, Rutten-Ramos S, Lindberg J, et al. Cardiovascular imaging trends in congenital heart disease: a single center experience. *J Cardiovasc Comput Tomogr*. Mosby Inc. 2013;7(6):361–6.
- Ibuki K, Watanabe K, Yoshimura N, Kakimoto T, Matsui M, Yoshida T, et al. The improvement of hypoxia correlates with neuroanatomic and developmental outcomes: comparison of midterm outcomes in infants with transposition of the great arteries or single-ventricle physiology. *J Thorac Cardiovasc Surg*. 2012;143(5):1077–85. The American Association for Thoracic Surgery.
- Kantor PF, Lougheed J, Dancea A, McGillion M, Barbosa N, Chan C, et al. Presentation, diagnosis, and medical management of heart failure in children: Canadian Cardiovascular Society guidelines. *Can J Cardiol*. 2013a;29(12):1535–52.
- Kantor PF, Andelfinger G, Dancea A, Khairy P. Heart failure in congenital heart disease. *Can J Cardiol*. 2013b;29(7):753–4.
- Karsdorp PA. Psychological and cognitive functioning in children and adolescents with congenital heart disease: a meta-analysis. *J Pediatr Psychol*. 2007;32(5):527–41.
- Kemper AR, Mahle WT, Martin GR, Cooley WC, Kumar P, Morrow WR, et al. Strategies for implementing screening for critical congenital heart disease. *Pediatrics*. 2011;128(5):e1259–67.
- Khairy P, Ionescu-Ittu R, MacKie AS, Abrahamowicz M, Pilote L, Marelli AJ. Changing mortality in congenital heart disease. *J Am Coll Cardiol*. Elsevier Inc. 2010;56(14):1149–57.
- Kindel SJ, Miller EM, Gupta R, Cripe LH, Hinton RB, Spicer RL, et al. Pediatric cardiomyopathy: importance of genetic and metabolic evaluation. *J Card Fail*. 2012;18(5):396–403.
- Krishnamurthy R. Pediatric cardiac MRI: anatomy and function. *Pediatr Radiol*. 2008;38(Suppl 2):192–9.
- Laitinen PJ, Brown KM, Piippo K, Swan H, Devaney JM, Brahmabhatt B, et al. Mutations of the cardiac ryanodine receptor (RyR2) gene in familial polymorphic ventricular tachycardia. *Circulation*. 2001;103(4):485–90.
- Liberthson R. Sudden death from cardiac causes in children and young adults. *N Engl J Med*. 1996;334:1039–44.
- Licht DJ, Shera DM, Clancy RR, Wernovsky G, Montenegro LM, Nicolson SC, et al. Brain maturation is delayed in infants with complex congenital heart defects. *J Thorac Cardiovasc Surg*. 2009;137(3):529–36; discussion 536–7. The American Association for Thoracic Surgery.
- Liesemer K, Casper TC, Korgenski K, Menon SC. Use and misuse of serum troponin assays in pediatric practice. *Am J Cardiol*. 2012;110(2):284–9.
- Limperopoulos C, Tworetzky W, McElhinney DB, Newburger JW, Brown DW, Robertson RL, et al. Brain volume and metabolism in fetuses with congenital heart disease: evaluation with quantitative magnetic resonance imaging and spectroscopy. *Circulation*. 2010;121(1):26–33.
- Lin CH, Lin WC, Ho YJ, Chang JS. Children with chest pain visiting the emergency department. *Pediatr Neonatol*. 2008;49(2):26–9.
- Longmuir PE, Brothers JA, De Ferranti SD, Hayman LL, Van Hare GF, Matherne GP, et al. Promotion of physical activity for children and adults with congenital heart disease: a scientific statement from the American Heart Association. *Circulation*. 2013;127(21):2147–59.
- Lurz P, Gaudin R, Taylor AM, Bonhoeffer P. Percutaneous pulmonary valve implantation. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu*. 2009;12(1):112–7.
- Mahle WT, Martin GR, Beekman RH III, Morrow WR, Rosenthal GL, Snyder CS, LuAnn Minich L, Mital S, Towbin JA, et al. Endorsement of health and human services recommendation for pulse oximetry screening for critical congenital heart disease. *Am Acad Pediatr*. 2012;129(1):190–2.
- Marelli AJ, Mackie AS, Ionescu-Ittu R, Rahme E, Pilote L. Congenital heart disease in the general population: changing prevalence and age distribution. *Circulation*. 2007;115(2):163–72.
- Marino BS, Lipkin PH, Newburger JW, Peacock G, Gerdes M, Gaynor JW, et al. Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a Scientific Statement From the American Heart Association. *Circulation*. 2012;126(9):1143–72.

- Maron BJ, Gardin JM, Flack JM, Gidding SS, Kurosaki TT, Bild DE. Prevalence of hypertrophic cardiomyopathy in a general population of young adults echocardiographic analysis of 4111 subjects in the CARDIA Study. *Circulation*. 1995;92(4):785–9.
- Maron BJ, Co-chair C, Zipes DP, Co-chair C. Title page. 2011 Int Conf Multimed Technol. 2011;45(8):1.
- Maron BJ, Maron MS, Semsarian C. Genetics of hypertrophic cardiomyopathy after 20 years: clinical perspectives. *J Am Coll Cardiol*. 2012;60(8):705–15.
- Massaro AN, El-dib M, Glass P, Aly H. Factors associated with adverse neurodevelopmental outcomes in infants with congenital heart disease. *Brain Dev*. 2008;30(7):437–46.
- Mellion K, Uzark K, Cassedy A, Drotar D, Wernovsky G, Newburger JW, et al. Health-related quality of life outcomes in children and adolescents with congenital heart disease. *J Pediatr*. 2014;164(4):781–8.e1. Elsevier Ltd.
- Members WC, Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011;124(24):2761–96.
- Mertens L, Ganame J, Eyskens B. What is new in pediatric cardiac imaging? *Eur J Pediatr*. 2008;167(1):1–8.
- Møller DV, Andersen PS, Hedley P, Ersbøll MK, Bundgaard H, Moolman-Smook J, et al. The role of sarcomere gene mutations in patients with idiopathic dilated cardiomyopathy. *Eur J Hum Genet*. 2009;17:1241–9.
- Momenah TS, El Oakley R, Al Najashi K, Khoshhal S, Al Qethamy H, Bonhoeffer P. Extended application of percutaneous pulmonary valve implantation. *J Am Coll Cardiol*. 2009;53(20):1859–63. American College of Cardiology Foundation.
- Moore A, Rouleau JSE. Congenital anomalies in Canada 2013: a perinatal health surveillance report. 2013;57–64.
- Moore J, Hegde S, El-Said H, Beekman R, Benson L, Bergersen L, et al. Transcatheter device closure of atrial septal defects: a safety review. *JACC Cardiovasc Interv*. 2013;6:433–42.
- Newburger JW, Wypij D, Bellinger DC, Du Plessis AJ, Kuban KCK, Rappaport LA, et al. Length of stay after infant heart surgery is related to cognitive outcome at age 8 years. *J Pediatr*. 2003;143(1):67–73.
- Nieminen HP, Jokinen EV, Sairanen HI. Causes of late deaths after pediatric cardiac surgery. A population-based study. *J Am Coll Cardiol*. 2007;50(13):1263–71.
- Nies M, Sekar P. Advances in noninvasive imaging in pediatric cardiology. *Adv Pediatr*. 2013;60(1):167–85. Elsevier Inc.
- Niklasson L, Rasmussen P, Oskarsdóttir S, Gillberg C. Chromosome 22q11 deletion syndrome (CATCH 22): neuropsychiatric and neuropsychological aspects. *Dev Med Child Neurol*. 2002;44(Catch 22):44–50.
- Ortinou C, Beca J, Lambeth J, Ferdman B, Alexopoulos D, Shimony JS, et al. Regional alterations in cerebral growth exist preoperatively in infants with congenital heart disease. *J Thorac Cardiovasc Surg*. The American Association for Thoracic Surgery. 2012;143(6):1264–70.
- Peterson C, Ailes E, Riehle-Colarusso T, Oster ME, Olney RS, Cassell CH, et al. Late detection of critical congenital heart disease among US infants. *JAMA Pediatr*. 2014a;168(4):361.
- Peterson C, Grosse SD, Glidewell J, Garg LF, Van Naarden Braun K, Knapp MM, et al. A public health economic assessment of hospitals' cost to screen newborns for critical congenital heart disease. *Public Health Rep*. 2014b;129(1):86–93.
- Priori SG, Napolitano C, Tiso N, Memmi M, Vignati G, Bloise R, et al. Mutations in the cardiac ryanodine receptor gene (hRyR2) underlie catecholaminergic polymorphic ventricular tachycardia. *Circulation*. 2001;103(2):196–200.
- Puranik R, Chow CK, Duflou JA, Kilborn MJ, McGuire MA. Sudden death in the young. *Heart Rhythm*. 2005;2(12):1277–82.
- Quartermain MD, Pasquali SK, Hill KD, Goldberg DJ, Huhta JC, Jacobs JP, et al. Variation in prenatal diagnosis of congenital heart disease in infants. *Pediatrics*. 2015;136(2):e378–85.
- Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, Cifkova R, Ferreira R, Foidart JM, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2011;32(24):3147–97.
- Ritter S, Tani LY, Etheridge SP, Williams RV, Craig JE, Minich LL. What is the yield of screening echocardiography in pediatric syncope? *Pediatrics*. 2000;105(5):E58.
- Roos-Hesselink JW, Ruys TPE, Stein JI, Thilén U, Webb GD, Niwa K, et al. Outcome of pregnancy in patients with structural or ischaemic heart disease: results of a registry of the European Society of Cardiology. *Eur Heart J*. 2013;34(9):657–65.
- Saleeb SF, Li WYV, Warren SZ, Lock JE. Effectiveness of screening for life-threatening chest pain in children. *Pediatrics*. 2011;128(5):e1062–8.
- Schaefer C, von Rhein M, Knirsch W, Huber R, Natalucci G, Caffisch J, et al. Neurodevelopmental outcome, psychological adjustment, and quality of life in adolescents with congenital heart disease. *Dev Med Child Neurol*. 2013;55(12):1143–9.
- Schaer M, Glaser B, Ottet MC, Schneider M, Cuadra MB, Debbané M, et al. Regional cortical volumes and congenital heart disease: a MRI study in 22q11.2 deletion syndrome. *J Neurodev Disord*. 2010;2(4):224–34.
- Silversides CK, Kiess M, Beauchesne L, Bradley T, Connelly M, Niwa K, et al. Canadian Cardiovascular Society 2009 Consensus Conference on the management of adults with congenital heart disease: outflow tract obstruction, coarctation of the aorta, tetralogy of Fallot, Ebstein anomaly and Marfan's syndrome. *Can J Cardiol*. 2010a;26(3):e80–97. Elsevier.

- Silversides CK, Salehian O, Oechslin E, Schwerzmann M, Vonder Muhll I, Khairy P, et al. Canadian Cardiovascular Society 2009 Consensus Conference on the management of adults with congenital heart disease: complex congenital cardiac lesions. *Can J Cardiol.* 2010b;26(3):e98–117. Elsevier.
- Silversides CK, Dore A, Poirier N, Taylor D, Harris L, Greutmann M, et al. Canadian Cardiovascular Society 2009 Consensus Conference on the management of adults with congenital heart disease: shunt lesions. *Can J Cardiol.* 2010c;26(3):e70–9. Elsevier.
- Siu SC, Sermer M, Colman JM, Alvarez AN, Mercier LA, Morton BC, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. *Circulation.* 2001;104(5):515–21.
- Splawski I, Shen J, Timothy KW, Lehmann MH, Priori S, Robinson JL, et al. Spectrum of mutations in long-QT syndrome genes. *KVLQT1, HERG, SCN5A, KCNE1, and KCNE2.* *Circulation.* 2000;102(10):1178–85.
- Stehlik J, Edwards LB, Kucheryavaya AY, Benden C, Christie JD, Dipchand AI, et al. The registry of the international society for heart and lung transplantation: 29th official adult heart transplant report—2012. *J Heart Lung Transplant.* Elsevier Inc. 2012;31(10):1052–64.
- Steinberg LA, Knilans TK. Syncope in children: diagnostic tests have a high cost and low yield. *J Pediatr.* 2005;146:355–8.
- Su XW, Ündar A. Brain protection during pediatric cardiopulmonary bypass. *Artif Organs.* 2010;34(4):E91–102.
- Tegnander E, Williams W, Johansens OJ, Blaas HGK, Eik-Nes SH. Prenatal detection of heart defects in a non-selected population of 30149 fetuses—detection rates and outcome. *Ultrasound Obstet Gynecol.* 2006;27(3):252–65.
- Tester DJ, Ackerman MJ. Genetic testing for potentially lethal, highly treatable inherited cardiomyopathies/channelopathies in clinical practice. *Circulation.* 2011;123(9):1021–37.
- Tester DJ, Will ML, Haglund CM, Ackerman MJ. Effect of clinical phenotype on yield of long QT syndrome genetic testing. *J Am Coll Cardiol.* 2006;47(4):764–8.
- Tester DJ, Will ML, Haglund CM, Ackerman MJ. Compendium of cardiac channel mutations in 541 consecutive unrelated patients referred for long QT syndrome genetic testing. *Heart Rhythm.* 2016;2(5):507–17. Elsevier.
- Thangaratnam S, Brown K, Zamora J, Khan KS, Ewer AK. Pulse oximetry screening for critical congenital heart defects in asymptomatic newborn babies: a systematic review and meta-analysis. *Lancet.* 2012;379:2459–64.
- Thorne S. Risks of contraception and pregnancy in heart disease. *Heart.* 2006;92(10):1520–5.
- Tomek V, Marek J, Jičínská H, Škovránek J. Fetal cardiology in the Czech Republic: current management of prenatally diagnosed congenital heart diseases and arrhythmias. *Physiol Res.* 2009;58(Suppl 2):159–66.
- Towbin JA, Lowe AM, Colan SD, Sleeper LA, Orav EJ, Clunie S, et al. Incidence, causes and outcomes of dilated cardiomyopathy in children. *JAMA.* 2006;296(15):1867–76.
- Trines J, Fruitman D, Zuo KJ, Smallhorn JF, Hornberger LK, Mackie AS. Effectiveness of prenatal screening for congenital heart disease: assessment in a jurisdiction with universal access to health care. *Can J Cardiol.* 2013;29(7):879–85.
- Tynan M, Finley JP, Fontes V, Hess J, Kan J. Balloon angioplasty for the treatment of native coarctation: results of Valvuloplasty and Angioplasty of Congenital Anomalies Registry. *Am J Cardiol.* 1990;65(11):790–2.
- Uzark K, Jones K, Slusher J, Limbers CA, Burwinkle TM, Varni JW. Quality of life in children with heart disease as perceived by children and parents. *Pediatrics.* 2008;121(5):e1060–7.
- Van Der Linde D, Konings EEM, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJM, et al. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *J Am Coll Cardiol.* 2011;58(21):2241–7. Elsevier Inc.
- Van Der Werf C, Hofman N, Tan HL, Van Dessel PF, Alders M, Van Der Wal AC, et al. Diagnostic yield in sudden unexplained death and aborted cardiac arrest in the young: the experience of a tertiary referral center in the Netherlands. *Heart Rhythm.* 2010;7(10):1383–9.
- Vezmar M, Chaturvedi R, Lee KJ, Almeida C, Manlhiot C, McCrindle BW, et al. Percutaneous pulmonary valve implantation in the young: 2-year follow-up. *JACC Cardiovasc Interv.* 2010;3:439–48.
- Visoosak J, Mahle WT, Kirshbom PM, Huddleston L, Caron-Besch M, Ransom A, et al. Neurodevelopmental outcomes in children with Down syndrome and congenital heart defects. *Am J Med Genet A.* 2011;155(11):2688–91.
- von Rhein M, Scheer I, Loenneker T, Huber R, Knirsch W, Latal B. Structural brain lesions in adolescents with congenital heart disease. *J Pediatr.* Mosby, Inc. 2011;158(6):984–9.
- Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, et al. ACC/AHA 2008 Guidelines for the management of adults with congenital heart disease. *J Am Coll Cardiol.* 2008;52(23):1890–947. American College of Cardiology Foundation.
- Wilson WM, Benson LN, Osten MD, Shah A, Horlick EM. Transcatheter pulmonary valve replacement with the edwards sapien system. *J Am Coll Cardiol Intv.* 2015;8(14):1819–27.
- Wren C, Reinhardt Z, Khawaja K. Twenty-year trends in diagnosis of life-threatening neonatal cardiovascular malformations. *Arch Dis Child Fetal Neonatal Ed.* 2008;93(1):F33–5.
- Yetman AT, Nykanen D, McCrindle BW, Sunnegardh J, Adatia I, Freedom RM, et al. Balloon angioplasty of recurrent coarctation: a 12-year review. *J Am Coll Cardiol.* 1997;30(3):811–6.

- Young C, Taylor AM, Owens CM. Paediatric cardiac computed tomography: a review of imaging techniques and radiation dose consideration. *Eur Radiol.* 2011;21(3):518–529.
- Yusen RD, Christie JD, Edwards LB, Kucheryavaya AY, Benden C, Dipchand AI, et al. The registry of the international society for heart and lung transplantation: thirtieth adult lung and heart-lung transplant report—2013; focus theme: age. *J Heart Lung Transplant.* 2013;32(10):965–78. Elsevier.
- Zou Y, Song L, Wang Z, Ma A, Liu T, Gu H, et al. Prevalence of idiopathic hypertrophic cardiomyopathy in China: a population-based echocardiographic analysis of 8080 adults. *Am J Med.* 2004;116(1):14–8.



Update in Child Maltreatment

4

Michelle G.K. Ward, Amy E. Ornstein,
Tanya Deurvorst Smith, and Karla Wentzel

Introduction

Every child has the right to grow up in a safe, healthy, and nurturing environment that helps them to meet their greatest potential. However, globally at least a billion children experience physical, sexual, emotional, or multiple types of violence. This includes greater than 50% of children living in North America (Hillis et al. 2016). Child maltreatment (abuse, neglect, and exposure to family violence) normalizes violence, undermines the health and development of children, and is linked with multiple negative physical and mental health outcomes in adulthood. It is hard to imagine a current health problem that has a greater effect on our population, than does violence, with child maltreatment representing violence that occurs within the context of a caregiving relationship.

In the United States, an estimated 3.6 million referrals involving 6.6 million children were made to child protection services in 2014 and in greater than 700,000 cases, child maltreatment was substantiated. This indicates that 9.4 per 1000 children in the United States are victims of substantiated maltreatment and greater than 240,000 children receive foster care services (U.S. Department of Health, and Human Services, Administration on Children, Youth and Families, Children's Bureau 2016). However, some studies suggest that up to one quarter of children in the US experience some form of child maltreatment (Finkelhor et al. 2013, 2015). In Canada, approximately 1.4% of children are the subjects of reports to child protection services that go on to be substantiated for abuse or neglect (Public Health Agency of Canada 2010). However, population studies demonstrate that up to 32% of

M.G.K. Ward, M.D., F.A.A.P., F.R.C.P.C. (✉)
Division of Child and Youth Protection,
Department of Pediatrics, Children's Hospital of
Eastern Ontario, 401 Smyth Rd, Ottawa K1H 8L1,
Ontario, Canada

Associate professor, Department of Pediatrics,
Faculty of Medicine, University of Ottawa,
Ottawa, ON, Canada
e-mail: mward@cheo.on.ca

A.E. Ornstein, M.D.C.M., M.Sc., F.R.C.P.C., F.A.A.P.
Department of Pediatrics, IWK Health Centre,
Halifax, NS, Canada

Department of Pediatrics, Dalhousie University,
Halifax, NS, Canada
e-mail: amy.ornstein@iwk.nshealth.ca

T.D. Smith, M.N., N.P.-Paediatrics • K. Wentzel,
M.N., N.P.-Paediatrics
The Suspected Child Abuse and Neglect (SCAN)
Program, The Hospital for Sick Children,
Toronto, ON, Canada

Lawrence S. Bloomberg Faculty of Nursing,
The University of Toronto, Toronto, ON, Canada
e-mail: Tanya.smith@sickkids.ca;
Karla.wentzel@sickkids.ca

women and men report physical abuse, sexual abuse, and/or exposure to domestic violence as children (Afifi et al. 2014). This implies that clinicians who are seeing children and youth regularly are likely encountering victims of maltreatment on a monthly, if not weekly or daily basis.

Although many clinicians feel poorly prepared to deal with cases of suspected abuse or neglect, they are in a unique position to identify concerns of maltreatment and to assist children and families. They also have an ethical responsibility, and in many jurisdictions a legal duty, to report concerns of maltreatment to authorities. Clinicians can take a standard clinical approach to this issue by generating a differential diagnosis, completing a history and physical examination, assessing with laboratory and radiographic testing, and synthesizing the information to arrive at a conclusion. Following this type of objective, structured approach will be familiar to clinicians and can provide a framework for assessment, during a time that may be emotional for all involved.

This chapter will provide a review and practical medical approach to the most common child maltreatment problems encountered by clinicians: physical abuse, sexual abuse, and neglect.

What Is Child Maltreatment?

The World Health Organization defines child maltreatment as "...the abuse and neglect that occurs to children under 18 years of age. It includes all types of physical and/or emotional ill-treatment, sexual abuse, neglect, negligence, and commercial or other exploitation, which results in actual or potential harm to the child's health, survival, development or dignity in the context of a relationship of responsibility, trust or power" (World Health Organization 2016). In other words, child maltreatment refers to the actions or inactions of a caregiver that result in actual or potential harm to a child's health or well-being.

In many countries, child protection and/or criminal laws outline the types of maltreatment to

which authorities can or must respond and these are usually categorized as physical abuse, sexual abuse, emotional abuse, and neglect. Many jurisdictions also consider exposure to intimate partner violence (also called domestic violence) as maltreatment for children because it places them at risk of harm in their home environment and because they often experience many of the same negative outcomes as children who are victims of direct maltreatment (Afifi et al. 2014; Rankin and Ornstein 2009).

Physical abuse is characterized by the use of physical force by a caregiver that results in harm or risk of harm to the child's health, safety or well-being.

Sexual abuse occurs when a caregiver or another person in a position of power, engages in any activity with a child for sexual purposes. This includes sexual contact (e.g., oral, anal, genital), and activities without physical contact, such as exploitation (eg. trafficking or facilitating prostitution or pornography), voyeurism, and exhibitionism. Different jurisdictions may have additional definitions and laws regarding the definition of sexual abuse, such as age-based laws for consent.

Neglect is generally viewed in the child protection system as a pattern of omissions of care by a parent or caregiver that leads to harm or a risk of harm for a child. However, neglect has also been defined from a child's perspective, as the child's needs not being met, whatever the cause (Dubowitz et al. 2005).

In addition to legal and clinical definitions of child maltreatment, culture plays a key role in defining child maltreatment. Parenting philosophies, methods, norms, disciplinary practices, and expectations of children's behaviour vary widely within and between different populations. These are often culturally-determined. As a result, there is variability in what is deemed acceptable in child rearing and what constitutes abuse or neglect. Notwithstanding these differences, clinicians should always advocate for parenting practices that are safe, healthy, and beneficial to helping children reach their best physical, developmental, and emotional potential (Ward et al. 2014).

How Does Maltreatment Affect Children?

In recent decades, a robust medical literature has demonstrated the negative effects of adverse childhood events, such as child abuse and neglect, on the long-term physical and emotional health of adults. These early childhood experiences are associated with stroke, cancer, heart disease, hypertension, diabetes, depression, suicide, substance abuse and other poor outcomes (Maguire et al. 2015). Moreover, disruptions in early childhood attachment and exposure to a stressful and unpredictable environment lead children to have maladaptive behaviours, difficulties regulating emotions and understanding social interactions, and an exaggerated stress response to normal minor life events, with subsequent high rates of mental health problems in adulthood (Afifi et al. 2014; Maguire et al. 2015). In the clinic, community, or classroom, this often demonstrates itself as aggression, anger, depression, or difficulty sustaining attention. Once established, these behavioural patterns may be difficult to manage using typical behaviour modification strategies because of the alteration in the child's neural physiology and their priming of the stress response. As a result, prevention and early intervention are essential, while promoting effective treatment for those already affected.

Terminology and Definitions

When maltreatment concerns are raised for a child, a variety of professionals may become involved including those from health care, child protection, law enforcement, social services, and/or the justice system. As a result, it is imperative that the language used by clinicians be objective, clear, and understandable to those within and outside of the health care system.

Clinicians need a way to communicate that they are concerned that a specific injury or health effect is related to maltreatment as opposed to being related to a medical illness or common childhood event (bump, fall etc.). At the same time, they must use language that does not over-

state the certainty of the medical information that the finding in question was caused by maltreatment. The clinician should also be aware that some words carry unintended meaning for the legal system, which may place greater emphasis on the intent behind an individual's actions.

Many different terms have been used to differentiate causes of injuries including the following pairs of terms: non-accidental and accidental, abusive and non-abusive, intentional and non-intentional, inflicted and non-inflicted.

For the purposes of this chapter, the term "accidental" will be used to refer to injuries or health effects that occur as a result of common minor life events (eg. bumps and falls), usually through the child's own actions. For example, bruising on the shins of a school age child that occurs through playing outdoors and bumping against the play structure at the park would be considered "accidental". Similarly, a buckle fracture of the radius that occurs from falling from a swing at the park would be considered "accidental". It is acknowledged that injury prevention specialists typically do not use "accident" as even the actions above may be viewed as preventable events.

The term "inflicted" will be used to refer to injuries or health effects that occur as a result of the direct actions of another person. For example, bruising on the back caused by an adult hitting a child with a belt would be considered inflicted. Similarly, if a parent grabbed their child by the elbow to stop them from running into traffic and this resulted in bruising, this would be considered inflicted. Used in this way, the term does not determine the intent of the action that caused injury, as the medical information alone (mark seen on the back or bruises on the elbow) is not able to determine the intent of the adult's action or to verify the circumstances surrounding the event.

The term "abuse" is used to refer to a legal determination that injuries or effects that occurred as a result of the direct actions of another person were intended and harmful. The determination of abuse typically occurs after an investigation by child protection and/or legal authorities, but the investigation may be *initiated* by concerns for abuse raised by a health professional. For the purposes of this

chapter, “abuse” will also be used to refer to findings in the literature that were deemed to be associated with abuse (whether determined medically, multi-disciplinarily or legally).

Identifying Maltreatment

Although child maltreatment is common, it often goes unrecognized in health care settings. In many cases it is difficult to recognize because the signs and symptoms may be non-specific and/or the child may be pre-verbal, unable or unwilling to disclose the maltreatment. Clinicians are trained to begin their assessment by taking a history. However, in these cases, the history provided by the caregiver may be incomplete, incorrect, or unknown to the person providing the information.

The following general concepts on assessment should prompt the clinician to carefully consider maltreatment as a possible cause, while also considering other traumatic possibilities (eg. accidental, birth, inflicted or self-inflicted injury) and medical conditions in the differential diagnosis, as appropriate. More specific “red flags” for different types of maltreatment are included in the sections below.

- Disclosure of maltreatment by a child, a witness, or someone else.
- No explanatory history or unknown history for a significant, uncommon, or unexpected traumatic injury.
- Injuries with characteristics that are more often associated with inflicted injury and/or physical abuse than with other injury mechanisms and a history that does not clearly explain the injury.
- Explanatory history for a traumatic injury(ies) that does not appear compatible with the observed injury because of factors related to the child (eg. age and developmental abilities) or the injury (eg. severity, number, type and/or approximate age of the injury).
- Pattern of injuries or medical issues (such as fractures, growth problems, genito-urinary symptoms) that does not appear compatible

with a reasonable traumatic or medical explanation and may be explained by maltreatment.

- Pattern of growth, development, behaviour, or emotional problems that is outside the norm and may be due to a caregiver’s actions or inactions.
- Pattern of non-adherence with medical, dental or psychological care recommendations such that the child experiences (or is at risk of) harm.
- Pattern of a child’s physical, emotional, developmental or educational needs not being met.
- Pattern of injuries or harm related to inadequate supervision.

Clinical Approach to Physical Injuries That May Be due to Maltreatment

General Approach

Questions of child maltreatment should be evaluated using a standard medical approach including a thorough pediatric history, full physical examination (including vital signs, growth parameters, and examination of the full skin surface, with a chaperone present when possible), laboratory testing and/or imaging when indicated, and synthesis of the relevant clinical information with the clinician’s understanding of the issues from current literature and experience. The clinician should approach this task without bias, with objectivity, and with an open mind regarding the cause of the injuries. Clinicians should demonstrate the same compassion, empathy, professionalism, and collaboration with caregivers in this clinical scenario as they do in all other situations.

In determining the likely cause of the injury, the health care provider should consider a broad differential that includes medical causes and traumatic causes for injuries or symptoms. Working through the differential diagnosis in a systematic way is recommended. Although health care professionals are used to using information gathered on history to guide their evaluation on physical exam, laboratory testing and imaging, in cases of possible maltreatment, the history of the injury event and symptoms may be incorrect, incomplete, or misleading. This is sometimes also true of non-maltreatment cases.

History

A standard pediatric history should be taken. In general, when maltreatment is being considered a detailed History of Presenting Illness (HPI) is required. Although, in most circumstances, it is not the role of the clinician to take a forensic history (unless they are specifically trained to do so), the clinician must take enough history to be able to assess and assist the child and family medically, and to determine if the concerns require a report to legal authorities. The clinician should be aware of relevant child protection laws, including mandatory reporting duties, for their jurisdiction.

On history, the clinician should take sufficient information in the initial assessment in order to answer the following questions:

1. What injuries or health effects are present? What associated features of maltreatment, trauma, or a medical condition might be present? What medical assessment, testing and management are indicated for this child for health purposes? How urgently are testing and/or treatment needed?
2. Does the information suggest harm or risk of harm to the child, such that a report to child protection/legal authorities is advisable according to regional legislative requirements?
3. Is there any indication for forensic samples to be collected (eg. sexual assault forensic evidence kit)?

If the child has a physical finding such as a bruise or fracture, the HPI, Review of Systems (ROS) Past Medical History (PMHx) including pregnancy and birth history, and Family History (FHx) should include specific questions about the finding in question. The purpose is to understand the course and effect of the finding (eg. is this the child's first episode of significant bruising, does the child have other symptoms of bleeding or is there a family history of such), as well as to look for possible underlying acute or chronic medical conditions that could predispose to the finding (eg. bleeding disorder or systemic illness). See below for specific questions to include for different types of physical findings.

The clinician should ask about allergies, immunization status, and whether the child takes any medications or uses alternative therapies.

A developmental history is important in order to understand a child's level of mobility, independence and/or any need for assistance with daily activities. These may need to be compared to the history that is presented (eg. the child crawled off the bed) to determine whether they are compatible. Developmental problems are common in children who have experienced maltreatment and/or suboptimal parenting. In particular, problems in the development of speech and language and in social skills are more sensitive to the child's environment and the degree and quality of caregiver stimulation. These can be screened for using a developmental history and/or a standardized and validated developmental screening tool. Motor skills tend to be less sensitive to the child's environment and level of caregiver interaction but can also be affected if the child is not challenged to move and/or given appropriate opportunities to practice motor skills.

Clinicians should make a special effort to ask about child behaviour, parental expectations, and discipline practices since most physical abuse occurs in the context of physical or corporal punishment. Clinicians can initiate this discussion as part of the developmental history or ROS when behaviour is reviewed. This is an opportunity for the clinician to convey their openness to discussing these issues. The clinician can also provide anticipatory guidance and counselling on these issues that are of importance to most parents.

Risk factors for the use of physical punishment include parental approval of physical punishment, parental anger in response to conflict with their child, parental history of physical punishment as a child, and parental assessment of child misbehaviour as intentional or serious (Ateah and Durrant 2005; Durrant et al. 1999; Bower-Russa et al. 2001; Durrant and Ensom 2004). Increased family stress with the presence of parental conflict or violence, greater number of children, and parental mental health or addiction problems are also linked to greater use of physical punishment. Possible protective factors include a warm and positive parental relationship

(especially if one parent experienced childhood violence), an appropriate source of parenting advice, and parents who are empathetic (Durrant and Ensom 2012; Afifi and MacMillan 2011).

Using a non-judgemental and supportive style, clinicians should encourage parents to talk about their challenges in parenting and help them make a concrete plan for dealing with the issues the next time they arise. They can also refer to appropriate supports in the community. The following are questions that may help the clinician to understand the parent's views and practices on child behaviour and physical discipline, and assess for the above risk factors:

- What is your child's behaviour like most of the time? Do you think it is appropriate for their age? How do you usually guide your child's behaviour?
- All children have moments when they misbehave or don't listen. Can you tell me about what your child is like at those times? When was the last time this occurred? Was this the "worst" time? What did you do? How were you feeling? The next time this occurs, would you do anything differently?
- Has your child's behaviour ever been so bad that you felt you had to spank, hit or do something physical to him/her? How often does this occur? Did your child ever get hurt as a result? If this scenario occurred again, would you do anything differently?
- Did your parents ever hit, spank or use physical punishment with you as a child? What do you think about that now?

As there is now ample evidence that physical discipline is not effective and can be harmful to children in the short and long-term, clinicians should advise against all forms of physical discipline (Durrant and Ensom 2004, 2012). Clinicians should guide parents on the use of positive parenting including safe, effective and healthy forms of guidance for children's behaviour. Many excellent resources for clinicians and parents exist including those by the American Academy of Pediatrics and the Canadian Paediatric Society.

Physical Examination

A head to toe evaluation, beginning with vital signs and the child's general appearance (hydration, nourishment, clothing, general health status) is recommended whenever child maltreatment is suspected. The clinician should observe for features that might suggest an underlying genetic condition. The weight and height should be plotted on a standardized and validated growth chart (eg. WHO, CDC) at each visit in order to appreciate trends that might not otherwise be seen. The head circumference should be plotted for all children under the age of 2 years as a rapidly increasing head size may be the first clue to an intracranial injury and stagnating head growth is an important health issue for a child with inadequate nutrition and/or prior trauma. These parameters may also highlight conditions that can contribute to or mimic injuries from maltreatment such as skeletal dysplasias and metabolic conditions (eg. glutaric aciduria).

Particular attention should be paid to the head and neck exam. The dentition often reflects environmental and caregiving factors such as feeding practices (eg. bottle caries), hygiene, and quality of nutrition, and may also be a clue to underlying conditions (eg. dentinogenesis imperfecta). During an evaluation, if the clinician notes speech and language delays and poor dental hygiene, further information should be sought about caregiving practices, daily routines and the home environment. This combination of findings is often seen in children who live in suboptimal environments.

The general physical examination may include an external genital examination. It is appropriate to examine the genitals when the presenting concern or symptoms involve the gastro-intestinal or genito-urinary system but it is often also appropriate to examine the genitals as part of the complete pediatric assessment. The health care provider can convey, in age-appropriate language, and using correct anatomical terms (or the terms that the child already knows and uses) that, like the other areas already examined, the genitals are another part of the body that should be examined periodically by a physician to ensure that they are healthy. The clinician should

acknowledge that the genitals are a private area of the body. This offers an opportunity to model a discussion with the child about privacy and safety in front of the caregiver. The child's permission for this part of the exam should be sought and respected. Gloves should be worn by the clinician when examining the genitalia or anus. Every effort should be made to help the child feel comfortable with this exam, including draping the child, taking more time for the exam, and having a supportive caregiver with the child. Further details of the genital exam are included in the section below on sexual abuse.

Documentation

When a clinician is asked to evaluate a child for a child maltreatment concern, or when one is identified in the course of an evaluation, special attention should be given to documentation. In addition to the usual notations made in the record, the clinician should include the time and length of the assessment, who accompanied the child, the reason for the assessment, and what information was provided prior to the assessment.

The clinician should use descriptive (and not interpretive) language throughout such as "the mother reports concerns of" or "the father states that". The diagnosis should be recorded as an objective medical determination (eg. bruising, fracture, head injury, alleged sexual assault). Where it is important to capture the context of the situation, the clinician can record "child maltreatment assessment" or other descriptor (eg. unexplained bruising instead of bruising) but should avoid making a "diagnosis" of abuse based on medical information alone.

The information given to the family, child protection worker or others should be recorded. Reviewing the documentation for legibility, accuracy and completeness is good practice as this documentation may be used for legal purposes and may be the only record by a professional. If the clinician is called to testify in the case in the future, they will need to rely on their written record.

Special documentation of skin and genital findings by drawing or photography should also be included when appropriate and is described in

the sections below. The reader is referred to sources for further information about documentation and legal considerations (Ornstein 2013).

Physical Abuse

Clinicians may be the first to identify concerns for physical abuse because of a specific physical finding or they may be asked to assess a child to provide an opinion on whether there are signs of physical abuse. When presented with these scenarios, clinicians should be cautious to follow their usual objective, empiric approach and to recognize both the breadth and limitations of their roles as a medical professional. The following key points should be borne in mind:

- On medical assessment, no injury on its own is pathognomonic for physical abuse
- All physical findings have a differential diagnosis which may include a variety of traumatic and medical causes
- Medical conditions and trauma are not mutually exclusive. The presence of one does not exclude the possibility of the other
- In most cases of suspected physical abuse, the objective medical findings, on their own, cannot determine the exact mechanism and circumstances of injury or the precise timing of injury
- The current understanding of the scientific basis of injuries, coupled with clinical experience, often can raise concern about physical abuse. Physicians with appropriate training, skills, and experience can identify concerns for maltreatment and provide an opinion on the likely cause or mechanism of injury and approximate time of injury. Physicians without this expertise should be cautious about providing an opinion that will be used for legal purposes

Bruising

Bruises are common in childhood and usually represent no significant health concern. However,

bruising is also the most common injury sustained from physical abuse (Public Health Agency of Canada 2010) and can sometimes be the first indication of an underlying medical illness. As a result, health care providers may be asked to provide an opinion on the likely cause of bruising on a child or they may be the first to raise concern for physical abuse or a medical illness as a result of their physical examination.

Bruises are skin injuries that are the result of bleeding beneath the skin. They can be caused by an impact, compression, crushing or penetrating force that damages the blood vessels, leading to bleeding into subcutaneous tissue layers. In children, bruises are usually caused by impact between a part of the body and a hard surface or object. Petechiae can also be seen on their own or in association with bruising.

Through active play, mobile children often sustain “normal childhood bruising”. This type of bruising is typically characterized by small, round-oval bruises over bony prominences on the front of the body and is considered “accidental”. These are most commonly seen on the forehead, knees, and shins and usually result from minor impacts against objects or the ground as a result of the child’s own activities (ie. bumps and falls through play). Areas with greater subcutaneous tissue (eg. buttocks, thighs, soft part of the cheeks) are less likely to bruise because of the cushioning effect of the tissues. “Normal childhood bruising” usually does not have a defined shape or pattern (Maguire and Mann 2013; Maguire et al. 2005a; Pierce et al. 2010; Labbe and Caouette 2001; Dunstan et al. 2002; Lux 2000). Of course, children are sometimes involved in more significant trauma (eg. falls from a height, sports injuries, motor vehicle collisions) and the resultant bruising may show characteristics that are not in keeping with “normal childhood bruising”. These bruises usually do not pose a problem for health care providers in determining their cause as these events are often witnessed and/or verifiable.

As “normal childhood bruising” occurs in children who are mobile and who cause skin injury through their own actions, bruising in very young and/or non-mobile children should not be

considered “normal childhood bruising” (Maguire and Mann 2013; Maguire et al. 2005a; Pierce et al. 2010; Labbe and Caouette 2001; Dunstan et al. 2002; Lux 2000; Sugar et al. 1999; Carpenter 1999; Harris and Flaherty 2011; Kemp et al. 2015). Many studies have shown that the amount of bruising on children is directly correlated with the child’s level of mobility. While non-mobile infants or children can sustain bruises (eg. a baby who is dropped or rolls from a change table), any unexplained bruising in young infants should be viewed as concerning and warrants further assessment for both the possibility of inflicted injury as well as an underlying medical condition.

In some cases, a question regarding the mechanism of injury may arise when the size, pattern, location or other features of the bruising do not appear compatible with the explanation provided. Numerous studies have outlined the most common locations and characteristics for “normal childhood bruising” versus bruising seen in physical abuse. However, the clinician should be cautious in drawing firm conclusions based on this data alone. The following “red flags” are provided for health care providers to use in the context of unexplained bruising or bruising that does not appear to fit with the explanation provided. These “red flags” should prompt clinicians to conduct a thorough history and physical as outlined above for the possibility of physical abuse as well as for an underlying medical condition (Table 4.1).

The colour of bruises has been used to estimate their age and bruises of different ages are sometimes interpreted as a “red flag” for trauma occurring on multiple occasions. However, the dating of bruises is now known to be inaccurate and the colour of bruises should not be used as evidence (on its own) to confirm that injuries occurred at different times (Maguire et al. 2005b; Stephenson and Bialas 1996; Grossman et al. 2011; Schwartz and Ricci 1996; Langlois and Gresham 1991; Pilling et al. 2010; Bariciak et al. 2003).

The overall assessment and opinion on the possible cause(s) of bruising should be arrived at using an objective structured approach whereby

Table 4.1 Bruise characteristics that are “red flags” for possible physical abuse

| Characteristic | “Red flags” |
|----------------|---|
| Age/mobility | Unexplained bruises in infants and young children who are not yet mobile (ie. not crawling or cruising) |
| Location | Bruises on the ears, neck, hands, feet, buttocks or torso (torso includes chest, back, abdomen, genitalia). Bruises on other “fleshy” areas of the body |
| Size | Bruises that are unusually large |
| Shape | Bruises that have a recognizable shape (eg. outline of a shoe, hand, or belt) |
| Pattern | Bruises that occur in clusters or have a defined shape that is repeated on various body surfaces |
| Number | Bruises that are more numerous than typically seen (especially during winter months or when children have less active outdoor play) |
| Explanation | Significant bruises with no explanation or an explanation that does not appear compatible with the bruise characteristics |

the health care provider assesses the location(s), size(s), shape(s), pattern(s), and number of bruises relative to what is considered “normal” within the child’s developmental abilities and the context of the history provided. The presence of one or more of these red flags may be sufficient to report concerns to child protection authorities but should not be taken, on its own, as proof of physical abuse. The medical information, on its own usually can determine whether the bruises are likely related to trauma, but is limited in its ability to determine precisely how the skin was impacted or otherwise injured by another object, surface, or person (ie. whether the impact was a result of the child’s own actions or the actions of another person).

When concerns for physical abuse are raised because of bruising on a child, the physician’s role is to assess for possible causes including medical conditions. This requires taking a comprehensive history and doing a physical examination. As discussed above, it is generally not the role of the health care provider to take a forensic history. The clinician should limit their questions

to those that are required for health purposes. Laboratory testing may also be indicated to rule out an inherited or acquired coagulopathy, as well as other illnesses. Imaging may be indicated to look for features of an underlying condition or for occult injuries in very young children.

Differential Diagnosis

Traumatic mechanisms, medical conditions, and mimics of bruising (eg. phytophotodermatitis, dyes) should be considered as possible causes of bruising. While the clinician should carefully assess for medical causes, they should also recognize that in many situations (eg. infants with bruising) medical conditions resulting in bruising are rare. Bruising from inflicted injury is more common than many of the conditions listed. Types of medical conditions that should be considered include:

- Coagulation disorders (eg. idiopathic thrombocytopenic purpura (ITP), von Willebrand disease, hemophilia, platelet disorders)
- Connective tissue disorders (eg. Ehlers Danlos, Osteogenesis imperfecta), infections (eg. meningococemia)
- Malignancies (eg. leukemia, neuroblastoma)
- Nutritional deficiencies (eg. vitamin K or C deficiency)
- Autoimmune and inflammatory disorders (eg. Henoch-Schonlein purpura)
- Other severe systemic illnesses (eg. disseminated intravascular coagulation)

History

The history for a presenting concern of bruising should include specific questions to evaluate for the diagnoses above, as well as a thorough bleeding history. It should also include a comprehensive general history with attention to factors such as the use of vitamin K at birth, feeding history, recent symptoms, and family history suggesting a bleeding disorder. Key symptoms on history (HPI, PMHx and FHx) for coagulopathy are dependent on the child’s age and are listed below. These are drawn from the standardized Pediatric Bleeding Questionnaire, which can be used as a guide (Mittal et al. 2015).

| Infant | Index child or family members |
|---|--|
| Postcircumcision bleeding | Spontaneous, easy or excessive bruising |
| Birth cephalohematoma | Mucocutaneous bleeding (eg, gingival bleeding) |
| Umbilical stump bleeding or delayed stump separation | Epistaxis that is spontaneous, lasts >10 min or requires medical treatment |
| Postvenipuncture bleeding | Bleeding from minor wounds that lasts >15 min or recurs within 7 days |
| Macroscopic hematuria | Prolonged bleeding after surgical procedures |
| Petechiae at clothing line pressure sites | Bruises with palpable lumps beneath them |
| Bruising at sites of object pressure, such as infant car seat fasteners | Joint swelling with minor injury |
| | Blood in the stool or urine |
| | Menorrhagia |
| | Unexplained anemia |
| | History of blood transfusion |

Physical Examination

The physical examination should be thorough and complete with visualization of all skin surfaces. The health care provider should look for signs of other injuries including in the mouth (eg, torn frenulum) and by palpation and observation of the bony structures of the head, chest, back, and extremities. Special attention should be paid to signs of any of the medical conditions discussed above, which should include examination of the liver, spleen and lymph nodes, joints for effusions or hyperlaxity, and facial features for dysmorphism.

Documentation of Physical Findings

When possible, the skin findings should be described in the written record in words and using a visual representation. For accuracy, skin marks can be measured. Clinicians can use a body diagram to draw the size and shape of bruises, scars, and other skin marks, indicating measurements, shape, and colour. Where possible, clinicians should name the skin findings,

such as bruises, lacerations, abrasions, areas of hyper or hypopigmentation, birth marks etc. For example, the clinician can draw the skin finding and note “3.0 × 1.5 cm irregular oval blue-green non-blanchable bruise on the mid forehead”. Photos can be taken but this is best done by a trained forensic photographer, where possible. Written consent from the legal guardian or child themselves may be required, depending on regional laws and practices. Colour balance palettes and standardized rulers should be used. Photos must be stored in a secure fashion, linked to the child’s medical record.

Medical Testing

While not all cases of bruising require laboratory testing or imaging, various professional groups and authors have recommended testing when it is indicated for clinical or legal purposes (Ward et al. 2013; Anderst et al. 2013; Royal College of Paediatrics and Child Health 2006; Khair and Liesner 2006; Liesner et al. 2004; Minford and Richards 2010). Testing may be done to evaluate for specific conditions or to evaluate for other injuries.

Bloodwork that is recommended to screen for bleeding disorders includes:

- Complete blood count (including platelet count)
- Peripheral blood smear
- Prothrombin time (PT)/International normalized ratio (INR)
- Activated partial thromboplastin time (aPTT)
- Fibrinogen
- Von Willebrand studies (antigen and activity)
- Factor VIII level
- Factor IX level
- Blood group (for interpretation of von Willebrand levels)
- Liver function tests (for secondary platelet dysfunction)
- Renal function tests (for secondary platelet dysfunction)

The above listed tests, and others that are available, should be tailored to the clinical situation. Consultation with a child maltreatment pediatrician and/or hematologist may be helpful

in determining which tests to do. A hematologist may also be helpful in interpreting abnormal results and making recommendations on whether further assessment or testing is needed.

Testing for Occult Injuries

Testing may be indicated to evaluate for other possible injuries when bruising raises a concern for physical abuse. A recent prospective study demonstrated that 50% of infants who presented with apparently isolated bruising and were evaluated by a child abuse pediatrician had at least one additional serious injury (fracture, abdominal trauma, head trauma) (Harper et al. 2014). Clinicians should consider whether the following types of injuries may be present and evaluate appropriately (Christian et al. 2015):

- **Abdominal injury:** When bruising occurs over the abdomen or the child is non-verbal, screening tests for abdominal injury should be considered. These include ALT, AST, lipase and/or amylase and urinalysis for red blood cells. Additional testing includes CT of the abdomen with IV contrast (and oral contrast when indicated). Please see section below on abdominal trauma for further details.
- **Skeletal injury:** When there is concern for physical abuse and the child is less than 2 years old and/or not routinely seen in the community by people other than the primary caregiver, and/or is non-verbal, a skeletal survey is indicated to evaluate for occult bone injury. Please see section below on fractures for further details.
- **Head injury:** When there is concern for physical abuse and head trauma is a possibility, the clinician should consider completing head imaging. For children less than 6 months of age (ie. non-mobile infants with unexplained bruising), head imaging should be performed. For children aged 6–12 months of age, head imaging is recommended in most cases. For children 12–24 months of age, head imaging should be considered. At any age, significant bruising on the face or head or clinical concerns for head injury, such vomiting or lethargy, should prompt the clinician to complete head

imaging. In most cases, a CT scan is recommended, although MRI can also be used if the traumatic event is non-acute (ie. more than 3 days prior to time of imaging). Head ultrasound is an insufficient test for the evaluation of possible head trauma and should not be relied upon to rule-out traumatic findings (American Academy of Pediatrics Section on Radiology. 2009). If a significant head injury is demonstrated on imaging, an eye exam should be performed by a trained ophthalmologist to evaluate for retinal trauma. Please see section on head trauma for further details.

When in doubt, consulting with a child abuse/maltreatment pediatrician, or another medical expert can be helpful.

Providing an Opinion on the Cause of Bruises

When concerns for physical abuse arise as a result of bruising, the health care provider should report these concerns to the appropriate authorities, per their regional laws, and explain the significance of the findings. The clinician should also outline the limitations of the medical information to confirm or disprove the possibility of abuse. Clinicians can help child protection authorities to understand that bruises usually represent trauma to the skin and can be caused in a variety of ways. They should indicate whether a medical condition is likely to explain the findings. Clinicians can articulate their level of concern for inflicted injury or physical abuse based on the characteristics of the bruising as described above. If asked to provide an opinion on the mechanism of injury for the bruising, the clinician should be cautious about offering a specific mechanism unless they have the appropriate training and expertise to do so.

Fractures

Fractures are a relatively frequent finding in young children evaluated for physical abuse and are also a frequent finding in urgent care health centers and emergency departments. Determining

which of the many fractures assessed should raise concern for physical abuse can be a challenge. Furthermore, many fractures diagnosed in the context of maltreatment are not the presenting complaint, may not be clinically obvious, and are often only identified because of standard screening x-rays (usually a skeletal survey). When multiple fractures are seen, the clinician will need to evaluate for both traumatic causes and an underlying bone condition predisposing to fracture.

Certain types and characteristics of fractures are seen more commonly with either physical abuse or medical conditions. No one type, location, or characteristic of fracture is pathognomonic for physical abuse. However, certain features are more likely to be seen with physical abuse than with accidental trauma or medical conditions (Kemp et al. 2008; Pierce et al. 2012; Leventhal et al. 2008; Maguire et al. 2013a). These features, or “red flags” are indicators to consider carefully whether physical abuse is a possible cause, while also considering other causes, both traumatic and medical. While these features are not pathognomonic for physical abuse, they may be sufficient to report concerns to child protection authorities.

In the absence of a clear trauma history to account for the injuries, “red flags” for possible physical abuse when evaluating fractures include the following:

- Any fracture in an infant or young child who is not yet walking
- Rib and long bone metaphyseal fractures, especially in infants and toddlers
- Fractures of the scapula, sternum, vertebral spinous processes or vertebral bodies, especially in infants and toddlers
- Femur or humerus fracture in a child <18 months old
- Multiple fractures without an apparent underlying medical cause
- Fractures that are clearly of different ages (eg. acute symptomatic femur fracture and healing rib fractures)
- Fractures that occur by an unusual mechanism, a mechanism that does not make biomechanical sense, or a mechanism that does not fit with the child’s developmental level
- Metabolic bone disorders related to osteomalacia (softened bones) (eg. vitamin-D deficiency rickets or hypophosphatemic rickets)
- Genetic/inherited bone fragility disorders (eg. osteogenesis imperfecta, osteopetrosis, hypophosphatasia, or Menkes syndrome)
- Structural bone abnormalities (eg. certain skeletal dysplasias)
- Focal bone abnormalities related to disease (eg. bone infection or malignancy)
- Systemic medical conditions that secondarily affect bone (eg. significant prematurity, nutritional deficiencies such as copper deficiency or vitamin C deficiency, malabsorption, leukemia, cholestatic liver disease, metabolic or kidney diseases that cause calcium wasting)
- Conditions resulting in low bone mass from decreased use, movement and/or weight

Differential Diagnosis

Fractures are generally caused by a traumatic event that involves forces being applied to the area of the body in question. Fractures result from a variety of types of forces exerted on the bone including impact (eg. against an object or surface), torsion or twisting, bending, compression, tensile or pulling, or a combination of these. As described elsewhere in this chapter, these forces can be applied to the child’s body in a variety of ways including through the birth process, medical interventions, or by inflicted, self-inflicted, or accidental means.

Certain normal anatomic variants can sometimes be mistaken for a fracture in a child. These include metaphyseal spurs and collars, physiologic periosteal reaction in infants, normal or accessory cranial suture lines, and accessory centres of ossification. It is therefore important that the diagnosis of fracture be confirmed by a radiologist with knowledge of normal pediatric variants.

Certain illnesses or conditions can predispose to developing a fracture with a lesser degree of trauma and, in some cases, with no significant trauma. Medical conditions that may contribute to a predisposition to fractures include bone, connective tissue, and systemic diseases such as those listed below:

bearing (eg. neuromuscular disorders, spina bifida, cerebral palsy, or prolonged immobilization)

- Certain toxins and medications (eg. glucocorticoids, some diuretics, methotrexate, lead)

History

The history for a presenting concern or finding of a fracture should include a detailed HPI to understand the events surrounding the time of injury, the types of forces that were likely exerted on the bone during the injury event, and the symptoms and signs since that time. For example, if the history is of the child falling down stairs, the clinician should take enough information to be able to form a picture of the event in their mind. This would include details about the stairs (how many, how high, carpeted or hardwood etc.), the event (how the child fell, the direction of the fall, the movements during the fall, whether there was impact with various parts of the stairs, and the position of landing), and the child (their reaction immediately and afterwards). Specific information about the related symptoms (eg. swelling, redness, bruising, pain, reduced movement) and their management by the family or other health care providers, should be sought. This information is needed for the clinician to decide whether the injuries are likely to be compatible with the described event. The clinician should also ask about other past injuries including fractures, unexplained bruises, burns or head injuries.

Although children commonly have falls, low level falls (eg. falls from beds and couches) rarely cause a fracture. When a fracture does occur, it is most likely to be a clavicular fracture or simple linear parietal skull fracture). Clinicians should be aware that spiral fractures of the tibia in newly ambulatory children (ie. “toddler’s fracture”) are not uncommon.

The PMHx should include pertinent pregnancy and birth history and whether the child has had any other fractures, in addition to a general review of the child’s prior health.

The ROS should include a feeding and nutritional history, history of exposure to sunlight, and symptoms that relate to the differential diagnoses. Specific questions regarding connective

tissue and bone disorders should be asked. The clinicians should also obtain information about medications, vitamins, or other supplements that the child may be taking.

The FHx is particularly helpful in evaluating for inherited disorders that may predispose to fractures. A detailed history of fractures, hearing loss, dental problems, spontaneous fetal losses, short stature, gastrointestinal, liver, renal, bone, connective tissue and other childhood diseases should be sought for at least the child’s parents, siblings, grandparents, and 1st degree cousins.

Physical Examination

A general pediatric physical examination with vital signs, growth parameters, and visualization of the full skin surface is recommended. The limb or area of the body with a fracture should be carefully examined by observation and palpation, noting the neuro-vascular status. Accompanying swelling, bruising, deformity, or other signs of injury should be documented.

The clinician should note physical features that may suggest a genetic disorder (eg. short stature, blue-grey sclerae, triangular shaped face, dental anomalies). Special attention should be paid to the general examination of the joints (eg. for swelling or hyperlaxity), skin (eg. for bruises, stretchy and fragile skin), and extremities, as well as the neuromuscular exam. When appropriate, signs of Rickets should be checked for, including craniotables, a rachitic rosary on palpation, bowing of the legs in an ambulatory child, and widening of the ends of the long bones (eg. at the wrists).

Medical Testing

In most cases, children presenting with a traumatic fracture will not require bloodwork or imaging beyond what is required to make the fracture diagnosis. However, when the cause of the fracture is unclear or unusual, or there is a specific concern that the injury may have resulted from physical abuse, it is beneficial to do further testing.

Laboratory testing that is recommended to screen for an underlying medical predisposition to fractures includes (Flaherty et al. 2014):

- Complete blood cell count
- Serum calcium, phosphate, magnesium, alkaline phosphatase, 25-hydroxy-vitamin D, parathyroid hormone
- Alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, albumin
- Blood urea nitrogen (BUN) and creatinine

Other tests that can be helpful include serum copper and ceruloplasmin, Vitamin C level, urinalysis, urine Calcium – Creatinine ratio, and genetic testing for osteogenesis imperfecta and specific connective tissue disorders (eg. Ehlers Danlos Syndrome) (Flaherty et al. 2014).

The laboratory tests chosen for an individual patient should be tailored to their specific clinical situation. Consultation with a child maltreatment pediatrician, a general pediatrician, an endocrinologist, geneticist, or orthopedist may be helpful.

Additional imaging may be indicated to evaluate for medical causes and/or occult fractures. The most common additional imaging study is a skeletal survey. The American College of Radiology and the Society for Pediatric Radiology have set out the standards in regards to technical aspects of completing a skeletal survey and recommend the following as indications for a skeletal survey (American College of Radiology and Society for Pediatric Radiology 2014):

- “Known or suspected physical abuse in infants and young children.
- Known or suspected skeletal dysplasias, syndromes, and metabolic disorders.
- Known or suspected neoplasia and related disorders.”

The American Academy of Pediatrics’ Committee on Child Abuse and Neglect recommends that a skeletal survey be completed for (Christian et al. 2015):

- “All children <2 years with obvious abusive injuries
- All children <2 years with any suspicious injury
- Infants with unexplained, unexpected sudden death

- Infants and young toddlers with unexplained intracranial injuries
- Infants and siblings <2 years and household contacts of an abused child
- Twins of abused infants and toddlers”

Because not all pediatric fractures may be visible acutely on X-ray, it is recommended that the skeletal survey be repeated approximately 2 weeks later (Christian et al. 2015). Rib and metaphyseal fractures are particularly difficult to diagnose acutely and repeating a skeletal survey has been shown to increase the identification of fractures by up to 25% (Kleinman et al. 1996). Even when the initial imaging is normal, the follow-up imaging may yield forensically important results (Bennett et al. 2011).

Testing may also be indicated to evaluate for other possible injuries when a fracture raises a concern for physical abuse. Clinicians should consider that abdominal and head injuries may also be present and occult. Please refer to the “testing for occult injuries” section within the bruising section above and the appropriate sections below for an approach to the evaluation for occult injuries. Head imaging should be considered for young infants in whom there is concern for physical abuse.

Providing an Opinion on the Cause of a Fracture

When a fracture raises concerns for physical abuse, this should be reported to the appropriate authorities, per jurisdictional laws. The clinician should clearly express the reasons for their concern based on the fracture characteristics, history, associated physical findings, and/or other factors. They should also articulate the limitations of the medical information to determine the precise cause and circumstances of the fracture. The clinician should discuss the differential diagnosis as including both traumatic and medical causes, when appropriate, and the information or testing that is relevant to this question. The health care provider can play an important role in identifying a concern for maltreatment and in assessing and managing the medical aspects of the situation.

Head and Spine Injuries

Head injuries from physical abuse represent a small proportion of child maltreatment cases but carry the highest morbidity and mortality. Crying (ie. parents' or caregivers' response to crying) is a known risk factor for inflicted head injuries in young children (Barr 2012, 2014; Barr et al. 2006). Infants, males, and children who are born prematurely or as multiple births are described to be at higher risk for this form of maltreatment (Xiang et al. 2013; Parks et al. 2012; Sieswerda-Hoogendoorn et al. 2013; Keenan et al. 2003; Lopes et al. 2013; Niederkröthaler et al. 2013). Up to 1/3 of identified victims die from their injuries, and up to 2/3 of survivors have significant neurological sequelae (King et al. 2003; Barlow et al. 2004, 2005; Lind et al. 2016; Acker et al. 2015). While subdural and retinal hemorrhages have historically been closely tied to traumatic head injuries due to physical abuse, it is important to recognize that each of these findings has a differential diagnosis that includes both traumatic and medical causes. These findings often are the first indication of an underlying head injury, however, the hemorrhages on their own are rarely the cause of significant symptoms. In the way that a fever is an indicator of underlying illness (due to infection, malignancy etc.) and usually does not cause harm itself, these findings are usually indicators of a prior trauma. The associated morbidity and mortality usually relates to the parenchymal injury (eg. edema, hypoxia and/or ischemia) to the brain and/or brain stem which may have occurred at the time of the initial injury (primary injury) or may be caused by the body's response to the injury (secondary injury).

In the past, head injuries from physical abuse were typically referred to as Shaken Baby Syndrome. This term has fallen out of favour for a variety of important reasons. Health professional organizations such as the World Health Organization, the Center for Disease Control, the American Academy of Pediatrics, the Canadian Paediatric Society, and the Royal College of Paediatrics and Child Health, and others agree that shaking an infant forcefully can cause significant head injuries with long-term conse-

quences. However, it is also widely recognized that other mechanisms of injury (eg. impact on its own or in combination with shaking) may cause similar injuries. Many have advocated for a term that is more accurate (eg. "baby" is not the only age group affected by such injuries) and does not predetermine the cause or mechanism of injury. In 2009, the American Academy of Pediatrics recommended the term Abusive Head Trauma and this has been widely adopted (Christian et al. 2009). However, this term has also been criticized for implying intent, something that is not typically determined by the medical assessment. An alternative for clinicians is to describe the injuries in a specific case using objective terms such as "traumatic head injury", followed by a descriptor or opinion, such as "most likely due to physical abuse/maltreatment/inflicted injury". In this way, the medical findings and the clinician's opinion can be viewed separately. The choice of terminology will vary and may be informed by the local context and case specific details.

Head injuries due to physical abuse are often difficult to recognize. This is especially true because they usually present in non-verbal children and with non-specific symptoms. For example, infants may present with poor feeding, respiratory difficulties, vomiting, lethargy or irritability. More overt signs of head injury include seizures, apnea and decreased level of consciousness. As a result, clinicians need to remain alert to this possibility and should consider head trauma with the signs and symptoms listed above, even when the child appears well. The most common misdiagnosis is gastroenteritis and most infants present on more than one occasion before a health care professional recognizes the true cause of the symptoms (Jenny et al. 1999). A normal neurological examination does not exclude the possibility of head injury, especially in very young children (King et al. 2003; Rubin et al. 2003).

As with other types of injuries discussed above, no single head injury finding is pathognomonic for physical abuse either on its own or in combination with others. This relates to the fact that injuries are a result of specific forces exerted on the tissues and that these forces can be

generated in a variety of ways. However, the scientific literature has linked certain physical findings more strongly with head injury due to maltreatment than with other traumatic causes (Maguire et al. 2009; Kemp et al. 2011; Piteau et al. 2012). These findings, on their own, may be sufficient to raise concerns for physical abuse and report these concerns to the appropriate authorities.

These “red flags” include:

- Intracranial subdural hemorrhages (especially, those that occur without a specific injury history)
- Skull fracture accompanied by an intracranial injury
- Head injury and rib fractures
- Head injury and classic metaphyseal lesions
- Head injury and cerebral ischemia
- Retinal hemorrhages that are numerous, multi-layered and which extend to the periphery of the retina(s)
- Retinoschisis (splitting of the layers of the retina, forming a pocket that fills with blood)
- Spinal subdural hemorrhages

Other injuries that can be seen with head injuries from physical abuse include scalp hematomas, skull fractures with no intracranial injury, facial bone fractures, head and/or facial bruising, orbital injury, neck injuries, spinal fractures, subconjunctival hemorrhages, vitreous hemorrhages, cerebral contusions, as well as subgaleal, epidural, subarachnoid, and intraparenchymal hemorrhages. Associated injuries also include bruising on other parts of the body, rib fractures and fractures of the long bones, including metaphyseal fractures (Maguire et al. 2009; Kemp et al. 2011; Piteau et al. 2012).

Differential Diagnosis

The most common finding to prompt concerns for traumatic head injury due to child maltreatment is subdural hemorrhage. This has a differential diagnosis that includes medical and traumatic causes. Medical conditions that may cause or contribute to subdural hemorrhages include:

- Bleeding disorders (eg. thrombocytopenia and platelet function disorders, disseminated intravascular coagulopathy, hemorrhagic disease of the newborn, acquired vitamin K deficiency, hemophilia, von Willebrand disease, congenital afibrinogenemia, and factor XIII deficiency)
- Infections (eg. meningitis and viral encephalitis, especially HSV)
- Metabolic disorders (eg. glutaric aciduria type 1, other inborn errors of metabolism resulting in cerebral atrophy)
- Vasculopathies and cerebral vessel abnormalities (eg. malformations, aneurysms)
- Malignancies (eg. various CNS tumours)
- Certain genetic conditions (eg. Menkes syndrome, Alagille syndrome)

Subdural hemorrhages may also result from re-bleeding of a prior bleed and may be seen more commonly with increased extra-axial fluid spaces (eg. benign external hydrocephalus in infants). In most cases, trauma is required to cause subdural hemorrhages even with the presence of a medical condition. However, hemorrhage may occur with a lesser degree of trauma and/or the hemorrhage may be more extensive when a predisposing medical condition is present.

A variety of traumatic causes should also be considered in the differential diagnosis for subdural hemorrhage. Subdural hemorrhage can be caused by birth trauma. This is more common in vacuum and forceps assisted vaginal deliveries but can also be seen in Cesarean-section deliveries following labour and in normal vaginal deliveries (Rooks et al. 2008).

Subdural hemorrhages can also be seen from focal impact, such as may occur with a fall. Even low level falls have been shown to cause subdural hemorrhages. These tend to be small, focal hemorrhages, often underlying a scalp hematoma and skull fracture, with a low likelihood of significant symptoms or sequelae (Ibrahim et al. 2012; Vinchon et al. 2004, 2005; Tung et al. 2006; Ewing-Cobbs et al. 1998). Signs of impact may or may not be easily visible on the scalp and therefore the absence of scalp swelling or bruising does not definitively exclude the possibility of impact as the mechanism of injury (Ibrahim et al. 2012).

Inertial trauma, caused by acceleration-deceleration or sudden deceleration of the head, as may occur with shaking, whiplash or the head stopping abruptly against a surface (eg. bed) is another mechanism that may cause head injury, including subdural hemorrhages and retinal hemorrhages. In these circumstances, signs of impact may not be seen and the subdural hemorrhage is often diffuse.

Crushing head trauma can also cause subdural hemorrhages and retinal findings. These are typically associated with complex skull fractures. Significant head and facial swelling, as well as cranial nerve injuries, may be seen. Cases of crushing head injury with subdural and retinal hemorrhages have been reported including cases involving a television falling on a young child (Ewing-Cobbs et al. 2000).

Retinal hemorrhages are another finding that has been linked with traumatic head injury due to physical abuse (Maguire et al. 2009; Piteau et al. 2012). Retinal hemorrhages also have a differential diagnosis. The retinal exam should be done by indirect ophthalmoscopy by an experienced ophthalmologist and the number, locations, and description of the hemorrhages should be provided. These factors affect the differential diagnosis by pointing towards or away from various possibilities.

Retinal hemorrhages can be caused or contributed to by the following:

- Ophthalmologic conditions (that usually have other associated retinopathy findings)
- Bleeding disorders
- Metabolic disorders (eg. glutaric aciduria type 1)
- Infections (eg. malaria)
- Vasculopathies and vessel abnormalities
- Malignancies (eg. leukemia)
- Certain genetic conditions (eg. osteogenesis imperfecta)
- Hematologic conditions (eg. severe anemia, sickle cell disease, hyperviscosity syndromes)

Retinal hemorrhages may also be caused by hypertension, extra-corporeal membrane oxygenation (ECMO), and rarely, seizures, cough-

ing, and vomiting (Kodikara and Pollanen 2012). Cardio-pulmonary resuscitation has rarely been associated with retinal hemorrhages, and in many of the cases, the child also had an underlying bleeding disorder. Increased intracranial pressure has also been described to cause a few intraretinal or preretinal hemorrhages in the posterior pole, especially around the optic nerve (Levin 2010). In most cases, retinal hemorrhages from these causes result in a pattern of a few hemorrhages, in specific locations, and/or with other associated retinal findings.

A variety of traumatic mechanisms can also lead to retinal hemorrhages. Trauma resulting from the birth process in vaginal deliveries, with or without instrumentation, as well as Cesarean-section deliveries, is a relatively common cause of retinal hemorrhages (Binenbaum et al. 2013a). These hemorrhages typically resolve by 4 weeks of age although they may persist for longer. These typically are benign and resolve without complication (Binenbaum et al. 2013a).

Direct eye trauma may cause retinal hemorrhages. Traumatic head injury (without direct trauma to the eye) from impact or inertial forces is also associated with retinal hemorrhages, whether “accidental” or “inflicted”. The severity of the eye injuries is typically associated with the severity of the head injury (Hughes et al. 2006). Multi-layered, “too-numerous-to-count” retinal hemorrhages that extend to the periphery of the retina have been described in inflicted head trauma, severe (usually fatal) crush head injury, and severe (usually fatal) accidental head trauma.

History

On clinical assessment, a detailed history should be taken. The prenatal and birth history should include information about any illnesses or complications during pregnancy, pre-natal tests, the labour and delivery, any neonatal resuscitation or complications. The growth parameters (head circumference, weight, height) from birth until the current time should be recorded. A developmental history is important to determine the child’s current level and pattern of development and mobility as well as signs of possible underlying neurologic issues in the past. The review of

systems can often be completed by walking through a typical 24 hour period beginning from the time the child awakens in the morning. In this way, the health care professional will obtain specific information about the child's feeding, sleeping, stooling, voiding, and behavioural patterns, as well as the typical activities and patterns of the caregivers. Specific questions about the child's crying pattern and how the caregiver consoles the baby should be included.

A history of recent and remote symptoms should be taken that includes questions about irritability, difficulties with feeding, vomiting, apneas or breathing abnormalities, seizures or abnormal movements, periods of lethargy or unarousability, and a change in the child's usual feeding, sleeping, and behavioural patterns. If the child is presenting with an acute injury or symptoms, the caregiver should be asked about the onset and progression of changes over time.

Often, children with traumatic head injuries present with a history of a fall. Details around the circumstances of the fall are important to obtain in order to plan appropriate medical testing and care, as well as to decide on whether a report is warranted to child protection authorities. This history should include when, where, and how the fall occurred, as well as who was present at the time. A detailed description of the fall, its height, the landing surface, the child's position and what happened before and after the fall should be obtained. If the child received care or resuscitation by the family, paramedics, or others prior to presentation, this should be recorded.

The past medical history should include details of the pregnancy and birth, as well as any illnesses or injuries since that time (especially bruising or oral injuries), and symptoms or signs of medical illnesses that are on the differential diagnosis for head injuries.

The family history is important for evaluating the possibility of an underlying predisposition to bleeding or head injury, as well as a predisposition to any associated injuries (eg. fractures) that may be present. The family history should include questions about bleeding disorders, fractures and

bone disorders, metabolic, genetic, or other childhood conditions, childhood deaths, recurrent spontaneous losses, and consanguinity.

Physical Examination

A full physical examination, with careful attention to the neurologic exam, should be completed. Subtle bulging of the fontanelle and/or an increase in head circumference may be the first sign on assessment of an underlying head injury. The full skin surface and the oropharynx should be examined for signs of injury (eg. bruises, torn frenulae). Vital signs and growth parameters should be documented. Physical features of an underlying genetic or other medical condition, relevant to the differential diagnosis, should be looked for.

Medical Testing

A CT scan (without contrast) is the test of choice when evaluating for a possible acute head injury (Binenbaum et al. 2013b; Section on Radiology; American Academy of Pediatrics 2009). If the injury event occurred at least 3–5 days earlier, an MRI can be done and provides more detailed information. MR angiogram and venogram (MRA and MRV) are helpful to assess for the possibility of thromboses, arterio-venous malformations, and other vessel abnormalities. MR spectrometry (MRS) is useful to obtain additional information regarding ischemia, infarction or chronic tissue injury. However, depending on the age of the child, an MRI may require sedation or a general anesthetic. Head ultrasound, which can be done on children with an open fontanelle, though less expensive and radiation-free, is not adequate imaging when head trauma is suspected (Binenbaum et al. 2013b; Section on Radiology; American Academy of Pediatrics 2009).

It should be noted that subdural, subarachnoid, and other intracranial collections cannot be dated with precision based on their radiographic appearance. Although most acute hemorrhages will appear bright (hyperdense) on CT scan and most non-acute hemorrhages will appear dark (hypodense), the overlap in first appearance and time of resolution is so great, that this feature

alone cannot determine the age of the collection (Tung et al. 2006; Silvera et al. 2015). Further, the presence of different densities does not confirm that there are hemorrhages of different ages (Tung et al. 2006; Silvera et al. 2015; Bradford et al. 2013).

More recently, it has been recognized that spinal imaging is also important in cases of head injury due to physical abuse (Dias et al. 1998). Subdural hemorrhages of the spine can be seen and may have clinical significance. Soft tissue injuries of the cervical spine can also be seen in some cases. While routine spinal imaging hasn't yet become the standard of care, when possible, it is recommended that the spine be imaged as well as the head. The health care provider should consider doing spinal imaging when there are clinical indicators of spinal injury and/or with symptomatic head injury. CT of the neck can be done for ligamentous and soft tissue injuries, as well as bony injuries. MRI of the full spine can be done when MRI of the head is also being performed. Imaging of the full spine should be considered when there is symptomatic head injury, rib or vertebral fractures.

In situations of suspected head injury due to physical abuse, it is important to consider whether other injuries may also be present. The following are recommended to evaluate for other injuries (Christian et al. 2009, 2015):

- Skeletal survey to be done routinely for children less than 2 years of age
- Skeletal survey in select cases for children 2–5 years of age
- Ophthalmology assessment using indirect ophthalmoscopy with dilated pupils
- Spine imaging (CT of cervical spine when CT used, MRI of full spine when MRI used)
- Abdominal imaging (as indicated above) if liver or pancreatic function tests or urinalysis indicate possible trauma to the abdomen

Depending on the types of injuries present, the following laboratory tests are recommended for evaluation of a possible underlying medical cause or contributor (Christian et al. 2009, 2015):

- Complete blood count including platelet count
- INR (international normalized ratio), aPTT (activated partial thromboplastin time), fibrinogen
- Factor VIII, von Willebrand testing (antigen and activity), blood group
- Factors IX, XI, XIII
- Bun and creatinine
- ALT, AST, GGT, lipase or amylase
- Blood culture, cerebrospinal fluid sample for bacterial culture and viral testing if the child is febrile or there is clinical suspicion of meningitis
- Review of newborn metabolic screen
- Total and free carnitine, acylcarnitines, amino acids, gas, lactate, ammonia, organic acid testing on urine if metabolic testing is clinically indicated

Providing an Opinion on the Cause of Head Injuries

When findings of a head injury raise concerns for physical abuse, the clinician should report their concerns to the appropriate authorities, per jurisdictional laws. The clinician should clearly express the reasons for their concern based on the history, physical, laboratory and imaging findings. They should also articulate the limitations of the medical information to determine the precise cause and circumstances of the head injury and explain what testing or results remain outstanding. The clinician should discuss the differential diagnosis as including both traumatic and medical causes, where appropriate. In general, it takes time to obtain the medical information regarding the possible causes of the findings and therefore the information and opinion on the possible causes will evolve. Consulting with a child maltreatment pediatrician or another qualified specialist in the region, is recommended.

Abdominal Trauma

Abdominal trauma is estimated to occur in up to 3% of cases of child physical abuse (Kleinman and Silvera 2015) and is the second leading cause

of death from abuse (Lindberg et al. 2013). Unlike other findings that raise concern for physical abuse, distinguishing abdominal injuries from medical conditions is rarely a difficulty. As with other types of injuries, there is no abdominal injury that, on its own, is pathognomonic for physical abuse and any abdominal injury that can occur through an accidental mechanism can occur in physical abuse (Barnes et al. 2005). Presenting symptoms are similar in children with accidental and inflicted abdominal injury and in both settings, there may be a “delay in seeking care” as symptoms can develop slowly (Lindberg 2012). However, hollow viscous injuries are more commonly seen with inflicted abdominal injury mechanisms and combined solid organ and hollow viscous injuries are rarely seen with accidental mechanisms (Trokel et al. 2006). While motor vehicle collisions are the most common cause of abdominal injuries in children, direct blows to the abdomen (as may occur with a bike handlebar injury) can cause severe abdominal injury (Barnes et al. 2005). Falls are an uncommon cause for significant abdominal injury (Wood et al. 2005; Lyons and Oates 1993; Rivara et al. 1993) and duodenal injuries in young children are rarely seen from accidental causes (Wang et al. 2001).

The “red flags” for possible physical abuse in abdominal injury are:

- Severity of injury greater than what would be expected for the described injury event
- Significant injury with no history of abdominal trauma
- Hollow viscous injury with a history of a minor trauma
- Duodenal injury in an infant, toddler or pre-school aged child
- Presence of other injuries (fractures, bruising, head injury etc.) that are unexplained, unusual or otherwise concerning for physical abuse

History

As with other types of injuries discussed in this chapter, a detailed history of the injury event is recommended. If the injury event included a fall, then the height and direction of the fall, landing

position and surface are important elements of the history. When there is no described injury event, a history for any traumatic events and possible foreign bodies (causing perforation) should be obtained.

It is important to explore possible injury events that may have occurred even several days prior to the onset of symptoms. For abdominal injury, the development and progression of symptoms is particularly helpful and should include questions about abdominal pain, change in feeding/eating habits, irritability or lethargy, vomiting, fever, hematemesis, hematochezia and any preceding illness.

A past medical history of gastrointestinal symptoms and prior surgeries is helpful. A developmental history, to understand the child’s level of mobility can be used to compare to the history provided. Other historical information related to pregnancy, birth, feeding, gastrointestinal symptoms, and illnesses is also important.

Physical Examination

A full pediatric exam is indicated, beginning with vital signs, growth parameters, and general appearance. Special attention should be paid to the skin surface (eg. for bruises or other signs of trauma), the mouth, and the musculoskeletal system. The abdomen should be observed for bruising or distension, bowel sounds should be auscultated, and palpation should be done for tenderness or masses. The clinician should make note of any peritoneal signs.

Medical Testing

Screening bloodwork should be done in the following circumstances, when physical abuse is considered possible (Christian et al. 2015; Barnes et al. 2005):

- A history of abdominal injury is provided
- Bruising is present on or near the abdomen
- Evaluation for possible physical abuse in a young child is being done because of other physical findings (eg. bruises, fractures, head injury)
- The child has symptoms of an abdominal injury as above

Recommended screening tests include (Christian et al. 2015; Barnes et al. 2005):

Complete blood count
AST, ALT
Lipase and/or amylase
Urinalysis (for blood)

The results of the liver enzymes should be interpreted with caution, recognizing that transaminases can be elevated with liver injury but also with damage to muscles or cardiac tissue, and in the setting of shock, hepatitis and other liver diseases. Some authors have suggested using an AST or ALT level of >80 IU/L as a threshold for performing abdominal imaging (Kleinman and Silvera 2015).

A CT scan of the abdomen is the test of choice for abdominal imaging for traumatic injuries. This should be done with intravenous contrast and consideration should also be given to using oral contrast (Christian et al. 2015; Barnes et al. 2005). Ultrasound, while useful in some cases as an adjunctive imaging modality, does not have the sensitivity required to reliably diagnose abdominal injuries and a false negative examination may result (Maguire et al. 2013b).

If a significant abdominal injury is suspected to be due to an inflicted mechanism in a young child, further evaluation for occult injuries is recommended. As recommended in other sections, with suspected physical abuse in a child less than 2 years of age, a skeletal survey should be performed. Head imaging should also be considered for younger infants.

Burns

Burns are a common reason for children to present to physician offices and emergency departments. Young children are particularly susceptible to burns because of their curious nature and propensity to explore their environment without judgement or awareness of safety concerns. In addition, younger children have thinner skin that burns more easily than the skin of older children and adults (Fox et al. 2011). As a result, they can

burn with a shorter exposure time to a hot liquid, flame, or object and can also burn at a lower temperature than can adults. All types of burns, including scalds, flame, radiation, caustic, and contact burns, can result from accidental and inflicted means. Potential lack of appropriate supervision may also be an important element in pediatric burns. It is estimated that severe burns may be present in 10–12% of all cases of child physical abuse and 10–20% of all burns are related to physical abuse or neglect (D’Souza et al. 2009; Chestser et al. 2006; Dissanaikie et al. 2010). Burns due to neglect are felt to be nine times more common than those resulting from physical abuse (Maguire et al. 2008).

Scalds are the most common type of burns in children, especially in children less than 5 years of age. In general, most accidental scald (spill) burns involve burns to the head, face, neck and/or chest from hot liquids other than water (often coffee or tea) while most inflicted scald burns involve burns to the lower extremities from hot water. Scald burns typically include areas of varying depth of burn (superficial, partial thickness, and full thickness) and the burn may indicate a flow pattern with decreasing depth of burn further from the site of first contact. Splash marks may or may not be present. Clothing or other objects in contact with the skin at the time of injury may affect the pattern and depth of the burn (Dissanaikie et al. 2010). More viscous liquids (eg. oil) may show a different burn pattern as they dissipate their heat more slowly and flow at a slower rate.

A systematic review of features differentiating “intentional” (term used in publication) scalds from accidental scald injuries highlighted the following “red flags” for physical abuse (Dissanaikie et al. 2010):

- Pattern suggesting immersion (instead of spill) with relatively uniform depth of burn and clear margins
- Burns involving the legs, buttocks and perineum or a combinations of these, especially when symmetrical and having clear margins
- “Stocking” or “glove” distribution

- Explanation for injury not in keeping with injury pattern (eg. history of flow/spill burn but pattern of immersion burn)
- Co-existent injuries such as bruises, lacerations, swellings, or fractures
- No history or incompatible history to explain burn

Burns that result from mechanisms other than scalds are typically less severe and are commonly caused by contact with household objects but may also be caused by flames, friction, chemicals, or electrical contact. “Red flags” for non-scald burns include (Maguire et al. 2004):

- Contact burns with a clear pattern (eg. cigarette, iron, hairdryer) or sharply demarcated edge
- Burns on the limbs, back or trunk and not on the palm or fingers
- Multiple non-scald burns
- Co-existent injuries such as bruises, lacerations, swellings, or fractures
- No history or incompatible history to explain burn

Differential Diagnosis

Burns can result from a variety of mechanisms that may be either accidental or inflicted. The following should be considered in the differential diagnosis:

- Certain skin conditions (eg. guttate psoriasis, pityriasis lichenoides, epidermolysis bullosa, chilblain)
- Infections (eg. impetigo, staphylococcal scalded skin syndrome, dermatitis herpetiformis)
- Allergies
- Drug eruptions
- Contact reactions (eg. phytophotodermatitis)

In some cases, traditional cultural or alternative health practices may also cause burns (eg. moxibustion, cupping, maquas, garlic burns).

History

A detailed HPI should include the mechanism, duration, timing, and events surrounding the burn

event, as well as the related symptoms and treatment applied. Details, such as the child’s position and clothing worn at the time of the burn, can be helpful. If the burn involved hot water, further information should be sought about the source of the hot water including water tank temperature settings, and unexpected changes in water temperature.

The past medical history should include information about any prior skin injuries or conditions, as well as recent illnesses or infectious symptoms. Similar questions should be asked in the family history. A developmental history, with attention to mobility and gross motor development should be taken.

Physical Examination

A full physical examination should be conducted with documentation of the skin findings. Special attention should be paid to the child’s vital signs and volume status, and appropriate treatment measures should be taken as necessary. Consultation and referral to a burn care center may be required. The clinician should note the distribution of the burn areas (as well as areas spared) and whether they are contiguous or separate (eg. splash marks), the degree or depth of burn, the percentage body surface area covered by the burn, and whether the burn(s) have a recognizable shape or pattern. The condition of the child’s clothing should also be noted indicating whether it is burned, wet, or otherwise altered. The remainder of the exam should be done in accordance with usual practices for burn victims, also noting any other signs of trauma, such as bruises, lacerations or limb deformities.

Documentation

When possible, the burn should be described in the written record in words and using visual representation. Clinicians can use a body diagram to draw the approximate size and shape of the burn, indicating measurements and burn severity. With appropriate consent, photos can be taken but this is best done by a trained forensic photographer. Colour balance palettes and standardized rulers should be used. Photos must be stored in a secure fashion, linked to the child’s medical record.

Spared areas are as important as burned areas when considering overall “pattern”.

Medical Testing

Medical testing should be guided by the clinical scenario. In regards to evaluation for occult injuries, burns should be considered similar to bruises or fractures such that concerns for physical abuse should prompt the clinician to order a skeletal survey in children less than 2 years of age and consider head imaging in young infants.

Sexual Abuse and Assault

According to the World Health Organization, one in five women and one in thirteen men report having been sexually abused as a child. Children and adolescents who have been sexually abused/assaulted will often arrive at a physician’s office, emergency department or urgent care center for medical evaluation. These children are assessed in settings by medical providers with varying levels of training and experience. Given the medico-legal nature of the evaluation of children and adolescents with suspected and/or confirmed sexual abuse/assault, a consistent, evidence based approach to the assessment and management of these children is critical. The goals of the medical evaluation are to obtain a history, identify and document findings, provide interpretation of the findings, collect forensic evidence as appropriate, diagnose and treat medical conditions as a result of the abuse/assault, assess psychosocial issues, reassure and support the family, and ultimately ensure the well-being of the child (Adams et al. 2007). It is important to remember that many children do not disclose sexual abuse until months or years after the abuse has occurred (Goodman-Brown et al. 2003). In one study, 75% of children did not disclose sexual abuse within the first year and 18% waited more than 5 years to disclose (Elliot and Briere 1994). Sexual abuse cases can be categorized into two groups: those requiring urgent or immediate medical care, and those that require less urgent evaluation.

Timing of Examination

All children and adolescents presenting with a reported history of sexual abuse/assault should be triaged immediately to determine the urgency of evaluation (Jenny et al. 2013; Palusci et al. 2006; Floyed et al. 2011; Gordo and Jaudees 1996; Hibbard 1998). Obtaining a brief summary of the abuse or assault concerns from the most appropriate source; the caregiver, child/adolescent, police or a child protection worker, is integral. When possible, information should not be collected directly from the child/adolescent, prior to a forensic interview that is typically conducted by police, a child protection worker or trained forensic interviewer (American College of Emergency Physicians 2013). When known, key pieces of information for the purposes of triaging include; when the abuse/assault occurred or the last contact was with the alleged offender, and the type of contact (genital-genital, oral-genital, genital-anal, digital-genital/anal etc.) (Christian 2011; Floyed et al. 2011; Delago et al. 2008). Medical concerns such as acute pain, bleeding or discharge, as well as psychological or safety concerns will also influence how urgently an examination is needed (Delago 2008; Melville et al. 2014).

The response to a “historical” allegation of sexual abuse differs from the management of a more recent or acute event. Nevertheless the disclosure of prior abuse/assault, no matter how remote, should be managed in a trauma-informed and systematic way. Consideration of the victim’s safety, and that of others, is critical and should be addressed immediately. Familiarity with jurisdictional reporting requirements as they pertain to the occurrence of sexual abuse, suspicion of sexual abuse, and ongoing risk of experiencing sexual harm to a child should be considered. Most jurisdictions require by law, that this type of information be reported to a local child protection agency. The specific requirements and definitions of the “mandated reporter” by practice jurisdiction should be known to the clinician. In many communities, child and youth advocacy centers offer a coordinated and

comprehensive response to victims of sexual assault/abuse. The clinician should be familiar with the available resources in their community. The medical evaluation of non-urgent cases can be conducted in a designated outpatient setting. All aspects of the sexual abuse medical evaluation are similar in the acute versus non-acute setting, however, timing will impact what interventions will or will not take place. Clinicians should consult with a child maltreatment pediatrician, a trained sexual assault nurse examiner, or other medical expert, if in doubt as to how to proceed.

History

The goal of the medical history is to gather information necessary to guide medical decision-making and potential forensic evidence collection (World Health Organization 2003; Finkel 2011). Rather than collecting the history directly from the child, information related to the abuse/assault should be gathered privately from the caregiver, police, or child protection worker (World Health Organization 2003; World Health Organization 2013; American College of Emergency Physicians 2013; In the case of adolescents, a medical history may be gathered directly with caution, using open ended questions. A forensic interview is a more specialized interview which is typically conducted by a trained interviewer to determine if sexual abuse/assault has occurred, and should ideally be conducted prior to the examination. In addition to the history outlined in the above section, a current and past medical history should be gathered.

Physical Examination

A complete head to toe examination should be conducted, including the assessment of skin injuries that may be a result of the alleged assault. It is important that certain principles be considered when performing a physical examination in the context of sexual abuse/assault. Ensuring patient

comfort and privacy is key, and one should never restrain, sedate, force or coerce a child into an examination. A genital examination may be difficult for a child or adolescent in the context of sexual abuse/assault and therefore support should be provided. The examination should be tailored to the developmental stage of the child or adolescent and he/she should be offered the choice of a support person. Asking the child about their understanding of the reason for the visit/examination and providing a detailed explanation of the procedures and what the child/adolescent may experience, as well as accurate information about the reasons for examination are important. Providing information, using distraction techniques, having a support person, and allowing the child to control some aspects of the examination have been found to decrease distress surrounding the exam (Waibel-Duncan 2004).

When examining children and adolescents it is important to determine their sexual maturity rating (SMR) which is a standard system used to assess child/adolescent physical development. SMRs utilize five stages (from prepubescent to adult) based on degree of maturation of secondary sexual characteristics during puberty (Bordini 2011). The SMR is important when considering testing for sexually transmitted infections, providing emergency contraception and collecting forensic evidence.

When conducting the ano-genital examination, the examiner should consider various positions which will optimize the examination with regards to visualization and specimen collection. Examining the child/adolescent in the supine position with legs in a frog leg position or feet resting in stirrups, often provides ideal visualization of the ano-genital structures. The prone knee chest position can also be considered for improved visualization, including the anal area. Examination should be of the external genitalia, with gentle traction and/or separation of the labia majora, allowing for visualization of the hymen and structures just beyond the labia.

An internal speculum examination of the vagina must not be done in pre-pubertal children, (World Health Organization 2003) and is rarely indicated in the context of a sexual abuse/assault

assessment. It should only be considered in the adolescent patient when there is ongoing bleeding (no external source), there is a need for collection of cervical specimens, or a foreign body is suspected. Measurement of the hymenal opening does not add value to the examination and should not be performed (Adams 2016). A digital rectal examination and/or the use of an anoscope is not recommended (Jenny 2013). An examination under anesthesia is rarely indicated in the context of sexual abuse/assault and should only be considered when medical signs and symptoms, such as ongoing bleeding (no external source), ongoing discharge (possible foreign body, or STI), or the need for surgical intervention are present. In these situations, consultation with a pediatric gynecologist is strongly recommended.

Interpretation of Findings

Recent literature indicates that in most cases, prepubertal girls who are assessed related to concerns of sexual abuse, have no findings of anal or genital injury on physical examination (Adams et al. 2007; Adams et al 1994; Heger et al. 2002; Andherst et al. 2009; Heppenstall-Heger et al. 2003; Berenson and Grady 2002). There are many reasons for this including; no injury was sustained related to the type of contact, the contact may have resulted in injuries that have healed, or tissues may have stretched without being injured (Adams et al. 2007). In many situations, formal documentation of the interpretation of findings may be requested by child protection workers and/or police. To ensure that accurate and relevant opinions are given, an evidence based approach to the interpretation of results of the ano-genital examination should be taken (Adams et al. 2007). Guided by published, evidence based summaries of genital examination findings and their interpretation, the clinician should identify the findings, and indicate into which of the three following categories they fall: findings documented in newborns or commonly seen in non-abused children; findings with no expert consensus on interpretation with respect to

sexual contact or trauma; and findings caused by trauma and/or sexual contact (Adams et al. 2016). If findings are considered to be those caused by trauma and/or sexual contact they should be photographed and immediately reviewed by a second professional with appropriate training and experience, for confirmation.

Documentation

Written documentation should include the medical history, details of the abuse/assault, the physical examination findings (including the ano-genital examination), laboratory testing, results and interpretation of findings. All genital and non-genital injuries or findings should be noted for type, appearance, location and measurement. It is helpful to use the face of a clock to document the location of genital findings with 12 o'clock representing the anterior portion of the hymen and 6 o'clock the posterior portion when the child/adolescent is in the supine position (Christian 2011). Photo-documentation of the genital examination is a recommended (especially for examinations with abnormal findings) with either a colposcope or a hand held digital camera (Adams et al. 2007). Clinicians, without specialized expertise and equipment, should ideally not photograph the genital exam and refer to a more specialized centre if needed, as appropriate storage and privacy parameters may not be in place. Diagnostic quality images allow for peer/expert review for the purposes of quality assurance, and teaching. A detailed written description of the examination findings should always accompany photographs (American College of Emergency Physicians 2013; Finkel et al. 1997; Adams et al. 2015). Photographic images are considered Personal Health Information and should be linked to the child's medical record and stored securely. Specific consent for photography must be obtained from the caregiver and/or patient as appropriate, and they should always have the right to refuse photo-documentation. Photographs should be taken, stored, transferred and retained according to the medical facility's policies.

Forensic Evidence Collection

The decision to collect forensic evidence should be based on the case history of the abuse/assault, the age and consent of the victim, the time interval between the assault and presentation to a medical facility, and specific factors such as bathing, voiding, and recent change of clothing. The collection of forensic evidence can be an intrusive undertaking, and therefore the clinician should consider the likely yield of findings prior to proceeding. Information from police may be needed in order to inform how best to proceed. Forensic evidence collection is recommended for sexual contact that may have resulted in the exchange of biologic material in the preceding 72 h. In adolescents, some portions of the sexual assault evidence kit may be considered for collection up to 7–12 days post-assault depending on the circumstances and type of contact (World Health Organization 2013; Adams et al. 2015; Giardet et al. 2011; Thackery et al. 2010).

Testing for Sexually Transmitted Infections

Each child/adolescent should be assessed on an individual basis with regards to testing for sexually transmitted infections (STI). The following situations put a child at higher risk for STIs and are indications for testing (American College of Emergency Physicians 2013; Public Health Agency of Canada 2013).

- The child has symptoms or signs of an STI (e.g. vaginal discharge or pain, genital itching or odor, urinary symptoms, genital ulcers or lesions).
- The suspected assailant is known to have an STI or to be at risk for an STI.
- Another child or adult in the household is known to have an STI.
- The prevalence of STIs in the community is high.
- There is information to suggest evidence of genital, oral, or anal contact.

Various testing methods for sexually transmitted infections exist (Black et al. 2009; Esernio-Jenssen and Barnes 2011; Sena et al. 2015; Hammerschlag 2010). Specimen sampling sites should be established based on the point of sexual contact as determined by the history, timing of potential exposures, and/or if symptoms are present. If there is no point of contact identified, consider how high risk for STI transmission may be, as testing may not be warranted. If potential exposure was recent, consider the potential incubation period for the particular STI to avoid potential false-positives and/or false-negatives. In other words, if it is an acute assault it may not be advantageous to conduct STI testing immediately as there maybe a time period as to when the organism may not be detected. Delaying testing in the acute sexual assault situation may assist in ensuring accurate results. However, if a child has symptoms such as vaginal discharge, STI testing should be conducted immediately. Vaginal swabs are recommended versus cervical swabs in pre-pubescent children. In the past, in pre-pubescent children, culture has been the preferred method of testing for medical-legal purposes. However, nucleic amplification acid tests (NAATs) may be acceptable and are commonly used. A study by Black et al, 2009 found that urine NAATs with process for confirmation of a positive result are adequate for use a new standard of Chlamydia and Gonorrhea in children suspected of sexual abuse (Black, Driebe et al. 2009). If the test is positive for an STI, the NAAT result should be confirmed by a second set of primers, a culture, or, in some cases, a second sample can be sent to another laboratory (Public Health Agency of Canada 2013). Anal and pharyngeal NAATs have not been formally approved in children and it is recommended checking with local laboratories.

Prophylaxis for gonorrhea and chlamydia immediately following a sexual abuse/assault is typically not recommended in pre-pubescent children (Public Health Agency of Canada. 2013). However, it can be considered in some cases, including adolescents, where follow-up may be difficult to ensure. Prophylaxis should not be provided if the samples for STI testing are

being collected, and follow up of the results is feasible as a positive STI result may add forensic value to a case and ensure proper diagnosis and treatment. It is common practice for children to have received the Hepatitis B vaccine, however, if they have not, the first dose of the vaccine should be provided at the time of assessment. If the Hepatitis B vaccine status is unknown, the clinician should consider checking the child's serology to determine Hepatitis B antibody titers. If the patient is unvaccinated and the alleged perpetrator is known to have Hepatitis B, providing Hepatitis B Immunoglobulin (HBIG) is recommended (Public Health Agency of Canada 2013).

HIV Post Exposure Prophylaxis

Human Immunodeficiency Virus (HIV) Post-Exposure Prophylaxis (PEP) should be offered to all children and adolescents who are considered at risk for HIV infection and who present within 72 h of a sexual assault or the last incident of sexual abuse (Sena et al. 2015). The sooner HIV PEP is initiated, the greater the likelihood that it will prevent transmission of the virus (American College of Emergency Physicians 2013; World Health Organization 2013; Sena et al. 2015). Baseline bloodwork should be collected, and the medication regimen and side effects discussed with the child/adolescent and caregiver to promote compliance of the HIV PEP protocol. Please refer to guidelines from the Centre for Disease Control or the American Academy of Pediatrics for the most current HIV PEP medication protocol.

Emergency Contraception

Emergency contraception should be offered and provided as soon as possible to all pubertal patients who report vaginal-penile penetration and present within 5 days of exposure (World Health Organization 2013; Katzman et al. 2010). A pregnancy test must be done prior to providing emergency contraception. When applicable, patients should be counseled that the emergency

contraceptive pill is less effective in women weighing 75–80 kg and not effective in women over 80 kg. If over 80 kg, insertion of an intra-uterine device can be considered as an alternative emergency contraceptive method (Katzman et al. 2010).

Psychosocial Support

Appropriate psychosocial support is integral to the care provided to sexual abuse/assault patients and their families. In the acute setting, various tools such as a trauma symptom screening (Cohen et al. 2008) and/or a suicide and/or self-harm risk assessment (Korczak 2015) may be useful in assessing psychosocial symptoms in a child/adolescent. In addition, it is critical to offer the non-offending caregivers education around responding to and supporting their child, as this is a strong predictor of positive psychosocial prognosis in children (Elliott and Carnes 2001). Trauma-focused cognitive behavioural therapy has been shown to be the most effective form of therapy when needed (Cohen et al. 2000) and therefore referrals should be made to an appropriate mental health professional, ideally in the family's community.

Discharge and Follow-Up

Health care providers should ensure the patient's medical and mental health needs related to the assault have been addressed. It may be important to arrange a follow-up appointment. Always ensure that a plan is in place to address the patient's safety and well-being after leaving the hospital.

Neglect

Neglect is the most common form of child maltreatment around the world and the most common form of maltreatment that is substantiated by child protection agencies in Canada and the United States (US Department of Health and

Human Services 2016; Public Health Agency of Canada 2008). Authors have proposed a variety of definitions for neglect which include either statements about omissions of care and the responsibility of parents in providing children's needs, an ecological perspective on the multifactorial factors that lead to parenting failure and neglect, or the effect on the child. For the clinician, it is useful to define neglect from the child's perspective as occurring when the child's basic needs are not met, whatever the cause (Dubowitz et al. 2005). This allows the clinician to remain focused on the child's needs, distances the conversation from blaming the parents, and allows for constructive solutions on how best to provide what is needed for the child to meet their best potential (Dubowitz 2009). Whatever the definition, neglect can have profound and lasting effects on a child's physical and mental health, as well as their social and cognitive development.

For clinical purposes, it is useful to consider neglect in four main categories:

1. Physical neglect—the child's physical needs for food, clothing, housing or safety are not met
2. Emotional neglect—the child's need for a nurturing and loving environment to foster healthy psychological, emotional or social development are not met
3. Medical neglect—the child's need for necessary medical, dental, or psychological care are not met
4. Educational neglect—the child's formal educational needs are not met

The degree to which a child's needs are met falls along a continuum for all children and all parents. Some children may benefit from all the material resources available but not be exposed to a loving household that helps them to develop emotionally. Other children may have warm, nurturing, caring parents who are unable to provide enough food for them to grow normally. Others may have their physical and emotional needs met but not be brought for medical care when needed.

Clinicians often find it difficult to judge when the child's needs are adequately but not optimally

met versus inadequately met. As with other forms of maltreatment, the standard of "harm or risk of harm" to the child is used to assess whether neglect is present. The clinician must therefore look at the lack or inadequacy of care in a specific area and its impact on the child. In a medical office, issues of neglect most often present as growth problems (eg. failure to thrive), developmental delays (eg. speech delay), poor dental health, poor general hygiene and care, injuries (eg. from inadequate supervision), and behaviour problems.

In a systematic review of features "indicative of neglect or emotional abuse in preschool children", aggression, passivity, developmental delay, and poor peer interaction were common. Studies in older children have shown that the symptoms overlap with features of attention deficit hyperactivity disorder (ADHD), and that school-aged children with neglect present with impulsivity, inattention or hyperactivity, as well as low self-esteem, poor relationships and friendships, and low academic performance. As a result, when children present with these features, both the assessment and management of the problem should consider neglect. Medication management for ADHD features in this context will not address the underlying issues or provide the needed benefit to children, particularly if used without other behavioural and family interventions.

Clinicians are sometimes in a position where they feel that a child's medical, dental, or psychological care needs are not being met. This usually occurs when children are not brought for care when it is needed or when children do not receive the care that is recommended by a health professional although it is necessary for the child's health or well-being (Jenny et al. 2007). Clinicians are referred to resources by the American Academy of Pediatrics, Canadian Paediatric Society and others for an approach to managing this problem (Jenny et al. 2007, Baird et al. 2017).

Health care professionals are in a unique position to speak to the needs of the child and the long-term negative consequences for a child to grow up without having their needs met. The clinician can play an important role by identify-

ing that a child's needs are not being met, ruling out medical causes for the child's issues (eg, an organic cause for failure to thrive, hearing loss for speech delay etc.), and working with the family and community supports to assist the child to have their needs met more completely. When harm or risk of harm is apparent, child protection authorities should also be notified as they can assess the child and family more thoroughly in the home and school environment and put other supports in place to assist the child and family.

References

- Acker SN, Roach JP, Partrick DA, Karrer FM, Bensard DD, Sirotiak AP. Beyond morbidity and mortality: the social and legal outcomes of non-accidental trauma. *J Pediatr Surg*. 2015;50(4):604–7.
- Adams JA, Harper K, Knudson S, Revilla J. Examination findings in legally confirmed child sexual abuse: it's normal to be normal. *Pediatrics*. 1994;94(3):829–37.
- Adams J, Kaplan RA, Starling SP, Mehta NH, Finkel MA, Botash AS, et al. Guidelines for medical care of children who may have been sexually abused. *J Pediatr Adolesc Gynecol*. 2007;20(3):163–72.
- Adams JA, Kellogg ND, Farst KJ, Harper NS, Palusci VJ, Frasier LD, et al. Updated guidelines for the medical assessment and care of children who may have been sexually abused. *Pediatr Adolesc Gynecol*. 2016;29(2):81–7.
- Affi TO, MacMillan HL. Resilience following child maltreatment: a review of protective factors. *Can J Psychiatr*. 2011;56(5):266–72.
- Affi TO, MacMillan HL, Boyle M, Taillieu T, Cheung K, Sareen J. Child abuse and mental disorders in Canada. *CMAJ*. 2014;186(9):e324–32.
- American Academy of Pediatrics Section on Radiology. Diagnostic Imaging of Child Abuse. *Pediatrics*. 2009;123(5):1430–1435.
- American College of Emergency Physicians. Evaluation and management of the sexually assaulted or sexually abused patient. 2013. <https://www.acep.org/content.aspx?id=29562>
- American College of Radiology, Society for Pediatric Radiology. ACR-SPR Practice parameter for skeletal surveys in children. 2014. <http://www.acr.org/~medi/9BDCDBEE99B84E87BAAC2B1695BC07B6.pdf>
- Anderst JD, Carpenter SL, Abshire TC, Section on Hematology/Oncology and Committee on Child Abuse and Neglect of the American Academy of Pediatrics. Clinical report: evaluation for bleeding disorders in suspected child abuse. *Pediatrics*. 2013;131(4):e1314–22.
- Andherst J, Kellogg N, Jung I. Reports of repetitive penile-genital penetration often have no definitive evidence of penetration. *Pediatrics*. 2009;124(3):e403–9.
- Ateah CA, Durrant JE. Maternal use of physical punishment in response to child misbehavior: implications for child abuse prevention. *Child Abuse Negl*. 2005;29(2):169–85.
- Baird B, Ward MG, Schwartz S, Thibault M, Child and Youth Maltreatment Section, Canadian Paediatric Society. Medical neglect of children and adolescents: a clinical perspective. *Paediatr Child Health*. Forthcoming 2017.
- Barciak E, Plint A, Gaboury I, et al. Dating of bruises in children: an assessment of physician accuracy. *Pediatrics*. 2003;112:804–7.
- Barlow K, Thompson E, Johnson D, Minns RA. The neurological outcome of non-accidental head injury. *Pediatr Rehabil*. 2004;7(3):195–203.
- Barlow K, Thomson E, Johnson D. Late neurologic and cognitive sequelae of inflicted traumatic brain injury in infancy. *Pediatrics*. 2005;116(2):e174–85.
- Barnes PM, Norton CM, Dunstan FD, Kemp AM, Yates DW, Silbert JR. Abdominal injury due to child abuse. *Lancet*. 2005;366(9481):234–5.
- Barr RG. Preventing abusive head trauma resulting from a failure of normal interaction between infants and their caregivers. *Proc Natl Acad Sci U S A*. 2012;109(Suppl 2):17294–301.
- Barr RG. Crying as a trigger for abusive head trauma: a key to prevention. *Pediatr Radiol*. 2014;44(Suppl 4):S559–64.
- Barr RG, Trent B, Cross J. Age-related incidence curve of hospitalized Shaken Baby Syndrome: convergent evidence for crying as a trigger to shaking. *Child Abuse Negl*. 2006;30(1):7–16.
- Bennett BL, Chua MS, Care M, Kachelmeyer A, Mahabee-Gittens M. Retrospective review to determine the utility of follow-up skeletal surveys in child abuse evaluations when the initial skeletal survey is normal. *BMC Res Notes*. 2011;4:354.
- Berenson A, Grady J. A longitudinal study of hymenal development from 3 to 9 years of age. *J Pediatr*. 2002;140(5):600–7.
- Binenbaum G, Rogers DL, Forbes BJ, Levin AV, Clark SA, Christian CW, et al. Patterns of retinal hemorrhage associated with increased intracranial pressure in children. *Pediatrics*. 2013a;132(2):e430–4.
- Binenbaum G, Christian CW, Ichord RN, Ying GS, Simon MA, Romero K, et al. Retinal hemorrhage and brain injury patterns on diffusion-weighted magnetic resonance imaging in children with head trauma. *J AAPOS*. 2013b;17(6):603–8.
- Black CM, Driebe EM, Howard LA, Fajman NN, Sawyer MK, Giardet RD, et al. Multicenter study of nucleic acid amplification tests for detection of Chlamydia Trachomatis and Neisseria gonorrhoeae in children being evaluated for sexual abuse. *Pediatr Infect Dis J*. 2009;28:608–13.
- Bordini BRR. Normal pubertal development Part II: clinical aspects of puberty. *Pediatr Rev*. 2011;32:281.

- Bower-Russa ME, Knutson JF, Winebarger A. Disciplinary history, adult disciplinary attitudes, and risk for abusive parenting. *J Comm Psychol*. 2001; 29(3):219–40.
- Bradford R, Choudhary AK, Dias MS. Serial neuroimaging in infants with abusive head trauma: timing abusive injuries. *J Neurosurg Pediatr*. 2013;12:110–9.
- Carpenter RF. The prevalence and distribution of bruising in babies. *Arch Dis Child*. 1999;80(4):363–6.
- Chestner DL, Jose RM, Aldiyami E, King H, Moiemens NS. Non-accidental burns in children—are we neglecting neglect? *Burns*. 2006;32:222–8.
- Christian C. Timing of the medical examination. *J Child Sex Abus*. 2011;20:505–20.
- Christian CW, Block R, Committee on Child Abuse and Neglect, American Academy of Pediatrics. Abusive head trauma in infants and children. *Pediatrics*. 2009;123:1409–11.
- Christian C, Committee on Child Abuse and Neglect, American Academy of Pediatrics. The evaluation of suspected child physical abuse. *Pediatrics*. 2015;135(5):e1337–54.
- Cohen JA, Mannarino A, Berliner L, Deblinger E. Trauma-focused cognitive behavioral therapy for children and adolescents. *J Interpers Violence*. 2000;15(11):1202–23.
- Cohen JA, Kelleher KJ, Mannarino AP. Identifying, treating and referring traumatized children: the role of pediatric providers. *Arch Pediatr Adolesc Med*. 2008;162(5):447–52.
- D'Souza AL, Nelson NG, McKenzie LB. Pediatric burn injuries treated in US emergency departments between 1990 and 2006. *Pediatrics*. 2009;124(5):1424–30.
- DeLago C, Deblinger E, Schroeder C, Finkel MA. Girls who disclose sexual abuse: urogenital symptoms and signs after genital contact. *Pediatrics*. 2008;122(2):e281–6.
- Dias MS, Backstrom J, Falk M, Li V. Serial radiography in the infant shaken impact syndrome. *Pediatr Neurosurg*. 1998;29(2):77–85.
- Dissanaike S, Wishnew J, Rahimi M, Zhang Y, Hester C, Griswold J. Burns as child abuse: risk factors and legal issues in West Texas and Eastern New Mexico. *J Burn Care Res*. 2010;31:176–83.
- Dubowitz H. Tackling child neglect: a role for pediatricians. *Pediatr Clin N Am*. 2009;56:363–78.
- Dubowitz H, Newton RR, Litrownik AJ, Lewis T, Briggs EC, Thompson R, et al. Examination of a conceptual model of child neglect. *Child Maltreat*. 2005;10(2):173–89.
- Duncan MK, Sanger M. Coping with the pediatric anogenital exam. *J Child Adolesc Psychiatr Nurs*. 2004;17(3):126–36.
- Dunstan FD, Buildea ZE, Kontos K, Kemp AM, Sibert JR. A scoring system for bruise patterns: a tool for identifying abuse. *Arch Dis Child*. 2002;86(5):330–3.
- Durrant JE, Ensom R. Coalition on physical punishment of children and youth. Ottawa: Coalition on Physical Punishment of Children and Youth; 2004. <http://www.cheo.on.ca/en/physicalpunishment>
- Durrant J, Ensom E. Physical punishment of children: lessons from 20 years of research. *CMAJ*. 2012;184(12):1373–7.
- Durrant JE, Broberg AG, Rose-Krasnor L. Predicting maternal use of physical punishment from maternal characteristics in Sweden and Canada. In: Hastings P, Piotrowski C, editors. *New directions in child development: conflict as a context for understanding maternal beliefs about child rearing and children's misbehavior*. San Francisco: Jossey-Bass; 1999. p. 25–41.
- Elliot D, Briere J. Forensic sexual abuse evaluations of older children: disclosures and symptomatology. *Behav Sci Law*. 1994;12:261–77.
- Elliott AN, Carnes CN. Reactions of nonoffending parents to the sexual abuse of their child: a review of the literature. *Child Maltreat*. 2001;6(4):314–31.
- Esernio-Jenssen D, Barnes M. Nucleic acid amplification testing in suspected child sexual abuse. *J Child Sex Abus*. 2011;20(6):612–21.
- Ewing-Cobbs L, Kramer L, Prasad M, Canales DN, Louis PT, Fletcher JM, et al. Neuroimaging, physical, and developmental findings after inflicted and noninflicted traumatic brain injury in young children. *Pediatrics*. 1998;102(2 pt 1):300–7.
- Ewing-Cobbs L, Prasad M, Kramer L, Louis PT, Baumgartner J, Fletcher JM, et al. Acute neuroradiologic findings in young children with inflicted or non-inflicted traumatic brain injury. *Childs Nervous Syst*. 2000;16(1):25–33; discussion 34.
- Finkel MA, Alexander RA. Conducting the medical history. *J Child Sex Abus*. 2011;20(5):486–504.
- Finkel M, Ricci LR. Documentation and preservation of visual evidence in child abuse. *Child Maltreat*. 1997;2:322–30.
- Finkelhor D, Turner HA, Ormond R, Hamby SL. Violence, crime, and abuse exposure in a national sample of children and youth: an update. *JAMA Pediatr*. 2013;167(7):614–21.
- Finkelhor D, Turner HA, Shattuck A, Hamby SL. Prevalence of childhood exposure to violence, crime and abuse: results from the National Survey of Children's Exposure to Violence. *JAMA Pediatr*. 2015;169(8):746–54.
- Flaherty EG, Perez-Rossello JM, Levine MA, Henrikus WL, American Academy of Pediatrics Committee on Child Abuse and Neglect; Section on Radiology, American Academy of Pediatrics; Section on Endocrinology, American Academy of Pediatrics; Section on Orthopaedics, American Academy of Pediatrics; Society for Pediatric Radiology. Evaluating children with fractures for child physical abuse. *Pediatrics*. 2014;133(2):e477–89.
- Floyed RL, Hirsh DA, Greenbaum VJ, Simon HK. Development of a screening tool for pediatric sexual assault may reduce emergency-department visits. *Pediatrics*. 2011;128(2):221–6.
- Fox JC, Boysen M, Gharahbaghian L, Cusick S, Ahmed SS, Anderson CL, et al. Test characteristics of focused assessment of sonography for trauma for clinically sig-

- nificant abdominal free fluid in pediatric blunt abdominal trauma. *Acad Emerg Med.* 2011;18:477–82.
- Giardet R, Bolton K, Lahoti S, Mowbray H, Giardino A, Isaac R, et al. Collection of forensic evidence from pediatric victims of sexual assault. *Pediatrics.* 2011;128:233–8.
- Goodman-Brown TB, Edelstein RS, Goodman GS, Jones DP, Gordon DS. Why children tell: a model of children's disclosure of sexual abuse. *Child Abuse Negl.* 2003;27(5):525–40.
- Gordo S, Jaudees PK. Sexual abuse evaluations in the emergency department: is the history reliable? *Child Abuse Negl.* 1996;20(4):315–22.
- Grossman SE, Johnston A, Vanezis P, Perrett D. Can we assess the age of bruises? An attempt to develop an objective technique. *Med Sci Law.* 2011;51(3):170–6.
- Hammerschlag MR, Guillén CD. Medical and legal implications of testing for sexually transmitted infections in children. *Clin Microbiol Rev.* 2010;23(3):493–506.
- Harper SN, Feldman KW, Sugar NF, Anderst JD, Lindberg DM, Examining Siblings To Recognize Abuse Investigators. Additional injuries in young infants with concern for abuse and apparently isolated bruises. *J Pediatr.* 2014;165(2):383–8.
- Harris TL, Flaherty EG. Bruises and skin lesions. In: Jenny C, editor. *Child abuse and neglect: diagnosis, treatment, and evidence.* Missouri: Elsevier-Saunders; 2011. p. 239–51.
- Heger A, Ticson L, Velasquez O, Bernier R. Children referred for possible sexual abuse: medical findings in 2384 children. *Child Abuse Negl.* 2002;26(6–7):645–59.
- Heppenstall-Heger A, McConnell G, Ticson L, Guerra L, Lister J, Zaragoza T. Healing patterns in anogenital injuries: a longitudinal study of injuries associated with sexual abuse, accidental injuries, or genital surgery in the preadolescent child. *Pediatrics.* 2003;112(4):829–37.
- Hibbard RA. Triage and referrals for child sexual abuse medical examinations from the sociological system. *Child Abuse Negl.* 1998;22(6):503–13.
- Hillis S, Mercy J, Amobi A, Kress H. Global prevalence of past-year violence against children: a systematic review and minimum estimates. *Pediatrics.* 2016;137(3):e20154079.
- Hughes LA, May K, Talbot JF, Parsons MA. Incidence, distribution, and duration of birth-related retinal hemorrhages: a prospective study. *J AAPOS.* 2006;10(2):102–6.
- Ibrahim NG, Wood J, Margulies SS, Christian CW. Influence of age and fall type on head injuries in infants and toddlers. *Int J Dev Neurosci.* 2012;30(3):201–6.
- Jenny C, Committee on Child Abuse and Neglect, American Academy of Pediatrics. Evaluating infants and young children with multiple fractures. *Pediatrics.* 2006;118(3):1299–303.
- Jenny C, Hymel KP, Ritzen A, Reinert SE, Hay TC. Analysis of missed cases of abusive head trauma. *JAMA.* 1999;281(7):621–6.
- Jenny C, Committee on Child Abuse and Neglect, American Academy of Pediatrics. Recognizing and responding to medical neglect. *Pediatrics.* 2007;120(6):1385–9.
- Jenny C, Crawford-Jakubiak JE, Committee on Child Abuse and Neglect, American Academy of Pediatrics. The evaluation of children in the primary care setting when sexual abuse is suspected. *Pediatrics.* 2013;132(2):e558–67.
- Katzman DK, Taddeo D, Adolescent Health Committee, Canadian Pediatric Society. Policy Statement: emergency Contraception. *Paediatr Child Health.* 2010;15(6):363–7.
- Keenan HT, Runyan DK, Marshall SW, Nocera MA, Merten DF, Sinal SH. A population-based study of inflicted traumatic brain injury in young children. *JAMA.* 2003;290(5):621–6.
- Kemp AM, Dunstan F, Harison S, Mann M, Rolfe K, Datta S, et al. Patterns of skeletal fractures in child abuse: systematic review. *BMJ.* 2008;337:a1518.
- Kemp AM, Jaspan T, Griffiths J, Stoodley N, Mann MK, Tempest V, et al. Neuroimaging: what neuroradiological features distinguish abusive from non-abusive head trauma? A systematic review. *Arch Dis Child.* 2011;96:1103–12.
- Kemp AM, Maguire SA, Lumb RC, Harris SM, Mann MK. Contact, cigarette and flame burns in physical abuse: a systematic review. *Child Abuse Rev.* 2014;23:35–47.
- Kemp AM, et al. Patterns of bruising in preschool children—a longitudinal study. *Arch Dis Child.* 2015;100:426–31.
- Khair K, Liesner R. Bruising and bleeding in infants and children—a practical approach. *Br J Haematol.* 2006;133:221–31.
- King WJ, MacKay M, Sirmick A, Canadian Shaken Baby Study Group. Shaken baby syndrome in Canada: clinical characteristics and outcomes of hospital cases. *CMAJ.* 2003;168(2):155–9.
- Kleinman PK, Silvera VM. Abusive craniocervical junction and spinal trauma. In: Kleinman PK, editor. *Diagnostic imaging of child abuse.* Cambridge: Cambridge University Press; 2015. p. 494–559.
- Kleinman PK, Nimkin K, Spevak MR, Rayder SM, Madansky DL, Shelton YA, et al. Follow-up skeletal surveys in suspected child abuse. *Am J Roentgenol.* 1996;167:893–6.
- Kodikara S, Pollanen M. Fatal pediatric head injury due to toppled television: does the injury pattern overlap with abusive head trauma? *Leg Med (Tokyo).* 2012;14(4):197–200.
- Korcza D. Suicidal ideation and behaviour. *Paediatr Child Health.* 2015;20(5):257–60.
- Labbe J, Caouette G. Recent skin injuries in normal children. *Pediatrics.* 2001;108(2):271–6.
- Langlois NEI, Gresham GA. The ageing of bruises: a review and study of the colour changes with time. *Forensic Sci Int.* 1991;50:227–38.
- Leventhal JM, Martin KD, Agnes AG. Incidence of fractures attributable to abuse in young hospitalized

- children: results from analysis of a United States database. *Pediatrics*. 2008;122:599–604.
- Levin AV. Retinal hemorrhage in abusive head trauma. *Pediatrics*. 2010;126(5):961–70.
- Liesner R, Hann I, Khair K. Non-accidental injury and the haematologist: the causes and investigation of easy bruising. *Blood Coagul Fibrinolysis*. 2004;15(Suppl 1):S41–8.
- Lind K, Toure H, Brugel D, Meyer P, Laurent-Vannier A, Chevignard M. Extended follow-up of neurological, cognitive, behavioral and academic outcomes after severe abusive head trauma. *Child Abuse Negl*. 2016;51:358–67.
- Lindberg DM. Abusive abdominal trauma—an update for the pediatric emergency medicine physician. *Clin Pediatr Emerg Med*. 2012;13(3):187–93.
- Lindberg DM, Shapiro RA, Blood EA, Steiner RD, Berger RP, ExSTRA Investigators. Utility of hepatic transaminases in children with concern for abuse. *Pediatrics*. 2013;131(2):268–75.
- Lopes NR, Eisenstein E, Williams LC. Abusive head trauma in children: a literature review. *J Pediatr*. 2013;89(5):426–33.
- Lux AL. Prevalence of bruising in babies. *Arch Dis Child*. 2000;82(3):266.
- Lyons TJ, Oates RK. Falling out of bed: a relatively benign occurrence. *Pediatrics*. 1993;92:125–7.
- Maguire S, Mann M. Systematic reviews of bruising in relation to child abuse—what have we learnt: an overview of review updates. *Evid Based Child Health*. 2013;8:255–63.
- Maguire S, Okolie C, Kemp AM. Burns as a consequence of child maltreatment. *Paediatr Child Health*. 2004;24(12):557–61.
- Maguire S, Mann MK, Sibert J, Kemp A. Are there patterns of bruising in childhood which are diagnostic or suggestive of abuse? A systematic review. *Arch Dis Child*. 2005a;90:182–6.
- Maguire S, Mann MK, Sibert J, Kemp A. Can you age bruises accurately in children? A systematic review. *Arch Dis Child*. 2005b;90:187–9.
- Maguire S, Moynihan S, Mann M, Potokar T, Kemp AM. A systematic review of the features that indicate intentional scalds in children. *Burns*. 2008;34(8):1072–81.
- Maguire S, Pickerd N, Farewell D, Mann M, Tempest V, Kemp AM. Which clinical features distinguish inflicted from non-inflicted brain injury? A systematic review. *Arch Dis Child*. 2009;94:860–7.
- Maguire S, Cowley L, Mann M, Kemp A. What does the recent literature add to the identification and investigation of fractures in child abuse: an overview of review updates 2005–2013. *Evid Based Child Health*. 2013a;8:2044–57.
- Maguire SA, Upadhyaya M, Evans A, Mann MK, Haroon MM, Tempest V, et al. A systematic review of abusive visceral injuries in childhood—their range and recognition. *Child Abuse Negl*. 2013b;37(7):430–45.
- Maguire SA, Williams B, Naughton AM, Cowley LE, Tempest V, Mann MK, et al. A systematic review of the emotional, behavioural and cognitive features exhibited by school-aged children experiencing neglect or emotional abuse. *Child Care Health Dev*. 2015;41(5):641–53.
- Melville JD, Kellogg ND, Perez N, Lukefahr JL. Assessment for self-blame and trauma symptoms during the medical evaluation of suspected sexual abuse. *Child Abuse Negl*. 2014;38(5):851–7.
- Minford AMB, Richards EM. Excluding medical and haematological conditions as a cause of bruising in suspected non-accidental injury. *Arch Dis Child Educ Pract Ed*. 2010;95:2–8.
- Mittal N, Pedersen R, James P, Shott S, Valentino LA. Utility of a Pediatric Bleeding Questionnaire as a screening tool for von Willebrand disease in apparently healthy children. *Haemophilia*. 2015;21(6):806–811.
- Niederkrotenthaler T, Xu L, Parks SE, Sugerman DE. Descriptive factors of abusive head trauma in young children—United States, 2000–2009. *Child Abuse Negl*. 2013;37(7):446–55.
- Ornstein AE. An approach to child maltreatment documentation and participation in the court system. *Paediatr Child Health*. 2013;18(8):e44–7.
- Palusci V, Cox E, Shatz EM, Schultze JM. Urgent medical assessment after child sexual abuse. *Child Abuse Negl*. 2006;30:367–80.
- Parks S, Sugerman D, Xu L, Coronado V. Characteristics of non-fatal abusive head trauma among children in the USA, 2003–2008: application of the CDC operational case definition to national hospital inpatient data. *Inj Prev*. 2012;18(6):392–8.
- Pierce MC, Kaczor K, Aldridge S, O'Flynn J, Lorenz DJ. Bruising characteristics discriminating physical child abuse from accidental trauma. *Pediatrics*. 2010;125:67.
- Pierce MC, Kaczor K, Lohr D, Richter K, Starling SP. A practical guide to differentiating abusive from accidental fractures: an injury plausibility approach. *Clin Pediatr Emerg Med*. 2012;13(3):166–77.
- Pilling ML, Vanezis P, Perrett D, Johnston A. Visual assessment of the timing of bruising by forensic experts. *J Forensic Legal Med*. 2010;17:143–9.
- Piteau SJ, Ward MG, Barrowman NJ, Plint AC. Clinical and radiographic characteristics associated with abusive and nonabusive head trauma: a systematic review. *Pediatrics*. 2012;130:315–23.
- Public Health Agency of Canada. Canadian incidence study of reported child abuse and Neglect—2008: major findings. Ottawa. 2010. http://www.publications.gc.ca/collections/collection_2010/aspc-phac/HP5-1-2008-eng.pdf
- Public Health Agency of Canada. Canadian guidelines on sexually transmitted infections. 2013. <http://www.phac-aspc.gc.ca/std-mts/sti-its/index-eng.php>
- Rankin JM, Ornstein AE. A commentary on mandatory reporting legislation in the United States, Canada, and Australia: a cross-jurisdictional review of key features, differences, and issues. *Child Maltreat*. 2009;14(1):121–3.

- Rivara FP, Alexander B, Johnston B, Soderberg R. Population-based study of fall injuries in children and adolescents resulting in hospitalization or death. *Pediatrics*. 1993;92:61–3.
- Rooks VJ, Eaton JP, Ruess L, Petermann GW, Keck-Wherley J, Pedersen RC. Prevalence and evolution of intracranial hemorrhage in asymptomatic term infants. *Am J Neuroradiol*. 2008;29(6):1082–9.
- Royal College of Paediatrics and Child Health. Child protection companion. London: RCPCH; 2006. p. P18–21.
- Rubin DM, Christian CW, Bilaniuk LT, Zazyczny KA, Durbin DR. Occult head injury in high-risk abused children. *Pediatrics*. 2003;111:1382–6.
- Schwartz AJ, Ricci LR. How accurately can bruises be aged in abused children? Literature review and synthesis. *Pediatrics*. 1996;97(2):254–7.
- Section on Radiology; American Academy of Pediatrics. Diagnostic imaging of child abuse. *Pediatrics*. 2009;123(5):1430–5.
- Sena AC, Hsu KK, Kellogg N, Girardet R, Christian CW, Linden J, et al. Sexual assault and sexually transmitted infections in adults, adolescents and children. *Clin Infect Dis*. 2015;61(Suppl 8):S856–64.
- Sieswerda-Hoogendoorn T, Bilo RA, van Duurling LL, Karst WA, Maaskant JM, van Aalderen WM, et al. Abusive head trauma in young children in the Netherlands: evidence for multiple incidents of abuse. *Acta Paediatr*. 2013;102(11):e497–501.
- Silvera VM, Grant PE, Hedlund GL, Kleinman PK. Abusive head trauma: intracranial imaging strategies. In: Kleinman PK, editor. *Diagnostic imaging of child abuse*. Cambridge: Cambridge University Press; 2015. p. 487–93.
- Stephenson T, Bialas Y. Estimation of the age of bruising. *Arch Dis Child*. 1996;74:53–5.
- Sugar NF, Taylor JA, Feldman KW. Bruises in infants and toddlers: those who don't bruise rarely bruise. *Arch Pediatr Adolesc Med*. 1999;153(4):399–403.
- Thackery JD, Horner G, Benziger EA, Scribano PV. Forensic evidence collection and DNA identification in acute child sexual assault. *Pediatrics*. 2010;128:227–32.
- Trokkel M, Discala C, Terrin NC, Sege RD. Patient and injury characteristics in abusive abdominal injuries. *Pediatr Emerg Care*. 2006;22(10):700–4.
- Tung GA, Kumar M, Richardson RC, Jenny C, Brown WD. Comparison of accidental and nonaccidental traumatic head injury in children on noncontrast computed tomography. *Pediatrics*. 2006;118:626–33.
- U.S. Department of Health & Human Services, Administration on Children, Youth and Families, Children's Bureau. *Child maltreat* 2014. 2016. <http://www.acf.hhs.gov/programs/cb/research-data-technology/statistics-research/child-maltreatment>
- U.S. Department of Justice. A national protocol for sexual assault medical forensic examinations: pediatric. 2016. <https://www.ncjrs.gov/pdffiles1/ovw/249871.pdf>
- Vinchon M, Defoort-Dhellemmes S, Noulé N, Duhem R, Dhellemmes P. Accidental or non-accidental brain injury in infants. Prospective study of 88 cases. *Presse Med*. 2004;33(17):1174–9.
- Vinchon M, Defoort-Dhellemmes S, Desurmont M, Dhellemmes P. Accidental and nonaccidental head injuries in infants: a prospective study. *J Neurosurg*. 2005;102(4 Suppl):380–4.
- Wang MY, Kim KA, Griffith PM, Summers S, McComb JG, Levy ML, et al. Injuries from falls in the pediatric population: an analysis of 729 cases. *J Pediatr Surg*. 2001;36:1528–34.
- Ward MGK, Ornstein A, Niec A, Murray L, Canadian Paediatric Society, Child and Youth Maltreatment Section. The medical assessment of bruising in suspected child maltreatment cases: a clinical perspective. *Paediatr Child Health*. 2013;18(8):433–7.
- Ward M, Azzopardi C, Morantz G. A mindful approach: assessing child maltreatment in a multicultural setting. In: Barozzino T, Hui C, editors. *Caring for kids new to Canada: a guide for health professionals working with immigrant and refugee children and youth*. Canadian Paediatric Society; 2014. <http://kidsnewtocanada.ca/screening/maltreatment>
- Wood J, Rubin DM, Nance ML, Christian CW. Distinguishing inflicted versus accidental abdominal injuries in young children. *J Trauma*. 2005;59(5):1203–8.
- World Health Organization. Guidelines of medico-legal care for victims of sexual violence. 2003. http://www.who.int/violence_injury_prevention/publications/violence/med_leg_guidelines/en/
- World Health Organization. Responding to intimate partner violence and sexual violence against women. 2013. http://apps.who.int/iris/bitstream/10665/85240/1/9789241548595_eng.pdf?ua=1
- World Health Organization. Child maltreatment—fact sheet. <http://www.who.int/mediacentre/factsheets/fs150/en/#>. Accessed 14 July 2016.
- Xiang J, Shi J, Wheeler KK, Yeates KO, Taylor HG, Smith GA. Paediatric patients with abusive head trauma treated in US Emergency Departments, 2006–2009. *Brain Inj*. 2013;27(13–14):1555–61.



Update in Pediatric Critical Care

5

Lisa A. DelSignore, Traci A. Wolbrink,
and Niranjan Kissoon

Introduction

Many advances have been made in pediatric critical care medicine over the last several years. This chapter will provide a broad overview to the most relevant advances in the following domains: patient monitoring, organ systems-based practice, educational training, global health, and quality improvement. Specific advances in the field of pediatric critical care discussed here represent those that have either demonstrated or have the potential to demonstrate improvement in patient outcomes, in addition to advances that are enablers to the provision of safe, efficacious, timely and equitable patient-centered care.

L.A. DelSignore, M.D. (✉)
Division of Pediatric Critical Care, Department of
Pediatrics, Floating Hospital for Children at Tufts
Medical Center, Tufts Medical School, 800 Washington
Avenue, Box 93, 02111 Boston, MA, USA
e-mail: ldesignore@tuftsmedicalcenter.org

T.A. Wolbrink, M.D., M.P.H.
Division of Critical Care Medicine, Department of
Anesthesia, Perioperative and Pain Management,
Boston Children's Hospital, Harvard Medical School,
300 Longwood Ave, Bader, 634 Boston, MA, USA

N. Kissoon, M.D.
Division of Critical Care and the Child
and Family Research Institute, Department of
Pediatrics, British Columbia's Children's Hospital,
University of British Columbia, Vancouver,
BC, Canada

Patient Monitoring

Over the last decade, there has been a general trend towards using less invasive, or non-invasive devices to monitor critically ill children as alternatives to invasive procedures that may be associated with significant risks during insertion and potential harm while in situ. Technologies that have gained prominence and acceptance in many pediatric intensive care units include near-infrared spectroscopy (NIRS), continuous EEG monitoring, advanced bioinformatics technologies, and bedside ultrasound use.

Near-Infrared Spectroscopy (NIRS)

Near-infrared spectroscopy (NIRS) monitoring is a technique that involves placing a sensor on the patient's skin, allowing for measurement of capillary oxyhemoglobin saturation based on the physics of light scatter and its differential absorptive properties. Unlike pulse oximetry, NIRS is not dependent on a pulsatile arterial signal, but instead reports an averaged concentration of hemoglobin saturation based on the absorption spectrum in the tissue region in proximity to the cutaneous sensor. The oxyhemoglobin present in the arterial system of tissues absorbs light between wavelengths of 800 and 850 nm. In contrast, deoxygenated hemoglobin, which absorbs light at a wavelength between 650 and 800 nanometers (nm) predominates because

of substantially larger venous capacitance and hence the NIRS reading will reflect a venous-weighted saturation (Ghanayem et al. 2011; Drayna et al. 2011).

NIRS monitoring has most commonly been used as surrogate to measure regional perfusion and oxygenation of end organs, especially the brain. Much of the early use of cerebral NIRS monitoring occurred in the perioperative setting of children undergoing corrective repair of congenital heart defects who required cardiopulmonary bypass (Ghanayem et al. 2011). Normative values have been established for various ages using comparative values to jugular venous bulb oxygen saturations, as this is a proxy for cerebral venous circulation returning to the central venous circulation (Drayna et al. 2011).

Monitoring NIRS trends rather than a single value allows for interpretation of real-time physiological changes, thus enabling timely therapeutic responses as opposed to the usual practice of relying on the results of laboratory or other diagnostic tests, which are usually delayed. Downward trending NIRS values (or saturations) are often indicative of clinical conditions involving increased oxygen extraction, such as hypermetabolic states, or conditions in which there is overall hypoperfusion or a low-flow perfusion state. Abnormally elevated NIRS values (or saturations) may represent clinical conditions in which there is decreased ability of the body to extract oxygen or inability of the body to utilize oxygen effectively. Further research is required to establish “critical values” that require immediate diagnostic or therapeutic interventions (Drayna et al. 2011).

NIRS monitoring is most commonly used for cerebral monitoring in critically ill children, such as neonates who have suffered birth asphyxia and post-operative cardiac surgical patients to ensure adequate cerebral perfusion to assist in preventing secondary hypoxic brain injury. Ongoing validation of cerebral NIRS monitoring in post-cardiac arrest patients with return of spontaneous circulation may provide useful information about management and prognosis of long-term neurodevelopmental outcomes (Ghanayem et al. 2011). The use of cerebral NIRS monitoring for patients

who have suffered traumatic brain injuries (TBI), global hypoperfused shock states, and for prediction of cerebral edema in patients with diabetic ketoacidosis awaits more information (Drayna et al. 2011).

NIRS provides data related to regional oximetry, rather than global oxygenation/perfusion status and hence clinical decisions should not be based solely on NIRS data. Rather, NIRS data is useful but should be interpreted in the context of the clinical status and other variables indicating pathophysiology. In addition, more needs to be done to determine what constitutes a “critical value” that requires immediate intervention, as well as to define targeted patient outcome measures related to NIRS monitoring.

Capnography

Recent advances have led to widespread use of end-tidal CO₂ monitoring of mechanically ventilated patients. End-tidal CO₂ monitoring, or time-based capnography, remains the gold standard for confirming proper placement of endotracheal tubes in patients. Other recently adopted use of end-tidal CO₂ monitoring include its use during active cardiopulmonary resuscitation in order to guide effective resuscitation efforts, given that the presence of significant end-tidal CO₂ values serve as a proxy for the adequacy of pulmonary blood flow as a result of high-quality chest compressions.

The use of volumetric capnography to monitor mechanically ventilated patients is being explored in critically ill patients (Blanch et al. 2006; Suarez-Sipmann et al. 2014; Cheifetz 2013). Volumetric capnography represents the amount of CO₂ expired as a total volume in a single breath. Given that volumetric capnography is not simply reflective of one specific time point during expiration, but instead is reflective of all phases of expiration, it allows for more in depth real-time analysis of a patient’s physiologic status and ability to achieve adequate gas exchange (Blanch et al. 2006; Suarez-Sipmann et al. 2014). It also allows for the assessment of total dead space ventilation (anatomic and physiologic) and

the ratio between the amount of dead space ventilation and the amount of total tidal ventilation (V_d/V_t) (Cheifetz 2013). This ratio can be trended over time in patients as a marker of changes in pulmonary compliance, which in turn may help influence real-time ventilator parameter changes in patients with severe lung disease. Volumetric capnography may potentially improve patient outcomes in those with acute lung injury, may assist in safer, more effective ventilator weaning, and predict extubation success and avoid the need for reintubation (Cheifetz 2013). Volumetric capnography may be a surrogate monitor of pulmonary blood flow in patients with stable minute ventilation who lack severe lung injury. As such, it may prove to be useful for monitoring patients with pulmonary vascular disease like pulmonary hypertension or pulmonary embolism, or as a proxy for low cardiac output states (Cheifetz 2013).

Continuous EEG

The use of continuous EEG (cEEG) monitoring has become increasingly prevalent in pediatric intensive care units especially in large academic medical centers with the considerable personnel and resources required. The common indications for use aside from generalized status epilepticus include altered mental status and other acute neurological deficits (Sanchez et al. 2013). Continuous EEG monitoring has benefits of gathering more than one time point of data, perhaps allowing for more timely diagnostic and management interventions and potentially the broader ability to standardize care for various neurological conditions, such as status epilepticus, that may result in improved patient outcomes.

Bioinformatics

The field of bioinformatics has emerged over the last decade and continues to evolve rapidly as computer hardware and software, patient monitoring devices, and web-based technologies improve. Many hospitals have adopted some

form of electronic medical record, which serves as a data storage platform of patient information to assist in the clinician decision support when ordering diagnostic procedures, medications, and other therapeutic interventions. The use of computerize physician order entry has been helpful in reducing prescribing errors (Grinspan et al. 2014). Patient monitors are increasingly compatible for integration with the electronic medical record such that patient vital signs trends can be incorporated directly from the monitor. Clinical-decision support tools can also be regularly configured into many electronic medical records, which can help prompt clinicians to review particular trends or alert clinicians to changes in a patient's clinical status or trajectory. Together these advances in bioinformatics, data collection and storage will help to promote safe and effective care for critically ill patients, allowing for access of real-time data and trends to assist in clinical decision making.

Ultrasound

Bedside ultrasound technology has improved dramatically over the last several years in terms of higher resolution image quality, smaller, more portable machines, and improved usability interfaces. Pediatric critical care providers are increasingly using ultrasound equipment to assist in the proper placement of central venous catheters (Srinivasan and Cornell 2011; Su et al. 2014; Lau and Chamberlain 2016). Dynamic ultrasound has superseded the traditional landmark identification techniques and is used universally to teach residents and fellows to place central lines. In children, vascular landmarks may be difficult to identify because of size, body habitus, and/or overall hemodynamic status, hence, direct vessel visualization by ultrasound during procedural placement is useful. The use of bedside ultrasound for central venous access and catheter placement improves safety, time to successful placement, and reduces procedural-associated complications (Lau and Chamberlain 2016).

Bedside ultrasound is now being used in arterial line placement, as well as evaluation a

patient's hemodynamic status, presence of pneumothorax, or pleural fluid assessment (Srinivasan and Cornell 2011; Su et al. 2014). Bedside ultrasound findings may corroborate suspicions based on clinical grounds and hence allow for timely therapy, suggest further tests and enable serial assessment of patient status. However, its potential in informing these clinical decisions with great certainty are not fully evaluated and thus caution is advised.

Standardized educational modules to certify pediatric critical care physicians in this skill remain in their infancy. Short, intensive, courses focused on the ultrasound physics, operator use and interpretation are becoming more common at national societal meetings in critical care and emergency care. There are emerging, intensive 1–2 day “boot-camp” type of educational training environments aimed at certification upon completion (Conlon et al. 2015), but overall the field lacks definitive criteria for what it means to be “competent” in bedside ultrasound use and interpretation.

Organ Systems-Based Updates

Neurology

Traumatic Brain Injury

Severe pediatric traumatic brain injury is defined as a patient with a Glasgow Coma Scale (GCS) ≤ 9 in the context of traumatic injury mechanism and is associated with high morbidity and mortality. Much research in the last decade has focused on the understanding of the pathophysiology and management of severe traumatic brain injury with the goal of optimizing both short- and long-term neurodevelopmental outcomes. In 2012, the second edition of the “Guidelines for the Acute Medical Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents” replaced that from 2003 (Kochanek et al. 2012). Primary changes in this edition were updates based on new evidence regarding the use of hypothermia, revised cerebral perfusion pressure targets by age, advances in brain tissue monitoring, and other targeted

management strategies at optimizing cerebral perfusion pressure and minimizing increased intracranial pressure. Overall there remains a lack of strong, high quality evidence on this topic of severe pediatric traumatic brain injury, such that many of the guidelines are based of less rigorous study designs (prospective and retrospective cohort data) (Kochanek et al. 2012).

Key guidelines to highlight include that active cooling to a temperature between 32 and 34°C (moderate hypothermia) should be avoided in children with severe traumatic brain injury within the initial 24 h of admission (Kochanek et al. 2012; Bell and Kochanek 2013). However, if there is severe intracranial hypertension associated with the traumatic brain injury, targeting moderate hypothermia starting 8 h post-injury to no longer than 48 h post-injury may be considered to reduce further intracranial hypertension. If moderate hypothermia is initiated, the guidelines recommend rewarming slowly to normothermia; that is, at a rate no greater than 0.5°C per hour (Kochanek et al. 2012; Bell and Kochanek 2013).

These updated guidelines continue to support the use of hypertonic saline (3%) as hyperosmolar therapy to reduce increased intracranial pressure associated with severe traumatic brain injury in the acute phase of illness (Kochanek et al. 2012; Bell and Kochanek 2013). Benefits of hypertonic saline use include establishing a euvolemic fluid balance, given that sodium is a volume expander, as opposed to mannitol, which while effective in treating cerebral edema also promotes an osmotic diuresis and hypovolemia which can decrease cerebral perfusion pressure. Hypertonic saline is also less toxic to the kidneys, and thus a higher serum osmolarity can be tolerated (360 mOsm/kg) as opposed to mannitol. However, evidence against the use of mannitol in the management of acute intracranial hypertension and severe traumatic brain injury is weak, and thus one must weigh the risks and benefits based on the clinical context. Evidence supporting specific doses of 3% saline is also weak, but there is stronger evidence to support the use of bolus doses as opposed to continuous infusions (Kochanek et al. 2012; Bell and Kochanek 2013).

The updated guidelines additionally provide weak evidence for the avoidance of steroids, avoidance of use of an immune-modulating diet, and avoidance of hyperventilation ($\text{PaCO}_2 < 30$ mmHg). Weak evidence supported the modification of cerebral perfusion pressure targets to consider maintaining a cerebral perfusion pressure of at least 40 mmHg, with a range of 40–65 mmHg representing an optimal continuum for various ages of pediatric patients (Kochanek et al. 2012; Bell and Kochanek 2013).

Delirium

Delirium in critically ill children is challenging to define, which in turn leads to challenges in monitoring and treatment. The current gold-standard diagnosis of pediatric delirium is very similar to adult criteria. However, as compared to adults, children have unique developmental, language, and cognitive stages that affect their behavior and influence their ability to communicate and interact with healthcare providers. As such, pediatric delirium is most likely underdiagnosed and requires further study and validation of tools to use for diagnosis and monitoring in order to better characterize its incidence and prevalence. This is a necessary needed first step to further investigate and characterize how patient outcomes are affected by delirium and in developing standardized approaches to diagnosis and management.

Several validated screening tools (Smith et al. 2011, 2016a; Traube et al. 2014) have recently been published to assist in diagnosing pediatric delirium. These tools have been adapted from existing adult-related screening tools and tailored to children to accommodate developmental differences. These tools are based on subjective and/or objective measures that can be documented during routine nursing assessment of critically ill patients. Each tool has been validated with high sensitivity with varying degrees of specificity for delirium. Specific screening tools that have been recently validated include the Pediatric Confusion Assessment Method (Smith et al. 2011) (pCAM-ICU), targeted at critically ill children greater than 5 years old, the Preschool Confusion

Assessment Method (Smith et al. 2016a) (psCAM-ICU), targeted specifically at children 6 months to 5 years of age, and the Cornell Assessment for Pediatric Delirium (Traube et al. 2014) (CAPD), targeted at various ages from newborn to adolescence.

The pCAM-ICU and ps-CAM are variations of the same screening tool with age-specific criteria for assessing four main categories: acute change in baseline mental status, presence of inattentive behaviors, overall level of alertness, and other abnormal behaviors from baseline including sleep-wake cycle disturbances, or the presence of irritability or confusion. The presence of an acute change in baseline mental status plus the presence of inattentive behaviors and either a change in level of alertness or presence of other abnormal behaviors as mentioned above are highly suggestive of a diagnosis of delirium (Smith et al. 2011, 2016a).

The CAPD tool was designed to screen for all types of delirium, including hyperactive, hypoactive, and mixed types of delirium. This screening tool includes specific anchored statements for what constitutes normal development at various ages in order to assist users in rating deviation from normal developmental behaviors. The screening questions are categorized within the major domains of delirium encountered in the DSM-IV manual: level of consciousness, cognitive ability, psychomotor activity, overall affect or level of distress (Traube et al. 2014).

Delirium management in the pediatric intensive care unit requires ongoing study for optimal and standardized treatment approaches. The hallmarks of treatment remain the identification and treatment of any underlying non-psychological causes, e.g. electrolyte derangements, infection, followed by implementation of non-pharmacological strategies that normalize the surrounding environment, including establishing routine schedules and constant re-orientation to surroundings and timing, followed by use of pharmacological strategies, especially for patients who remain agitated (Van Tuijl et al. 2015). Many of the specific agents used are “off-label” for pediatric patients, and thus there is not consensus across PICUs as to which agents to utilize first.

Status Epilepticus

Status epilepticus is a common pediatric neurological emergency encountered in the PICU. According to guidelines from the Neurocritical Care Society (Abend et al. 2014), refractory status epilepticus is considered present once an appropriate initial dose of benzodiazepine has been administered followed by a second anti-seizure medication, regardless of time of patient's seizure. This includes the presence of either clinical seizures or electrographic seizures after initial medication administration.

Many institutions have protocolled approaches to the management of status epilepticus, including immediate assessment and stabilization of airway, breathing, and circulation, followed by immediate administration of a short-acting benzodiazepine, and subsequent specified time points at which the administration of additional anti-seizure medications are indicated (Smith et al. 2016b). More focus in recent years has been on determining a protocolled management approach for the timely and aggressive treatment of refractory status epilepticus in order to prevent ongoing morbidities and avoid permanent neurological sequelae. The Neurocritical Care Society currently recommends an aggressive stepwise pharmacological approach that rapidly progresses to pharmacological coma (Abend et al. 2014). Advances in neurological monitoring, specifically continuous EEG monitoring, has allowed for timely and aggressive up-titration of pharmacological therapies at the bedside. Two agents most commonly used in the treatment of refractory status epilepticus include continuous midazolam infusions and pentobarbital infusions, both initiated and up-titrated with bolus dosing in order to achieve rapid serum drug levels. Therapeutic goals of these medications target either clinical seizure resolution, electrographic seizure resolution, or burst suppression on cEEG, based on clinical setting and severity (Abend et al. 2014). Consensus continues to lack regarding the duration of these therapies for treatment of refractory status epilepticus. Generally, these therapies should be continued for 24–48 h after achievement of seizure resolution (or burst suppression) prior to consideration of weaning

(Abend et al. 2014). Critically ill patients with refractory status epilepticus will often require intubation and mechanical ventilation for airway protection and require close monitoring for hypotension.

Respiratory

Acute Respiratory Distress Syndrome (ARDS)

Acute lung injury (ALI) and Acute Respiratory Distress Syndrome (ARDS) remain prevalent conditions that contribute significant morbidity and mortality across PICUs worldwide. Defining ARDS for the pediatric population continues to be a challenge. Current definitions are extrapolated from the adult literature. A new set of criteria for ARDS in adults, the Berlin definition, was introduced in 2011 (ARDS Definition Task Force 2012). The Berlin definition of ARDS reclassified ALI and ARDS into mild, moderate and severe, with mild ARDS being, the older American-European Consensus Committee (AECC) definition of ALI. In this classification scheme, patients are still classified based on the ratio between arterial partial pressure of oxygen (PaO_2) to the amount of supplemental inspired oxygen (FiO_2), but also taking into account the amount of PEEP patients are receiving at the time of calculating the P/F ratio. Similar to the AECC definition, the lung injury insult must occur within 7 days of onset, be accompanied by new infiltrates on chest imaging, and have no contribution from high left atrial pressures.

The Pediatric Acute Lung Injury and Sepsis committee group on ARDS has developed consensus recommendations (The Pediatric Acute Lung Injury Consensus Conference Group 2015) based on the adult and pediatric data for the diagnosis and management of pediatric ARDS. The consensus group agreed with adult recommendations that the inciting event leading to lung injury occurs within 7 days of illness, radiographic findings consistent with new parenchymal lung disease must be present, and there must be absence of a cardiac etiology explaining

hypoxemia (The Pediatric Acute Lung Injury Consensus Conference Group 2015).

The PALISI guidelines also clarify that particular groups of pediatric patients who have other reasons for hypoxemia or may have some degree of baseline hypoxemia, such as cyanotic congenital heart disease, or chronic lung disease can also develop ARDS if they fit the criteria of acute onset of illness, new radiographic findings, and lack of worsening underlying etiology as the cause of hypoxemia (The Pediatric Acute Lung Injury Consensus Conference Group 2015).

Despite the common practice of PICU clinicians using P/F ratios in the severity diagnosis of ARDS, the consensus group recommends trending the oxygenation index (OI) as opposed to the P/F ratio to quantify the severity of illness of mechanically ventilated patients with ARDS (The Pediatric Acute Lung Injury Consensus Conference Group 2015). The OI is defined as $[(MAP * FiO_2)/PaO_2]$, where MAP = mean airway pressure, FiO_2 = amount of inspiratory oxygen, and PaO_2 = partial pressure of arterial oxygen. The suggestion to trend the OIs in mechanically ventilated patients is based on the fact that the amount of mean airway pressure required to effectively oxygenate and ventilate the patient is more reflective of disease severity.

General invasive mechanical ventilation guidelines and therapeutic strategies for pediatric ARDS continue to be extrapolated from adult data because of limited data in children. Thus, the pediatric guidelines are based on weak consensus. However, the general standard of care involves avoidance of ventilator-induced trauma, by using low tidal volume ventilation (5–7 mL/kg) and accepting permissive hypercapnea, and using high-PEEP (typically >10 cmH₂O) strategies to avoid high peak inspiratory and plateau pressures while targeting oxygen saturations between 88 and 92%. Permissive hypercapnea goals involve tolerating a serum pH range of 7.15–7.30, as long as the patient does not have other underlying comorbidities that would require a higher pH (e.g. pulmonary hypertension, cardiac dysfunction, increased intracranial pressure) (The Pediatric Acute Lung Injury Consensus Conference Group 2015).

There is no data to support the use of sustained ventilator recruitment maneuvers, i.e. using high ventilator pressures for a brief period of time to try to open atelectatic areas of lung in order to improve gas exchange (The Pediatric Acute Lung Injury Consensus Conference Group 2015). Thus, these maneuvers have largely fallen out of favor in the routine approach in treating patients with severe ARDS. High frequency oscillatory ventilation (HFOV) remains an alternative mode of ventilation for patients with severe, sustained, hypoxemia. Use of HFOV and stepwise titration of mean airway pressure requires close monitoring of patient vital signs and serum blood gases given that the clinical respiratory and cardiac exam is difficult to assess in these patients.

Other strategies that are beneficial in managing patients with ARDS include adequate sedation and possible use of muscle relaxation in order to optimize gas exchange and patient tolerance of high ventilator settings, providing adequate nutrition, and avoiding excessive fluid intake once patients have been adequately fluid resuscitated and have a stable hemodynamic profile (The Pediatric Acute Lung Injury Consensus Conference Group 2015).

Although commonly used, there is minimal data to support the use of inhaled nitric oxide, prone positioning, and steroid use (The Pediatric Acute Lung Injury Consensus Conference Group 2015). Finally, in patients with severe ARDS and the inability to oxygenate or ventilate effectively, consideration of extracorporeal support should be considered.

Cardiology

Cardiopulmonary Resuscitation

Pediatric Advanced Life Support (de Caen et al. 2015) (PALS) has undergone two recent guidelines revisions, 2010 and 2015. The major focus in teaching effective cardiopulmonary resuscitation continues to be the delivery of high-quality chest compressions, as this has been demonstrated to improve patient survival rates. Given this fact and the recently updated adult guidelines, the pediat-

ric basic life support (BLS) algorithm order was changed from A-B-C (airway-breathing-circulation) to C-A-B (circulation-airway-breathing) in 2010. Adults experiencing out of hospital cardiac arrests typically result from a cardiac etiology, and thus the timing and delivery of optimal chest compressions is key to the return of spontaneous circulation and ultimately survival, inciting this change in the BLS guidelines. Recognizing that many out-of-hospital and in-hospital cardiac arrests in children are more often the result of a respiratory etiology, the pediatric resuscitation guidelines continues to emphasis the importance of rescue breaths in addition to providing timely, high-quality chest compressions (de Caen et al. 2015).

High-quality CPR in children entails delivering chest compressions at a rate between 100 and 120 compressions per minute, compressing at a depth of at least 1/3 anterior-posterior chest diameter, allowing full chest recoil between individual compressions, minimizing interruptions in chest compressions, avoiding excessive respirations during chest compressions, and avoiding compressor fatigue by switching compressors at least every two minute cycle of CPR. The recommended ratio of chest compressions to rescue breaths for pediatric CPR has not changed from prior guidelines, and remain 15:2 for a two-person resuscitation, 30:2 for a single-person resuscitation, and continuous chest compressions with 8–10 breaths per minute when advanced airways are present (de Caen et al. 2015).

Post-cardiac Arrest Management

The 2015 American Heart Association (AHA)/ Pediatric Advanced Life Support (PALS) updated the guidelines for the management of the arrest victim after return of spontaneous circulation (ROSC) has been achieved. These guidelines incorporate the most recent findings from post-ROSC studies performed on targeted temperature management in children after out of hospital cardiac arrest, where death and disabilities were similar in children who were actively cooled between 32 and 34°C to those who had tempera-

tures maintained between 36 and 37°C (Moler et al. 2015). The AHA/PALS guidelines suggest the avoidance of fever, but more specifically comment that for comatose children post-ROSC who suffered an out-of-hospital cardiac arrest, core temperature management should involve either targeting normothermia (36–37°C) for 5 days, or targeting moderate hypothermia (32–34°C) for 2 days, followed by normothermia for 3 days post-out of hospital cardiac arrest (de Caen et al. 2015; Moler et al. 2015). There is not enough evidence to provide specific guidelines for pediatric patients who suffer in-hospital cardiac arrest with ROSC at this current time, but many clinicians generally avoid fever in this context.

Other pediatric post-cardiac arrest guidelines recommend avoiding hyperoxia by targeting oxygen saturations of 94–99% post-ROSC. Excessive oxygen administration can lead to the development of free radicals and further oxidative stress, which can cause long-term tissue damage and negatively affect end-organ function. Hypotension should also be avoided, by maintaining blood pressure at least 5% of normal for age and height using fluids and vasoactive agents as indicated in order to support optimal end-organ perfusion. Hypocarbia and hypercarbia should be avoided, and the current guidelines suggest setting specific pCO₂ targets based on patients' underlying clinical conditions prior to cardiac arrest (de Caen et al. 2015).

Gastroenterology/Nutrition

Nutritional Guidelines

Critical illness is a significant stress on the body and as such is associated with lean muscle-mass breakdown and protein catabolism in the acute illness phase. Thus, optimal nutrition during critical illness is important to promote adequate healing and decrease morbidities associated with malnutrition (Mehta 2014). Standardized nutritional therapy is lacking in critically ill children based on a lack of large randomized clinical trials and varying practices across institutions. Despite this, the American

Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) published suggested guidelines in 2009 for an approach to delivering optimal nutrition in critically ill children (Mehta et al. 2009). These guidelines support the use of enteral nutrition as the preferred mode of nutrient delivery in those children with a functioning gastrointestinal tract. The optimal timing and mode of delivery (gastric versus post-pyloric) for enteral nutrition is not settled. Generally, in children who were previously well-nourished, initiation of enteral nutrition can wait until 5–7 days into the acute illness (Mehta et al. 2009). However, recent literature investigating the use of early enteral nutrition (within 48 h of admission) suggests that there may be a decreased mortality benefit in those critically ill children who were previously well-nourished (Mikhaliyov et al. 2014). While this finding is encouraging, more research is needed to validate this finding.

Parenteral nutrition should be considered in those patients who are unable to tolerate enteral feeds or have other contraindications to enteral feeding, such as gastrointestinal surgery. A recent study comparing early initiation (within 48 h) of parenteral nutrition as compared to late initiation (after 1 week) showed no benefit to early initiation of parenteral nutrition (Fivez et al. 2016). Later initiation of parenteral nutrition was associated with fewer infections, shorter length of PICU stay and shorter length of overall hospital stay. PICU mortality was similar in both groups in this study (Fivez et al. 2016).

Indirect Calorimetry

Indirect calorimetry has become increasingly popular within PICUs to directly assess the amount of calories critically ill patients require in an attempt to avoid both under- and over-feeding. Under- and over-feeding are associated with poor healing, increased inflammation, or difficulty weaning from mechanical ventilation (Sion-Sarid et al. 2013). Other methods of estimating nutritional needs are based solely on mathematical equations related to resting energy expenditure. These formulas may over- or under-estimate

nutritional needs in critically ill children. In comparison, indirect calorimetry provides a window into more direct measurement of the amount of energy the patient is expending by directly measuring the amounts of oxygen consumed and carbon dioxide produced. This can be easily done in mechanically ventilated patients who have a closed ventilator circuit where oxygen can be measured via the inspiratory limb of the ventilator and carbon dioxide can be measured via the expiratory limb. These data can be used to calculate the respiratory quotient (R/Q), which can be used to help define the patients' nutritional status and assist in suggesting the amount of calories the patient actually needs for optimal nutrition (Sion-Sarid et al. 2013). Indirect calorimetry values should be followed over time, especially as the patient's clinical condition and illness trajectory change.

Glycemic Control

Hyperglycemia is commonly encountered in critically ill patients as part of the body's stress response to critical illness. Much has been investigated over recent years in regards to how aggressive to control blood glucose levels in the PICU in order to prevent morbidity and mortality associated with hyperglycemia. One of the major risks of tight glucose control in this setting is hypoglycemia, which can lead to seizures, among other neurological morbidities, and is also associated with an increased risk of mortality.

The benefits of tight glucose control in children in the setting of critical illness remains unclear, and there are ongoing studies to further investigate clinical outcomes associated with tight glucose control. The strongest consensus statement that currently exists recommends consideration of treating persistent hyperglycemia in critically ill children, as defined by serum blood glucose ≥ 180 –200 mg/dL, with an insulin infusion targeting a blood glucose range of 100–180 mg/dL in an attempt to avoid significant hypoglycemia (Jacobi et al. 2012). If an insulin infusion is initiated for tight glucose control, then frequent monitoring of blood glucose levels and patient's clinical status is essential.

Hematology

Transfusion Strategies

The decision to transfuse critically ill children based on varying degrees of anemia varies widely in clinical practice. Historically, targeting a hemoglobin (Hgb) level of 10 g/dL had been common practice in order to promote optimal oxygen delivery to ensure adequate tissue perfusion and oxygen utilization. A recent study found that a restrictive transfusion practice of transfusing to a Hgb of 7 g/dL was not inferior to transfusing to a level of 10 g/dL in stable, critically ill children, and in fact decreased exposure to blood products and the overall number of transfusions administered (Lacroix et al. 2007). Thus, the most recent guidelines and approach to packed red blood cell transfusions in stable, critically ill children favors a more restrictive transfusion practice in order to avoid unnecessary risks and complications associated with blood product transfusions. A lower transfusion threshold for critically ill children who are hemodynamically unstable, have evidence of acute blood loss, or have significant cyanotic congenital cardiac disease, among other specific clinical contexts is reasonable.

Transfusion practices for other blood products including platelets, coagulation factors, and leukocytes tend to vary based on the clinical context and the decision to transfuse under those circumstances requires clinician judgment as opposed to having any specific clinical values or guidelines associated with transfusion practices.

Thromboprophylaxis

Prophylaxis for deep venous thrombosis and pulmonary embolism in children has been a recent “hot topic” in the field of pediatric critical care. Thromboembolic disease is an underestimated complication in children and young adults, and decisions regarding appropriate prophylactic measures in the PICU setting varies across institutions. It is common practice for critically ill adults with no anticoagulation contraindications to receive pharmacological thromboprophylaxis with agents such as subcutaneous heparin or

enoxaparin. It remains unclear what populations of children should require pharmacological thromboprophylaxis in the critically ill setting, and ongoing research in this field is attempting to define current PICU practices in order to assist in forming more standardized clinical practice guidelines (Faustino et al. 2014).

Infectious Disease/Immunology

Sepsis

Sepsis and septic shock remain a major cause of morbidity and mortality in children worldwide. Much emphasis in recent years has been focused on understanding the epidemiology of sepsis, the molecular biology and immunology associated with the immune system and inflammatory cascade, defining clinical biomarkers and how the genotypic and phenotypic variation of these biomarkers in individuals may predispose them to varying disease susceptibility and host responses.

One major challenge over the last several decades has been lack of a unifying “diagnosis” of sepsis, as it encompasses a clinical syndrome as opposed to a specific single diagnostic entity. Therefore, the approach to finding diagnostic tests or identifying specific clinical biomarkers that can assist with early diagnosis and treatment remains a challenge.

Several groups have developed standardized guidelines to treat septic patients with early goal-directed therapies in order to improve morbidity and mortality (Rivers et al. 2001; Dellinger et al. 2013; Brierley et al. 2009). A consensus of pediatric sepsis investigators published the most recent pediatric “Surviving Sepsis Campaign” guidelines in 2012 (Dellinger et al. 2013). According to these guidelines, if there is concern for sepsis and impaired perfusion, up to a total of 60 mL/kg of fluid boluses administered in 20 mL/kg aliquots should be considered within the first 15 min of clinical presentation. Monitoring for response to fluid by observing clinical changes in vital signs and physical exam findings should occur in real-time to aid in consideration of fluid-responsiveness or not. Broad-spectrum antimicrobial therapy should also be administered

during this time as soon as possible (Dellinger et al. 2013; Brierley et al. 2009).

For those children who have received 60 mL/kg of normal saline boluses and continue to have evidence of impaired perfusion, then vasoactive support should be initiated, with further consideration of the need for invasive mechanical ventilation and invasive hemodynamic monitoring via central venous catheter placement (Dellinger et al. 2013; Brierley et al. 2009). Placement of central venous access allows monitoring of goal-directed targets, including mixed venous oxygen saturations and central venous pressure. Additional therapies, such as packed red blood cell transfusions and corticosteroids may be considered based on clinical setting and laboratory values. Refractory shock to all of the above therapies is a consideration for extracorporeal support, which requires transfer to a clinical facility with the resources to do so.

The approach to early-goal directed therapy has been called into question in resource-limited settings after results published in 2011 from the “Fluid Expansion as Supported Therapy” (FEAST) trial completed in sub-Saharan Africa (Maitland et al. 2011). Resource-limited settings often have poor access to ventilators and/or vasoactive medications, which must be taken into consideration in caring for children with sepsis who may have fluid-refractory shock, or develop capillary leak and edema exacerbated by fluid administration. The results of the FEAST trial demonstrated that children with febrile illnesses and some signs of impaired perfusion treated with fluid boluses on hospital admission (0.9% saline or 5% albumin in 20–40 mL/kg aliquots) had higher mortality rates at 48 h as compared to similar children who did not receive fluid boluses (Maitland et al. 2011).

Quality Improvement

Standardized Handover Tools

Suboptimal communication is one of the major factors contributing to medical errors and “near-miss” events. Sub-optimal communication is

common during the handover process of patient care from one healthcare provider to another. Standardized patient handovers are essential in high reliability environments such as the pediatric intensive care unit where patients are at high risk of potential complications related to their disease severity and complexity of care.

An approach to improve this area of communication has involved the development of a variety of standardized handover tools, based on specific clinical settings, in order to improve patient safety and outcomes. One such tool has been the standardization of postoperative handovers from patients in the operating room (or other procedural locations) and admission to the PICU. There is data to support that such a standardized handover tool has the ability to improve handover communication and improve patient outcomes by decreasing inaccuracies in information, and expediting patient care activities, such as timely analgesia administration without unnecessarily prolonging the handover communication (Breuer et al. 2015). The communication tool involves standardizing a format in what information is given in a systematic order while allowing for clarifying questions on the receiving end, and summarized by a brief verbal feedback of information received to ensure all information was communicated correctly (Breuer et al. 2015). Ongoing research in this area continues to focus on developing and validating these types of standardized handover tools for all environments and transfer of care between varying hospital environments.

Pediatric Early Warning Scores

Pediatric early warning scores (PEWS) have been incorporated into routine bedside monitoring of inpatient pediatric ward patients across many hospitals. Pediatric early warning scores were developed as an objective screening tool for the early detection of hospitalized patients at high risk of cardiopulmonary decompensation in an attempt to improve patient safety and decrease rates of out-of-PICU in-hospital cardiopulmonary arrests (Akre et al. 2010). PEWS classifies

information from three domains of the patients clinical status: behavioral, cardiovascular, and respiratory into a composite score to determine when care should be escalated (Akre et al. 2010). In general, the “higher” the score, the more severe deviation are the patient’s vitals and clinical status from baseline, and thus the patient is likely at higher risk of experiencing critical deterioration. Many institutions have also incorporated a subjective element to the scoring system involved adding various points for family or staff concerns about the patient’s clinical status (Akre et al. 2010).

More recent research regarding the use PEWS scores has validated the use of these scores in specific sub-specialty populations of pediatric patients, such as the cardiac (McLellan et al. 2014) and oncology (Agulnik et al. 2016) populations, with or without minor modifications made to the score based on the normal vital sign values found within that specific patient population. Additional studies are being done to extrapolate and validate the use of PEWS in other areas throughout the hospital, including the emergency room and operating room settings.

Patient Care Bundles

Many patient safety initiatives over the years have encouraged the development of protocolized patient care bundles targeted at many preventable adverse events, such as catheter-associated blood stream infections (CLABSI), catheter-associated urinary tract infections (CAUTI), ventilator-associated pneumonias (VAP), among others. Protocols for central line placement, hand hygiene practices, urinary catheter care, etc., have been well validated and implemented as the standard of care across many PICUs. Implementation of such patient care bundles has universally demonstrated reduction in the associated morbidity.

Furthermore, technology advances have provided a unique opportunity to incorporate checklists associated with these protocols into the electronic medical record. The introduction of a CLABSI checklist within an electronic medical

record provided a visual dashboard for all health-care providers to see and track patients in their unit, leading towards increase compliance in the use of these bundles and demonstrated sustained decreased rates of CLABSIs (Pageler et al. 2014). This specific CLABSI checklist also alerted providers to the number of days in which the current line had been in place, as an added reminder to review the necessity of central line access daily with the goal of removing the line as soon as possible (Pageler et al. 2014).

Education

Courses

Many formal courses exist for training health care providers’ knowledge, behaviors, and skills relevant for pediatric critical care medicine. Pediatric Advanced Life Support (PALS), European Pediatric Advanced Life Support (EPALS), Advanced Pediatric Life Support (APLS), and Pediatric Advanced Emergency Assessment, Recognition and Stabilization (PEARS) are examples of these types of courses that are delivered, often to teams, and may be a part of required credentialing practice for health care professionals caring for critically ill children. In the lower resource setting, Emergency Triage Assessment at Treatment (ETAT) may be delivered. These courses cover assessment, basic life support (including cardiopulmonary resuscitation), treatment algorithms, teamwork, and communication. Over the past decade, Pediatric Fundamental Critical Care Support (PFCCS) and Paediatric BASIC have been developed to train more advanced skills including mechanical ventilation, and management of specific pediatric critical conditions (i.e. congenital heart disease, traumatic brain injury).

Simulation

The use of simulation for training in the pediatric critical care environment has undergone dramatic growth in the past decade. Simulation training

has shown improvement in knowledge, skills and behaviors across health care professions (O’Leary et al. 2015) and in a variety of topics in skills training (Jeffers et al. 2016), mock scenarios (Dugan et al. 2016), teamwork (crisis resource management) (Figuroa et al. 2013), boot camps (Nishisaki et al. 2009), and just-in-time training (Scholtz et al. 2013). Manikin fidelity and debriefing techniques differ between each type of simulation. Current research efforts focus on understanding optimal integration of simulation activities into an education curriculum, defining appropriate debriefing techniques, determining the frequency of simulation retraining for optimal retention, developing standardized assessment strategies, and utilizing emerging innovations, such as 3D printing, into practice.

E-Learning

E-learning is another area that has been rapidly developing to meet demands from emerging pressures in health professionals education globally. Advances in information technology and sharing of educational resources has been cited as a way to strengthen the education of health professionals (Frenk et al. 2010). Many online resources currently exist that include content relevant for pediatric critical care medicine (Kleinpell et al. 2011), including two websites specifically designed for pediatric critical care providers, [PedsCCM.org](http://www.pedsccm.org) (www.pedsccm.org) and [OPENPediatrics](http://www.openpediatrics.org) (www.openpediatrics.org) (Wolbrink et al. 2014).

E-learning technologies have been rapidly advancing in quality, interactivity, and fidelity. E-learning resources have been used as stand-alone educational materials (online text, videos, curricula, games, simulations) for a wide variety of topics, and have also been incorporated into blended learning models. As an example of a blended learning model, Basic Life Support courses now use an online simulator combined with in-person skills training, which has demonstrated improvement in learners’ basic CPR skills in comparison to those

who took a traditional instructor-led course (Kardong-Edgren et al. 2010).

Despite these rapidly evolving technologies, much work is still needed to better understand optimal e-learning practices. Current research efforts focus on investigating optimal e-learning design and implementation, integration of e-learning activities into an educational curriculum, knowledge retention following e-learning activities, and translation of learning into clinical practice.

Conclusion

The topics discussed here represent a sample of the most recent and impactful updates in pediatric critical care that have either improved patient outcomes, or represent encouraging advances and further areas of study that will assist in providing safe, efficacious, timely, and equitable patient care.

Acknowledgements Declared none.

Conflict of Interest The author(s) confirm that this chapter contents have no conflict of interest.

References

- Abend NS, Bearden D, Helbig I, et al. Status epilepticus and refractory status epilepticus management. *Semin Pediatr Neurol.* 2014;21:263–74.
- Agulnik A, Forbes PN, Stenquist N, et al. Validation of a Pediatric Early Warning Score in hospitalized pediatric oncology and hematopoietic stem cell transplant patients. *Pediatr Crit Care Med.* 2016;17(4): e146–53.
- Akre M, Finkelstein M, Erickson M, et al. Sensitivity of the Pediatric Early Warning Score to identify patient deterioration. *Pediatrics.* 2010;125:e763–9.
- ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin definition. *JAMA.* 2012;307(23):2526–33.
- Bell MJ, Kochanek PM. Pediatric traumatic brain injury in 2012: the year with new guidelines and common data elements. *Crit Care Clin.* 2013;29(2):223–38.
- Blanch L, Romero PV, Lucangelo U. Volumetric capnography in the mechanically ventilated patient. *Minerva Anesthesiol.* 2006;72:577–85.
- Breuer RK, Taicher B, Turner DA, et al. Standardizing postoperative PICU handovers improves handover metrics and patient outcomes. *Pediatr Crit Care Med.* 2015;16:256–63.

- Brierley J, Carcillo JA, Choong K, et al. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. *Crit Care Med*. 2009;37(2):666–88.
- Cheifetz IM. Advances in monitoring and management of pediatric acute lung injury. *Pediatr Clin N Am*. 2013;60:621–39.
- Conlon TW, Himebauch AS, Fitzgerald JC, et al. Implementation of a pediatric critical care focused bedside ultrasound training program in a large academic PICU. *Pediatr Crit Care Med*. 2015;16(3):219–26.
- de Caen AR, Berg MD, Chameides L, Gooden CK, Hickey RW, Scott HF, Sutton RM, Tijssen JA, Topjian A, van der Jagt E, Schexnayder SM, Samson RA. Part 12: pediatric advanced life support: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2015;132(Suppl 2):S526–42.
- Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med*. 2013;39:165–228.
- Drayna PC, Abramo TJ, Estrada C. Near-infrared spectroscopy in the critical setting. *Pediatr Emerg Care*. 2011;27(5):432–9.
- Dugan MC, McCracken CE, Hebbar KB. Does simulation improve recognition and management of pediatric septic shock, and if one simulation is good, is more simulation better? *Pediatr Crit Care Med*. 2016;17(7):605–14.
- Faustino EVS, Hanson S, Spinella PC, et al. A multinational study of thromboprophylaxis practice in critically ill children. *Crit Care Med*. 2014;42(5):1232–40.
- Figueroa MI, Sepanski R, Goldberg SP, Shah S. Improving teamwork, confidence, and collaboration among members of a pediatric cardiovascular intensive care unit multidisciplinary team using simulation-based team training. *Pediatr Cardiol*. 2013;34(3):612–9.
- Fivez T, Kerklaan D, Mesotten D, et al. Early versus late parenteral nutrition in critically ill children. *N Engl J Med*. 2016;374(12):1111–22.
- Frenk J, Chen L, Bhutta ZA, et al. Health professionals for a new century: transforming education to strengthen health systems in an interdependent world. *Lancet*. 2010;376(9756):1923–58.
- Ghanayem NS, Wernovsky G, Hoffman GM. Near-infrared spectroscopy as a hemodynamic monitor in critical illness. *Pediatr Crit Care Med*. 2011;12(4 Suppl):S27–32.
- Grinspan ZM, Pon S, Greenfield JP, et al. Multimodal monitoring in the pediatric intensive care unit: new modalities and informatics challenges. *Semin Pediatr Neurol*. 2014;21:291–8.
- Jacobi J, et al. Guidelines for the use of an insulin infusion for the management of hyperglycemia in critically ill patients. *Crit Care Med*. 2012;40(12):3251–76.
- Jeffers J, Eppich W, Trainor J, Mobley B, Adler M. Development and evaluation of a learning intervention targeting first-year resident defibrillation skills. *Pediatr Emerg Care*. 2016;32(4):210–6.
- Kardong-Edgren SE, Oermann MH, Odom-Maryon T, Ha Y. Comparison of two instructional modalities for nursing student CPR skill acquisition. *Resuscitation*. 2010;81(8):1019–24.
- Kleinpell R, Ely EW, Williams G, Liolios A, Ward N, Tisherman SA. Web-based resources for critical care education. *Crit Care Med*. 2011;39(3):541–53.
- Kochanek PM, Carney N, Adelson PD, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents—second edition. *Pediatr Crit Care Med*. 2012;13(Suppl 1):S1–82.
- Lacroix J, Hebert PC, Hutchison JS, et al. Transfusion strategies for patients in pediatric intensive care units. *N Engl J Med*. 2007;356(16):1609–18.
- Lau CS, Chamberlain RS. Ultrasound-guided central venous catheter placement increases success rates in pediatric patients: a meta-analysis. *Pediatr Res*. 2016;80(2):178–84.
- Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. *N Engl J Med*. 2011;364(26):2483–95.
- McLellan MC, Gauvreau K, Connor JA. Validation of the Cardiac Children’s Hospital Early Warning Score: an early warning score tool to prevent cardiopulmonary arrests in children with heart disease. *Congenit Heart Dis*. 2014;9(3):194–202.
- Mehta NM. Feeding the gut during critical illness—it is about time. *J Parenter Enteral Nutr*. 2014;38(4):410–4.
- Mehta NM, Compher C, A.S.P.E.N. Board of Directors. A.S.P.E.N. Clinical guidelines: nutrition support of the critically ill child. *J Parenter Enteral Nutr*. 2009;33(3):260–76.
- Mikhailov TA, Kuhn EM, Manzi J, et al. Early enteral nutrition is associated with lower mortality in children. *J Parenter Enteral Nutr*. 2014;38(4):459–66.
- Moler FW, Silverstein FS, Holubkov R, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest in children. *N Engl J Med*. 2015;372(29):1898–908.
- Nishisaki A, Hales R, Biagas K, et al. A multi-institutional high-fidelity simulation “boot camp” orientation and training program for first year pediatric critical care fellows. *Pediatr Crit Care Med*. 2009;10(2):157–62.
- O’Leary JA, Nash R, Lewis PA. High fidelity patient simulation as an educational tool in paediatric intensive care: a systematic review. *Nurse Educ Today*. 2015;35(10):e8–12.
- Pageler NM, Longhurst CA, Wood M, et al. Use of electronic medical record-enhanced checklist and electronic dashboard to decrease CLASBIs. *Pediatrics*. 2014;133:e738–46.
- Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345(19):1368–77.
- Sanchez SM, Carpenter J, Chapman KE, et al. Pediatric ICU EEG monitoring: current resources and practice

- in the United States and Canada. *J Clin Neurophysiol*. 2013;30:156–60.
- Scholtz AK, Monachino AM, Nishisaki A, Nadkarni VM, Lengetti E. Central venous catheter dress rehearsals: translating simulation training to patient care and outcomes. *Simul Healthc*. 2013;8(5):341–9.
- Sion-Sarid R, Cohen J, Houry Z, Singer P. Indirect calorimetry: a guide for optimizing nutritional support in the critically ill child. *Nutrition*. 2013;29:1094–9.
- Smith HAB, Boyd J, Fuchs C, et al. Diagnosing delirium in critically ill children: validity and reliability of the Pediatric Confusion Assessment Method for the intensive care unit*. *Crit Care Med*. 2011;39(1):150–7.
- Smith HAB, Gangopadhyay M, Goben CM, et al. The pre-school confusion assessment method for the ICU: valid and reliable delirium monitoring for critically ill infants and children*. *Crit Care Med*. 2016a;44:592–600.
- Smith DM, McGinnis EL, Walleigh DJ, Abend NS. Management of status epilepticus in children. *J Clin Med*. 2016b;5(47):1–19.
- Srinivasan S, Cornell T. Bedside ultrasound in pediatric critical care: a review. *Pediatr Crit Care Med*. 2011;12(6):667–74.
- Su E, Pustavoitau A, Hirshberg EL, et al. Establishing intensivist-driven ultrasound at the PICU bedside—it's about time. *Pediatr Crit Care Med*. 2014;15:649–52.
- Suarez-Sipmann F, Bohm SH, Tusman G. Volumetric capnography: the time has come. *Curr Opin Crit Care*. 2014;20:333–9.
- The Pediatric Acute Lung Injury Consensus Conference Group. Pediatric acute respiratory distress syndrome: consensus recommendations from the pediatric acute lung injury consensus conference*. *Pediatr Crit Care Med*. 2015;16:428–39.
- Traube C, Silver G, Kearney J, et al. Cornell assessment of pediatric delirium: a valid, rapid, observational tool for screening delirium in the PICU*. *Crit Care Med*. 2014;42:656–63.
- Van Tuijl SGL, Van Cauteren YJM, Pikhart T, et al. Management of pediatric delirium in critical illness: a practical update. *Minerva Anesthesiol*. 2015;81:333–41.
- Wolbrink TA, Kissoon N, Burns JP. The development of an internet-based knowledge exchange platform for pediatric critical care clinicians worldwide*. *Pediatr Crit Care Med*. 2014;15(3):197–205.



Update in Development: Section A—Infant Development

6

Madhavi Moharir and Chaya Kulkarni

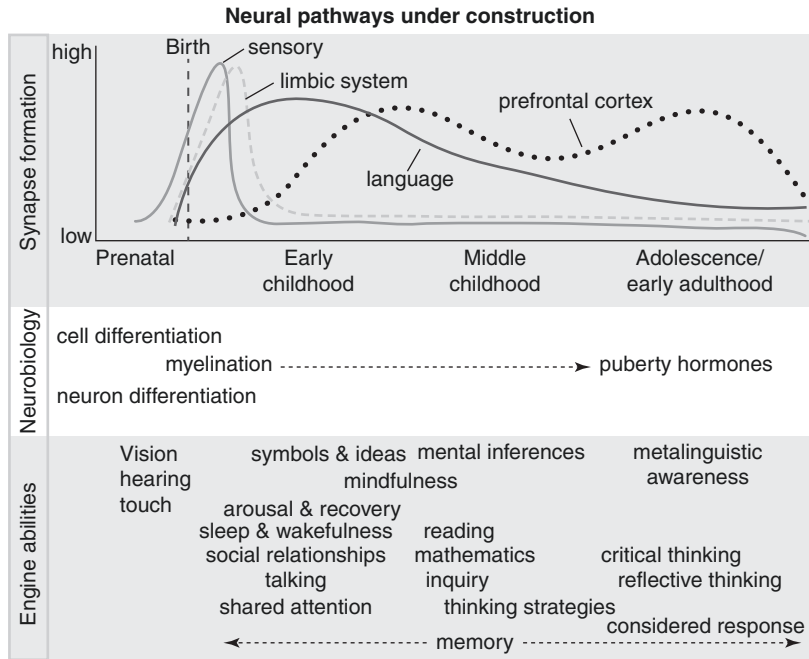
Infant Mental Health: Awareness Among Physicians

The early childhood period (birth to age 5) is considered to be the most important developmental phase throughout an individual's life. The human brain is the 'master organ' of development, which undergoes its most sensitive periods in its early years of life (Grantham-McGregor et al. 2007). The development of neurons is mostly completed at birth, but the interconnections between neurons i.e. the synapses—are still developing at an incredible rate. 700 synaptic connections form per second in a child's brain in the first few months of life, a rate that is unrivalled throughout his or her lifespan (Zero to Three

2002; Center on the Developing Child Harvard University 2012). The formation of synapses peaks between the third trimester of pregnancy and the second birthday. Synaptogenesis then continues throughout childhood into adolescence, but at a slower rate. Basic sensory circuits like vision, hearing and touch form first. These serve as foundation blocks for the development of more complex brain circuits, responsible for reflective thinking, behavior and cognitive functions. Synapses that are stimulated by frequent use during early years get hardwired, whereas those that are rarely used are eliminated by a process called 'pruning'. Repeated pruning results in a sophisticated brain architecture of intricate neural connections.

M. Moharir · C. Kulkarni (✉)
Infant Mental Health Promotion, HSC,
Toronto, ON, Canada
e-mail: chaya.kulkarni@sickkids.ca

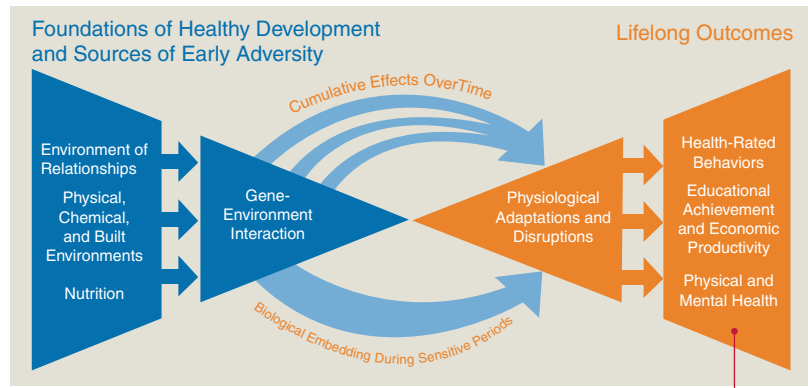
Image from: McCain, M.N., Mustard, J.F., & McCuaig, K. (2011). *Early Years Study 3: Making Decisions, Taking Action*. Toronto: Margaret & Wallace McCain Family Foundation. p.32



Growing evidence suggests that the social environment has profound impact upon the function of one’s genes by providing the stimulus for the variable expression of an inherited genetic code (Denberg and Daneman 2010; McEwen 2008). Epigenetics—a branch of science that studies processes that can alter gene expression temporarily or permanently without changing the DNA sequence—can draw associations between one’s social experience and his or her gene expression (Mellor et al. 2008, National Scientific Council on the Developing Child 2010a, b). During any stage in life but particularly in early childhood, environmental experiences act as external stimuli and the sensory inputs are carried to the brain

as electrical discharges. Biochemical cascades (changes in DNA methylation and histone modification of chromatin) ensue in response to the environmental cues, triggering structural and chemical changes to the genes (Mellor et al. 2008; Berger 2007; Kouzarides 2007; Glaser 2000). Much like operation of a light switch, some gene sequences are “switched on” or activated while others are “switched off” or silenced. These collective personalized chemical signatures are called epigenomes (Mellor et al. 2008) and they resemble the software in a computer, determining the dos-and-don’ts of the genetic hardware (structural genome). (National Scientific Council on the Developing Child 2010a, b)

Image: A biodevelopmental framework can relate the multiple influences during development to lifelong outcomes. SOURCE: Center on the Developing Child at Harvard University 2010. Reprinted with permission. Copyright 2010 Center on the Developing Child at Harvard University



Serve and Return Interaction Shapes Brain Circuitry

Babies are born relationship-ready and in fact, their development is relationship dependent. The formation of a secure attachment relationship with a primary caregiver in the first year of life is crucial for healthy infant development. This relationship will influence the connections made between brain cells and the strength of connections literally driving brain architecture. Positive interactions are more likely to lead to positive connections. Conversely poor interactions are more likely to lead to poor connections. When infants and toddlers experience persistent neglect and/or maltreatment, the absence of serve and return, their brains look different when compared to those children living in a responsive environment. The absence of serve and return relationships ultimately influences a child's developmental trajectory. Positive serve and return relationships support many developmental constructs that begin to form early in life with the most significant one being the secure attachment. The parent's consistent response to their baby's distress is the single most important "serve and return" interaction that influences the creation of this relationship. When in place, the secure attachment acts as an external regulation system that the baby learns to count on when distressed. This attachment forms the foundation for regulation and resilience across the child's life span. A child who is responded to appropriately and consistently, is more likely to learn how to regulate and manage their emotion

and behavior. Furthermore, while all children are born with the capacity to be resilient they are not born resilient. Resilience, the ability to recover from a difficult situation, is influenced by both the secure attachment relationship and a child's ability to regulate. Both regulation and resilience therefore depend on the secure attachment being in place and both will develop over many years.

Overview of Social Emotional Development

Relationships during the first 3 years drive development including the development of mental health. Having an understanding of what to look for and what to expect developmentally in the domains of social emotional development is important for a physician. Because infants can't speak and tell their experiences, for those who may be vulnerable to poor outcomes in any domain, knowing what to expect should guide the observations of a young child during every visit. Observing both caregiving and care getting behaviors can give insight to developmental status.

Below is an overview of social emotional milestones birth to 3 years of age. These should be seen as a guide. What is essential is that consideration be given to:

- How a child is developing compared to his peers of the same age
- How a child is developing on a continuum of development

- What developmental goals are next for a child, based on current status rather than age
- What strategies can be shared with parents to support the emergence of the next milestone

Hand in Hand: Growing Together Everyday: Social Emotional Milestones Overview

0–3 Months

Babies are born relationship ready and in their first 3 months of life are actively trying to make sense of their world. Before they can even speak, babies communicate with their facial expressions, voices and body language. As caregivers and babies get to know each other, babies will depend on their caregivers to recognize their cues and respond to their needs in a sensitive, timely and consistent way. This is the beginning of a trusting relationship that will extend to the wider world in later years. Babies' relationships and experiences lay the foundation for their mental health now, throughout their childhood, and well into their adult years.

Over the first 3 months, a baby will:

- **Gaze at her caregiver's face and look in the direction of her caregiver's voice.**
Baby's caregivers should bring their faces close so that baby can see their features and expressions. Baby may not initially make eye contact since her vision has not fully developed, but she will enjoy looking up and seeing her caregivers' faces.
- **Smile spontaneously.**
By 2–3 months, a baby's social smiles are signs that she knows her caregivers.
- **Recognize a familiar voice.**
For months before baby was born, her mother's voice was what she heard most. She will follow that voice, turning her head in that direction, and will prefer it over others. Make cooing sounds when she is happy, contented and communicative. Be soothed when picked up and comforted (most of the time).

- **Express her emotions and needs through her cries and actions.**

Baby will find a way to let her caregivers know that she needs attention when hungry, tired or uncomfortable, e.g., in need of a diaper change.

4–6 Months

With loving, nurturing early relationships baby is beginning to understand his physical and social surroundings and learning to discover his world. He knows who his caregivers are and who he can trust to respond to his needs. This is the start of the attachment relationship and will be dependent on how well caregivers provide consistent, responsive and appropriate care. As baby continues to learn about his world and to make sense of the things around him, his caregivers need to continue to provide loving and responsive relationships to help guide him through those experiences.

By 6 months a baby will begin to:

- **Intentionally express his emotions.**
He will cry or get agitated when he wants attention, e.g., he may laugh and smile while interacting with his caregivers or he may show that he is excited by quickly waving his arms and legs around.
- **Recognize his primary caregivers.**
A baby feels safest around his primary caregivers and seeks a familiar presence. He knows who his primary caregivers are and that they will respond to his needs.
- **Make eye contact.**
Baby will begin to focus for longer periods of time as his vision has developed more since birth and he can now see things more clearly and farther away. When a caregiver sings, babbles or imitates the sounds baby makes, baby will look up at his caregiver and make eye contact. He engages by cooing and babbling back.
- **Read facial and vocal expressions and learn what different forms of interaction mean.**
When his caregivers engage with him, e.g., talking, singing, cooing or babbling, baby will

respond and make eye contact. When he hears his caregivers getting angry and speaking in a voice that is louder than normal, he might become scared and cry. He will know something is not right and may become agitated and seek his caregivers' attention.

- **Form an attachment with his primary caregivers.**

When caregivers respond to their baby's needs especially when he is distressed, baby will know he can trust and depend on his caregivers. With positive, consistent care, baby will form secure attachments with his caregivers.

7–12 Months

By the age of one, baby is learning more about her world and may even have an opinion about things she likes or dislikes. She is beginning to get around by crawling, walking by holding onto furniture or perhaps even on her own with no support. She is curious to learn about the things around her and can now actively explore. Baby can now understand simple language and words like “no,” “bye,” or “shoes.”

Baby will:

- **Begin to intentionally tell her caregivers what she wants.**

Baby will make gestures or point at objects that she wants. She will begin to put her arms out or up when she wants to be picked up. She will begin to babble more and may even say a couple of words to interact and communicate.

- **Begin to miss her caregivers when they are not around.**

When her caregivers leave the room baby will notice, become upset and may begin to cry. She misses her caregivers when they're not there and looks for them.

- **Begin to seek comfort from her caregivers.**

When baby gets upset or hurt she will want and need to be comforted by her caregivers. It is important to respond to baby's distress by comforting her. Comfort her and give her words to help her label her feelings.

- **Show her caregivers her emotions.**

When baby gets scared she will want to be near her caregivers and maybe cling to them. When she gets mad she might make a frustrated face. Or when she feels shy she may hide behind them or try to cover her face.

- **Begin to show affection towards her caregivers.**

Baby will want to be hugged and kissed and in return she will hug and kiss her caregivers back. She will begin to understand the words “hug” and “kiss” and do these things spontaneously.

- **Develop a sense of herself as a separate person with her own likes and dislikes.**

Baby is starting to have dislikes and likes about her experiences, her toys and the people around her. She will let her caregivers know what she enjoys doing and being around, and what she does not like to do.

13–18 Months

Baby is starting to understand more of what he hears and is enjoying the use of language. He enjoys hearing short stories and simple songs. He will point at pictures in books and try and sing along to songs he is familiar with. Baby enjoys reading the same books and hearing the same songs over and over; he enjoys knowing what will happen next in the book or song. Repetition helps him memorize simple songs which will help him build his vocabulary.

Baby will:

- **Become more confident and have a greater sense of himself.**

Baby has more likes and dislikes when it comes to what he plays with, who he wants to play with and when he wants to interact with people.

- **Begin to take ownership of objects belonging to him, such as toys.**

Baby will have a difficult time with sharing since his toys right now belong to him. His caregivers will hear him using words like “no,” “mine,” etc.

- **Notice his peers.**

Baby is becoming interested in what others are doing or what they are playing with. He may not join in and play with them but rather sit beside them and play on his own. He will watch his peers but may not initiate any interaction with them.

- **Express his emotions to his caregivers.**

Baby will still feel a lot of emotions, so his caregivers should comfort him and help him label his feelings. Labeling feelings will give baby ownership of his emotions, and with time he will learn how to express them.

19–24 Months

Baby is growing into an independent toddler. She is mastering things on her own and seeks less help from her caregivers. She is beginning to engage in imaginary play. As she watches and observes her surroundings, she will begin to imitate the actions of others and try to role-play. She might pick up a broom to “houseclean,” or play “mom” with her dolls, etc. She is beginning to use simple sentences with the words she knows and is beginning to communicate and use language more easily. She notices her peers around her and enjoys their company but may need help mastering her social play skills, like sharing and turn taking.

A toddler will:

- **Begin to learn about others’ feelings and the concept of empathy.**

Baby is aware of her peers and is beginning to understand they have feelings just like she does. When someone takes a toy away from a friend or hits a friend, it hurts her and she may cry too. She is beginning to develop empathy for the people she cares for and realizes other people also get sad. Baby is developing the ability to take another person’s perspective.

- **Want to make her own choices and decisions about how she does things.**

Baby is becoming more independent as she masters doing things on her own. She will still look for assistance from her caregivers when

she needs help. She is still dependent on them and knows they will comfort her and respond to her when needed.

Begin to develop a sense of imagination as she takes on different roles and engages in pretend play.

- **Have more words that she uses to express herself and to get what she wants.**

By the age of two, baby’s communication will evolve from using simple two-word sentences to more complex complete sentences.

- **Parallel play starts with toddlers playing next to each other.**

They may not share or be doing the same activity but they will play next to each other.

25–36 Months

Toddlers are confidently exploring the world, and when given the chance, are socially engaged with other children and adults. They are beginning to understand the children’s stories read to them and are talking about their own personal experiences and the events they are involved in. They are also engaged in more complex imaginary play, from watching and imitating people around them to pretending to be characters they hear about in the books read to them.

A toddler will:

- **Be actively forming friendships with his peers when given the chance.**

A toddler may have one specific friend that he always plays with and prefers to be around. He learns to play, engage and interact with others. Ensuring he has consistent play experiences is important for his development.

- **Use more language between these months.**

A toddler will communicate what he wants and how he feels. He is starting to have conversations with peers and the adults he’s around, sharing details about himself and his adventures. He has a grasp of language and his speech is now more easily understood. His use of words, complete sentences and overall vocabulary will increase significantly.

- **Begin to use words to express his feelings.**
Caregivers will know when a toddler is happy, scared, sad or mad. With encouragement he will try and use words to express these feelings, but of course, he will still use gestures, such as walking away, crying or throwing something.
- **Engage in more imaginative play.**
Not only will a toddler imitate the people around him, but he will begin to use his imagination with several objects. He will enjoy pretending different objects symbolize something else—a block turns into a train or playdough turns into a dinosaur.
- **Become more aware of peers and will be increasingly sympathetic toward them when they are upset.**
A toddler will recognize others' feelings and might even comfort peers when he sees they are upset.
- **Become more engaged in social play skills.**
A toddler is beginning to learn how to share and take turns. Cooperative play may still be difficult but he is learning to play with others and enjoy their company.

This chapter presents a focus on social emotional development. However, a holistic view of the child development is essential. Often, for infants and toddlers who may be vulnerable for poor development, monitoring development, noting when milestones in any domain are not reached can be critical.

Below is a sample of what you will find. In this particular resource *Comfort, Play and Teach Ages and Stages Developmental Milestones*, (created by the experts at Invest in Kids and now hosted by Infant Mental Health Promotion and the Phoenix Centre for Children and Families) a young child's developmental milestones are mapped out in the various domains of development (Social, Emotional, Language, Intellectual, Gross and Fine Motor). The Milestones are grouped by ages outlining typical and emerging skills, and what you can do to promote development in those domains. This resource can easily be printed to share with families to

communicate typical and emerging skills in early childhood development (for more detailed information on developmental milestones visit: <http://www.imhpromotion.ca/Resources/CPT-DevelopmentalMilestones.aspx>). However, the developmental milestones outlined are only guidelines. Each child develops at their own pace, with some skills emerging early, and others appearing later.

Ages and Stages Developmental Milestones

Six Areas of Child Development

Social Development means being able to make friends and get along with others, work as part of a team and be a good leader. These skills are all built on self-confidence, cooperation and trust.

Emotional Development means the development of a full range of emotions from sad to happy to angry, and learning to deal with them appropriately. This helps build self-esteem and leads to such deeper qualities as sympathy, caring, resiliency, assertiveness and empathy and the ability to rise to life's challenges.

Language Development is the ability to understand and express verbal and non-verbal communication. This is followed by the capacity to use words and sentences in correct grammatical structure in order to communicate wishes, ideas, information and needs.

Intellectual Development means being able to think creatively and abstractly, to pay attention, solve problems and develop keen judgement along with a lifelong readiness to learn.

Gross Motor Development allows a child to gain balance and bring large muscles under control in order to master physical activities such as sitting, crawling, walking, running, climbing, jumping and generally enjoy all that his body allows him to do.

Fine Motor Development means mastering precise and accurate small muscle movements of the fingers and hands in order to reach, grasp and manipulate small objects.

The Amazing World of Your Baby: An Overview of Baby's Development Birth to 6 Months

Infancy is a very exciting time. You and your baby are discovering each other and your baby is discovering the world. She's learning and doing more and more, but she still depends on you for everything. As you spend time with her, you will come to know her likes and dislikes, her style of learning and her personality. In short, you'll discover a whole new person.

In her first 6 months, your baby will go from being totally dependent on you to being able to stay alert for 2 h at a time. She will explore her environment—reaching, grasping and putting things in her mouth—while she sits supported or lays on her stomach with head and chest held high.

At this time, your baby will show how happy she is to be close to those she trusts. She'll begin to squeal coo, gurgle and babble to get your

attention, especially when she wants to keep the simple games you've created together going. At this point, she will start to build a healthy sense of herself and although her emotions and moods can change quickly, she is learning how to comfort and soothe herself by sucking or holding onto a special toy.

Your Baby at 1 Month

Welcome to the first month of your baby's life. Some amazing things are set to happen. For example, you'll notice your baby will begin to:

- Stare at colourful objects.
- Study your face when you smile.
- Respond positively to comfort and soothing.
- Cry to tell you she's hungry or uncomfortable.
- Enjoy being talked to and respond with her own special happy dance—on her back, waving her arms and legs.

SOCIAL Skills at 1 month

| Typical skills | Emerging skills |
|--|---|
| <ul style="list-style-type: none"> • Fixes eyes on your face in response to your smile • Moves body in response to your voice during interaction • Quiets down when looking at familiar faces • Engages in eye contact | <ul style="list-style-type: none"> • May smile back at face or voice • Listens to voices and coos • Recognizes parents' voices |



Comfort

If you...



Your baby will...

| | |
|---|---|
| <ul style="list-style-type: none"> • Make eye contact with your baby • Smile and make happy faces | <ul style="list-style-type: none"> • Become familiar with your face • Explore your face and expressions |
|---|---|



Play

If you...



Your baby will...

| | |
|--|--|
| <ul style="list-style-type: none"> • Gently rock and cuddle your baby • Hold her closely and dance slowly to music | <ul style="list-style-type: none"> • Learn to relax and feel secure in your arms • Feel rhythm and movement in a secure hold |
|--|--|



Teach

If you...



Your baby will...

| | |
|---|---|
| <ul style="list-style-type: none"> • Recognize the signs your baby uses to show what he is feeling • Pause, observe and respond appropriately to your baby's reaction | <ul style="list-style-type: none"> • Feel cared for and that he is getting his message across • Become engaged in the interaction |
|---|---|

EMOTIONAL SKILLS at 1 month

| Typical skills | Emerging skills |
|---|---|
| <ul style="list-style-type: none"> Enjoys/needs a great deal of physical contact and tactile stimulation Responds positively to comfort and satisfaction Primary negative response is distress or pain | <ul style="list-style-type: none"> Recognizes and calms down to a familiar voice Communicates moods through different cries |



Comfort

If you...



Your baby will...

| | |
|---|--|
| <ul style="list-style-type: none"> Respond quickly and sensitively to your baby’s cry or discomfort Tell your baby how much he is loved | <ul style="list-style-type: none"> Feel his needs are being met Feel secure and valued |
|---|--|



Play

If you...



Your baby will...

| | |
|---|---|
| <ul style="list-style-type: none"> Provide soft, lullaby music When feeding your baby, (breast or bottle) let her grasp your finger | <ul style="list-style-type: none"> Enjoy new sounds that are as comforting as speech Practice this skill and feel more and more confident with her ability to grasp |
|---|---|



Teach

If you...



Your baby will...

| | |
|--|--|
| <ul style="list-style-type: none"> Feed your baby whenever he is hungry | <ul style="list-style-type: none"> Trust that his needs will be met |
|--|--|

INTELLECTUAL SKILLS at 1 month

| Typical skills | Emerging skills |
|--|--|
| <ul style="list-style-type: none"> Cries when hungry or uncomfortable May make throaty sounds like ‘oohh’ or ‘aaaah’ Enjoys being talked to and responds to voices/sounds Pays close attention to faces of those closest to him Responds to loud or sudden noises with a sudden start (early signs of a developing response system) Will focus on high contrast patterns and faces; prefers these to bright or big objects | <ul style="list-style-type: none"> Turns toward familiar sounds and voices Can distinguish men from women, and mother from other women’s voices Can distinguish everyday speech from non-speech sounds Able to read and respond to positive and negative expressions as well as subtle differences in parent’s voice Able to co-ordinates eyes and track objects, e.g., follows toy from side to centre of his body but only if it is in his line of vision |



Comfort

If you...



Your baby will...

| | |
|---|---|
| <ul style="list-style-type: none"> Respond to your baby’s cry with a song, a soothing voice and a hug Respond when your baby is startled by noise | <ul style="list-style-type: none"> Feel his needs are being responded to Feel a sense of security in your response to his needs |
|---|---|



Play



If you...



Your baby will...



| | |
|--|---|
| <ul style="list-style-type: none"> Hold your baby and let her see your face as much as possible Say rhymes, sing songs or speak softly | <ul style="list-style-type: none"> Study and learn your facial features Responds to the sound and pitch of her parents’ voices, i.e., may quiet down, gurgle, coo, etc. |
|--|---|



INTELLECTUAL SKILLS at 1 month



| Typical skills | Emerging skills |
|---|--|
|  Teach If you...  Your baby will... | |
| <ul style="list-style-type: none"> • Tell your baby about all the caregiving routines you are going through | <ul style="list-style-type: none"> • Learn to associate a positive tone with nurturing activities |

GROSS MOTOR at 1 month

| Typical skills | Emerging skills |
|--|---|
| <ul style="list-style-type: none"> • Lifts his head when held at your shoulder; his head sags, flops forward or backwards when not supported • All arm, leg and hand movements are still reflexive, they move with little control; when lying on back, tonic neck reflex characterized by bobbing head (fencer's position) still predominates; arms and legs are thrust in play • When on tummy, turns head to clear nose from bed; lifts head briefly • Rolls partway onto side from back | <ul style="list-style-type: none"> • Fits his form to yours when held; grasps, clasps people • Lifts head temporarily when lying on stomach • Holds head in line with back when pulled to sitting position |

| | |
|---|---|
|  Comfort If you...  Your baby will... | |
| <ul style="list-style-type: none"> • Gently touch your baby during feeding, changing and bath time • Massage your baby's arms, legs and tummy | <ul style="list-style-type: none"> • Help you learn what type of touch he likes • Learn that his caregivers want to make him feel comfortable |



| | |
|---|--|
|  Play If you...  Your baby will... | |
| <ul style="list-style-type: none"> • Support your baby's head against your shoulder as you walk her around the house • Give your baby some tummy time | <ul style="list-style-type: none"> • Get to see more of her environment • Strengthen her neck muscles as she lifts her head to see her world |



| | |
|---|---|
|  Teach If you...  Your baby will... | |
| <ul style="list-style-type: none"> • Tell him what body parts you are washing during bath time • Use his name when you come towards him | <ul style="list-style-type: none"> • Start to eventually learn the words for parts of his body • Start to learn his name and your voice |

FINE MOTOR at 1 month

| Typical skills | Emerging skills |
|--|--|
| <ul style="list-style-type: none"> • Stares at colourful objects 8–14 in. away • Follows person with eyes while lying on back • Generally keeps hands closed in a fist or slightly open • When fingers are pried open (usual position is a fist), grasps handle of spoon or rattle, but drops it quickly | <ul style="list-style-type: none"> • Holds object for a few moments without any intent or purpose • Coordinates eyes better to track moving objects • Becomes fascinated by her own hands |

FINE MOTOR at 1 month

| Typical skills | Emerging skills |
|---|--|
|  Comfort | |
| If you... |  |
| Your baby will... | |
| <ul style="list-style-type: none"> • Take your baby’s hands and gently rub them on your face • Move your face slowly from side to side in front of your baby’s face | <ul style="list-style-type: none"> • Watch, feel and learn about your face • Look and follow your face with his eyes |

| | |
|---|---|
|  Play | |
| If you... |  |
| Your baby will... | |
| <ul style="list-style-type: none"> • Suspend a colourful toy over the crib • With baby lying on her back, alternate the position of her head and feet in the crib | <ul style="list-style-type: none"> • Practice looking at things when on her back • Look at objects using both sides of her head; also prevents “flathead” condition |

| | |
|--|---|
|  Teach | |
| If you... |  |
| Your baby will... | |
| <ul style="list-style-type: none"> • Give your baby a rattle to hold | <ul style="list-style-type: none"> • Learn to hold it briefly |



Your Baby at 2 Months

As your baby enters his second month, he will gain new skills right before your eyes. At this stage you will notice that your baby is beginning to:

- Turn his head to both sides.
- Follow objects and people with his eyes.
- Smile when others talk to him and smile at him.
- Show excitement or delight with small throaty sounds.
- Recognize familiar voices and people.

SOCIAL SKILLS at 2 months

| Typical skills | Emerging skills |
|---|--|
| <ul style="list-style-type: none"> • Smiles in social contact with others besides his mother • Listens to voices and coos • Studies faces alertly and directly, then gets excited; is more oriented to her surroundings; moves arms and legs and ‘talks’ in response to what she sees • Visually follows a moving person • Recognizes and becomes quiet for a familiar, gentle voice or face | <ul style="list-style-type: none"> • Stays awake longer if people interact with him • Shows excitement when she sees familiar people and things • Becomes more expressive with her face, body/muscle tone and voice |

| | |
|--|--|
|  Comfort | |
| If you... |  |
| Your baby will... | |
| <ul style="list-style-type: none"> • Talk to your baby during diapering and feeding routines • Sing to your baby | <ul style="list-style-type: none"> • Become familiar with the voices of those who care for her most often • Take comfort in songs and sounds she knows |

SOCIAL SKILLS at 2 months

| Typical skills | Emerging skills |
|----------------|-----------------|
|----------------|-----------------|



Play

If you...



Your baby will...

- | | |
|---|---|
| <ul style="list-style-type: none"> • Use a mix of high and low pitched voices • Exaggerate a big smile or wide eyes | <ul style="list-style-type: none"> • Be more interested in interacting with you • Love to look at your face |
|---|---|



Teach

If you...



Your baby will...

- | | |
|--|--|
| <ul style="list-style-type: none"> • Engage in face-to-face conversations about any topic, for example, plans for the day, pictures hanging on the wall, etc. | <ul style="list-style-type: none"> • Become engaged in dialogue as well as be entertained |
|--|--|

EMOTIONAL SKILLS at 2 months

| Typical skills | Emerging skills |
|----------------|-----------------|
|----------------|-----------------|

- | | |
|--|--|
| <ul style="list-style-type: none"> • Communicates moods of distress with different cries and excitement and delight with small throaty sounds • Can quiet himself by sucking his fingers, a pacifier, etc. • Expresses contentment when touched and cuddled • Able to express discontent, e.g., fusses at loud noises • Displays different emotions as seen with peaks of irritability and crying | <ul style="list-style-type: none"> • Fits her form to yours and relaxes body when held • Makes appropriate facial expressions in response to emotions, for example, fear, joy, anger |
|--|--|



Comfort

If you...



Your baby will...

- | | |
|--|--|
| <ul style="list-style-type: none"> • Show awareness of your baby's cues that tell you how he likes to be handled and touched • Respond to baby's cues consistently and appropriately | <ul style="list-style-type: none"> • Feel secure and understood |
|--|--|



Play

If you...



Your baby will...

- | | |
|--|--|
| <ul style="list-style-type: none"> • Respond to your baby's choice to stop an interaction • Copy the faces your baby makes | <ul style="list-style-type: none"> • Communicate to you more often knowing that you understand his cues |
|--|--|



Teach

If you...



Your baby will...

- | | |
|--|--|
| <ul style="list-style-type: none"> • Create routines • Respond to your baby's signals in the same way every time | <ul style="list-style-type: none"> • Begin to understand that her feelings are important and valued • Respond with her own smiles to copy you and others • Learn to anticipate what comes next • Feel secure |
|--|--|

INTELLECTUAL SKILLS at 2 months

| Typical skills | Emerging skills |
|--|---|
| <ul style="list-style-type: none"> • Gurgles, coos and squeals • Shows responsiveness to touch and to oral and visual stimulation • Stares at surroundings or attractive large, moving objects from several feet; moving or contoured objects hold his attention longer • Clearly discriminates voices, people, tastes, proximity and object size • Recognizes a few objects, for example, a bottle or rattle | <ul style="list-style-type: none"> • Repeats actions for his own sake • Holds onto objects briefly as his voluntary grasp replaces reflex grasp • Begins to look at his hands as objects for examination <p>Starts to associate people with behaviour, for example, mother and feeding</p> <ul style="list-style-type: none"> • Begins to sense that hands and feet are extensions of himself with limits and opportunities |



Comfort

If you...



Your baby will...

| | |
|--|---|
| <ul style="list-style-type: none"> • Look at your baby, smile at her, and offer soothing words • Answer your baby's happy noises | <ul style="list-style-type: none"> • Respond to eye contact and the sound of your familiar voice with her own coos and smiles • Begin to know she can count on you to respond |
|--|---|



Play

If you...



Your baby will...

| | |
|---|--|
| <ul style="list-style-type: none"> • Sing simple songs or do short finger plays with repeating sounds • Play a game of taking turns by copying sounds your baby makes | <ul style="list-style-type: none"> • Show you what gives him pleasure and indicate what he wants more of, for example, by kicking arms/legs • Begin to understand that conversation is a partnership and his sounds are equally valued |
|---|--|



Teach

If you...



Your baby will...

| | |
|--|---|
| <ul style="list-style-type: none"> • Talk to your baby during daily routines • Repeat favourite rhymes and songs | <ul style="list-style-type: none"> • Begin to understand the words and tone of voice that go with regular routines • Learn to recognize certain words and actions |
|--|---|

GROSS MOTOR at 2 months

| Typical skills | Emerging skills |
|--|---|
| <ul style="list-style-type: none"> • Movements are more deliberate, for example, turns head to both sides when lying down • Moves arms and legs and 'bicycles' with legs when excited • Lifts head temporarily when lying on stomach • When sitting, keeps head erect; head may bob as she tries this out • Rolls from side to back • Muscle reflex is developing, e.g., body startles involuntarily | <ul style="list-style-type: none"> • Can hold head up at 45° angle for a few minutes • Arms and legs cycle more smoothly • Arms move more symmetrically to reach for a toy |



Comfort

If you...



Your baby will...

| | |
|---|--|
| <ul style="list-style-type: none"> • Blow on your baby's tummy • Prop your baby on his side using a rolled up towel behind his back | <ul style="list-style-type: none"> • Enjoy the sensation as he works his abdominal muscles • Enjoy looking at the world from a different angle |
|---|--|

GROSS MOTOR at 2 months

| Typical skills | Emerging skills |
|----------------|-----------------|
|----------------|-----------------|



Play

If you...



Your baby will...

- | | |
|--|---|
| <ul style="list-style-type: none"> • Push gently against the bottom of your baby's feet • Lie on your back and slowly and gently raise and lower your baby off your chest in a horizontal position | <ul style="list-style-type: none"> • Kick and stretch in this resistance game • Enjoy looking at your face from a new vantage point |
|--|---|



Teach

If you...



Your baby will...

- | | |
|--|--|
| <ul style="list-style-type: none"> • Lay on the floor with your baby on your thighs; then curl up to kiss her | <ul style="list-style-type: none"> • Learn to anticipate receiving the kiss at a set interval of time |
|--|--|

FINE MOTOR at 2 months

| Typical skills | Emerging skills |
|----------------|-----------------|
|----------------|-----------------|

- Keeps hands closed in a tight fist most of the time
- Follows objects with eyes, for example, a mobile is a source of pleasure
- Fascinated by own hands; watches them and turns them over momentarily
- Holds objects briefly

- Grasps at things become voluntary
- May swipe at objects



Comfort

If you...



Your baby will...

- | | |
|---|---|
| <ul style="list-style-type: none"> • Help your baby grasp your pinky finger while making eye contact, talking or singing • Open your baby's hand and help him explore your face, moving his hand over your eyes, nose and mouth | <ul style="list-style-type: none"> • Begin to move fingers out of the fist position • Begin to open his fist to explore things; will also begin to feel safe and confident to explore further |
|---|---|



Play

If you...



Your baby will...

- | | |
|--|--|
| <ul style="list-style-type: none"> • Move a colourful toy slowly from left to right in front of your baby's eyes • Place your thumbs in baby's palms and when she grasps them, open her arms wide; bring her arms together and cross them over her chest, slowly and gently, using rhythmic movements and a song | <ul style="list-style-type: none"> • Learn to coordinate both of her eyes to follow an object • Enjoy the physical sensations of exercising both sides of her body |
|--|--|



Teach

If you...



Your baby will...

- | | |
|--|--|
| <ul style="list-style-type: none"> • Hold your face close to your baby's and let her try to reach for your nose • Open your baby's fist and rub her hand over different textures | <ul style="list-style-type: none"> • Begin to try to reach out or swipe at your nose and other things, such as earrings • Begin to experience touch on different parts of her hand |
|--|--|

Your Baby at 3 Months

Your baby will start to demonstrate more predictable skills. He will start to:

- Hold his head up with more control.
- Play with his hands by clasping them and bringing them to his mouth.
- Stop sucking so that he can hear sounds.
- Use his voice in response to adult talk and smiles.
- Coo with open ('aaaah') and closed ('eee') vowel sounds.
- Study objects for a long time, even turning them upside down to get another view.

SOCIAL SKILLS at 3 months

| Typical skills | Emerging skills |
|---|---|
| <ul style="list-style-type: none"> • Smiles immediately and spontaneously • Responds in excitement with total body and vocalizes to familiar people or things • Enjoys socializing and playing with other people; watches speaker's eyes and mouth • Stops sucking to hear sounds around him; then looks around and sucks at the same time • Turns head to follow moving objects, voices, or music • Vocalizes in response to adult talk and smiles | <ul style="list-style-type: none"> • Knows difference between family members and strangers • Cries less often as he finds other ways to communicate and as parents' ability to understand his needs improve |



Comfort

If you...



Your baby will...

- | | |
|--|--|
| <ul style="list-style-type: none"> • Return your baby's smiles • Spend close, personal time with your baby every day | <ul style="list-style-type: none"> • Respond with smiles with other family members • Enjoy relating to adults who love her |
|--|--|



Play

If you...



Your baby will...

- | | |
|--|---|
| <ul style="list-style-type: none"> • Mimic and exaggerate your baby's facial expressions • Get down on the floor next to your baby to talk, read a book or sing to her | <ul style="list-style-type: none"> • Try to imitate your facial expressions • Enjoy sharing time with you |
|--|---|



Teach

If you...



Your baby will...

- | | |
|---|---|
| <ul style="list-style-type: none"> • Give your baby time to react and then respond to her • Suspend objects that make a noise | <ul style="list-style-type: none"> • Learn about the basics of taking turns in conversation • Watch and listen to the objects as he moves |
|---|---|

EMOTIONAL SKILLS at 3 months

| Typical skills | Emerging skills |
|--|--|
| <ul style="list-style-type: none"> • Shows appropriate facial expressions in response to such emotions as anger, fear, joy • Reflects feelings of happiness with chortles or squeals; frustration with whimpers; and hunger with smacking lips • Begins to show sadness • Responds to familiar people; may stop or start crying according to who holds him • Can distinguish and express discomfort | <ul style="list-style-type: none"> • Starts to laugh • Starts to show anger when he cannot get what he desires |

EMOTIONAL SKILLS at 3 months

| Typical skills | Emerging skills |
|----------------|-----------------|
|----------------|-----------------|



Comfort

If you...



Your baby will...

- | | |
|---|---|
| <ul style="list-style-type: none"> Respond to your baby with positive encouragement during interactions, for example, say “Good reaching,” when he reaches out for something Provide soft toys, blankets and other “soothers” | <ul style="list-style-type: none"> Develop a positive sense of self Begin to quiet down on his own after an upset |
|---|---|



Play

If you...



Your baby will...

- | | |
|---|---|
| <ul style="list-style-type: none"> Know your baby’s signals when she has had enough Build bits of exciting physical activity into your baby’s day | <ul style="list-style-type: none"> Learn to trust that you will not push her beyond the limits of what she enjoys Learn how to get excited and then calm herself down |
|---|---|



Teach

If you...



Your baby will...

- | | |
|--|--|
| <ul style="list-style-type: none"> Be consistent with routines and responses Be aware of toys and objects that comfort your baby and make them available whenever he is distressed | <ul style="list-style-type: none"> Feel secure as he learns to predict what comes Understand that his feelings count |
|--|--|

LANGUAGE SKILLS at 3 months

| Typical skills | Emerging skills |
|----------------|-----------------|
|----------------|-----------------|

- | | |
|---|---|
| <ul style="list-style-type: none"> Coos with both open vowel sounds (i.e., ‘aaah’); and closed vowels (i.e., ‘eee’) Responds to speech stimulation by gurgling, cooing, and squealing Expresses himself regardless of what else is going on around him Distinguishes speech from sounds you make Expresses different cries for different needs | <ul style="list-style-type: none"> Begins to babble and amuse self with new noises Begins to imitate sounds |
|---|---|



Comfort

If you...



Your baby will...

- | | |
|--|---|
| <ul style="list-style-type: none"> Tell your baby what you are doing as well as what she is feeling and hearing during all routines | <ul style="list-style-type: none"> Enjoy listening to your voice and come to expect certain routines |
|--|---|



Play

If you...



Your baby will...

- | | |
|--|--|
| <ul style="list-style-type: none"> Imitate the sounds your baby makes to start a game of taking turns | <ul style="list-style-type: none"> Chat and experiment with different sounds then start to take turns |
|--|--|



Teach

If you...



Your baby will...

- | | |
|---|--|
| <ul style="list-style-type: none"> Repeat favourite rhymes and songs | <ul style="list-style-type: none"> Learn to recognize certain words and actions |
|---|--|

INTELLECTUAL SKILLS at 3 months

| Typical skills | Emerging skills |
|--|--|
| <ul style="list-style-type: none"> • Begins to become aware of himself as a person by looking, examining and feeling what he can do with his own toes, feet, fingers and mouth as well as objects • Begins to show memory, for example, waits for an expected reward, e.g., sitting in a highchair and anticipating mealtime • Recognizes familiar objects and people, even at a distance • Enjoys repetitive games and repeating a newly learned activity • Tries to prolong a pleasing image or action by continuing to look, listen or grasp | <ul style="list-style-type: none"> • Repeats actions for his own sake • May associate a specific action with a result; very preliminary indications of understanding cause and effect relationships • Retains an object in hand voluntarily • Manipulates a large ring or rattle |



Comfort

If you...



Your baby will...

| | |
|---|--|
| <ul style="list-style-type: none"> • Call your baby's name when she is not looking | <ul style="list-style-type: none"> • Learn to locate sounds |
|---|--|



Play

If you...



Your baby will...

| | |
|--|--|
| <ul style="list-style-type: none"> • Play simple tickling games | <ul style="list-style-type: none"> • Learn that certain actions have specific results, for example, tickling means fun and laughing |
|--|--|



Teach

If you...



Your baby will...

| | |
|--|---|
| <ul style="list-style-type: none"> • Hit a toy that makes a noise while your baby is looking • Place a toy close enough for your baby's kicks to hit it and make a sound | <ul style="list-style-type: none"> • Begin to sense a connection between what his fingers and hands can do with objects • Discover that he can cause something to move and make a noise |
|--|---|

GROSS MOTOR at 3 months

| Typical skills | Emerging skills |
|---|--|
| <ul style="list-style-type: none"> • Keeps head in mid-position while on her back, and moves her arm and leg on one side in unison, then the arm and leg of the other side • Raises head and chest when on tummy • Holds head up with more control • Sits with support on a lap • Briefly bears weight on legs by pushing down with legs when placed on a hard surface | <ul style="list-style-type: none"> • Swipes with arms • Tonic neck reflex (characterized by bobbing head) begins to disappear • When pulled to stand, presses feet against surface and stands briefly • Lifts head and supports chest on extended forearms • Splashes and kicks with hands and feet when in the bathtub |



Comfort

If you...



Your baby will...

| | |
|---|---|
| <ul style="list-style-type: none"> • Shift your baby to different positions, for example, on tummy or back, or on your lap | <ul style="list-style-type: none"> • Be less likely to get bored with his immediate surroundings |
|---|---|

GROSS MOTOR at 3 months

Typical skills

Emerging skills



Play

If you...



Your baby will...

- Tilt your baby from side to side on your lap while singing a song
- Bounce your baby gently on your knees to different rhymes or short songs

- Learns to balance and strengthen muscles needed for sitting
- Learn to control her head in this action game



Teach

If you...



Your baby will...

- Place baby on his tummy and lay down on the floor in front of him

- Practice holding up his head and chest to see your face

FINE MOTOR at 3 months

Typical skills

Emerging skills

- Plays with hands by bringing them together and clasping them
- Hands/fingers stay open more as grasp reflex fades
- Bring hands to mouth
- Reaches for objects with both arms, starting at sides and closing in front of body; often contacts object with closed fists

- Begins to swipe for dangling objects, but may be far off target
- Looks from one object to another
- Watches and touches fingers of both hands as they move toward midline and meet; early stages of eye-hand coordination



Comfort

If you...



Your baby will...

- Allow your baby to suck on his fingers/thumb
- Carry your baby around from room to room or outside to familiarize him with his surroundings

- Learn to use his own body to soothe or calm himself
- Become familiar with his surroundings; learn to look at and follow different objects



Play

If you...



Your baby will...

- Clap your baby's hands together to play "Pat-a-cake"
- Give your baby different textures to touch e.g., furry, hard, squishy

- Learn what her hands can do in a fun way
- Learn that materials have different sensations when touched



Teach

If you...



Your baby will...

- Hold dangling objects in front of your baby's eyes to encourage him to reach out and touch them

- Learn how to use his eyes and hands together in order to obtain objects within reach

Your Baby at 4 Months

As your baby’s fourth month begins, you will see some truly awesome changes. This is when your baby begins to:

- Lift her head and chest when she’s on her tummy, and extend her arms.
- Try to grasp objects with fingers and palm now that her hands are open.

- Laugh out loud when tickled or during social games.
- Show anticipation and excitement by breathing heavily.
- Turn his head to find out where a sound comes from.

SOCIAL SKILLS at 4 months

| Typical skills | Emerging skills |
|---|--|
| <ul style="list-style-type: none"> • Gazes into your eyes during feeding or diapering • Uses her voice to initiate socializing; coughs or clicks tongue • Responds to and enjoys your touch • Makes social gestures such as waving or kicking when she sees a familiar person, for example, she will signal “pick me up” • Enjoys social games and play and will laugh out loud when tickled or when playing peek-a-boo with a scarf • Smiles and vocalizes to an actual face rather than to an image | <ul style="list-style-type: none"> • May prefer one toy over others • Interested in and smiles at her mirror image |



Comfort

If you...



Your baby will...

- Sing and talk to your baby as much as possible
- Let her spend special time with siblings every day

- Take comfort in the songs and sounds she knows
- Build relationships with key family members



Play

If you...



Your baby will...

- Sing action songs such as “Head & Shoulders” or “The Wheels on the Bus”
- Use different voice tones for songs

- Get to know the tune and movements and come to expect certain actions
- Become familiar with different pitches of sound



Teach

If you...



Your baby will...

- Call your baby’s name when she is not looking
- Talk about what you hear, for example, “the phone is ringing”, or “there’s daddy’s car”

- Eventually respond to his name
- Learn to listen and become familiar with household sounds

EMOTIONAL SKILLS at 4 months

| Typical skills | Emerging skills |
|---|--|
| <ul style="list-style-type: none"> • Fusses or cries to gain attention from familiar adults, or when attention or toy is taken away from him • Yawns and arches back or turns away when he has had enough interaction or there is too much noise • Shows anticipation and excitement by breathing heavily • Shows he's not sure (stops cooing and smiling) or he's afraid (fusses) if a new person moves toward him; turns his head into shoulder of parent when a new person approaches • Stops crying when he hears your voice or caregiver's, he attempts to soothe himself | <ul style="list-style-type: none"> • Expresses anger when he cannot get desired effect • May differentiate between mother's image and his own in the mirror; turns to see mother's "real" face • Follows someone with eyes and continues to look at the door when that person leaves the room |



Comfort

If you...



Your baby will...

| | |
|--|--|
| <ul style="list-style-type: none"> • Are responsive to your baby's feelings • Find out the best ways to soothe your baby's upset or distress | <ul style="list-style-type: none"> • Feel that her emotions are understood • Feel loved and secure |
|--|--|



Play

If you...



Your baby will...

| | |
|--|---|
| <ul style="list-style-type: none"> • Play games like "peek-a-boo" or "Mummy's coming to get you" • Use your baby's name often as you talk to her | <ul style="list-style-type: none"> • Learn that you leave but you come back • Become familiar with her own name |
|--|---|



Teach

If you...



Your baby will...

| | |
|---|--|
| <ul style="list-style-type: none"> • Call out to your baby when he starts to fuss • Respect your baby's hesitancy with new people by being close or holding him | <ul style="list-style-type: none"> • Learn to calm down to the sound of your voice • Feel a sense of security even in frightening situations |
|---|--|

LANGUAGE SKILLS at 4 months

| Typical skills | Emerging skills |
|---|---|
| <ul style="list-style-type: none"> • Babbles strings of syllable-like sounds • Experiments with sounds using variation in pitch and tone • Communicates pain, fear, and loneliness through crying; joy or interest by cooing sounds • Uses his own special kind of cry when hungry • Makes babbling sounds when looking at toys or people • Listens to music or a music box | <ul style="list-style-type: none"> • Attempts to make consonant sounds |



Comfort

If you...



Your baby will...

| | |
|---|---|
| <ul style="list-style-type: none"> • Babble back to sounds she makes | <ul style="list-style-type: none"> • Feel the sounds she makes are as important as yours |
|---|---|

LANGUAGE SKILLS at 4 months

| Typical skills | Emerging skills |
|----------------|-----------------|
|----------------|-----------------|



Play

If you...



Your baby will...

- | | |
|---|--|
| <ul style="list-style-type: none"> Shake simple noise makers (small bottles or yogurt pots with a toy inside) in front and to both sides of your baby's head | <ul style="list-style-type: none"> Respond to sound with eye movements and head turning |
|---|--|



Teach

If you...



Your baby will...

- | | |
|---|---|
| <ul style="list-style-type: none"> Introduce a new finger play each week | <ul style="list-style-type: none"> Watch and listen to words and actions |
|---|---|

INTELLECTUAL SKILLS at 4 months

| Typical skills | Emerging skills |
|----------------|-----------------|
|----------------|-----------------|

- | | |
|---|---|
| <ul style="list-style-type: none"> Starts to explore things by bringing them to his mouth Turns head toward sound to find out where it comes from Uses entire body (arching, kicking, stretching) to reach towards a toy that intrigues him Has mental model for human face; knows mother or father and may resent strangers Becomes aware of his own fingers and how they feel different from another's | <ul style="list-style-type: none"> Finds an object that is partially hidden May transfer a toy from one hand to the other Swipes at objects with open hand of one arm but often misses Begins to figure out appropriate responses to other people's actions |
|---|---|



Comfort

If you...



Your baby will...

- | | |
|---|--|
| <ul style="list-style-type: none"> Are predictable in your actions | <ul style="list-style-type: none"> Begin to respond to routines and patterns of behaviour |
|---|--|



Play

If you...



Your baby will...

- | | |
|--|--|
| <ul style="list-style-type: none"> Offer objects with different textures to explore | <ul style="list-style-type: none"> Experience and eventually learn to distinguish different textures, e.g., hard, soft, bumpy, etc. |
|--|--|



Teach

If you...



Your baby will...

- | | |
|--|---|
| <ul style="list-style-type: none"> Make a small photo album of the family | <ul style="list-style-type: none"> Learn to recognize familiar faces in the family |
|--|---|

GROSS MOTOR at 4 months

| Typical skills | Emerging skills |
|--|--|
| <ul style="list-style-type: none"> Lifts head and chest when on her stomach and supports herself on forearms or on outstretched arms Turns head in all directions to follow a toy when lying on stomach Brings both hands to chest and keeps head in midline when lying on back Holds head steady when supported in a sitting position; may prefer sitting to lying down Thrusts legs and feet against bottom of crib over and over Rolls from side to side on stomach | <ul style="list-style-type: none"> Rolls from stomach to back Uses protective extension i.e., stretches arms and legs downward |

**Comfort**

If you...



Your baby will...

| | |
|--|--|
| <ul style="list-style-type: none"> Change your baby's position throughout the day, for example, from your shoulder to your lap, from his back to his tummy Observe your baby's positions to learn what he likes and dislikes | <ul style="list-style-type: none"> Enjoy a variety of physical positions and be less bored Feel respected and valued |
|--|--|

**Play**

If you...



Your baby will...

| | |
|---|---|
| <ul style="list-style-type: none"> Place colourful toys in front of and to your baby's sides when she is on her tummy Bend your baby's knees up to her chest and her toes up to her chin in time to a rhythmic song | <ul style="list-style-type: none"> Be encouraged to push chest up, lean on her forearms and turn her head so she can get a better look Feel the physical sensation of her legs and toes as they are exercised |
|---|---|

**Teach**

If you...



Your baby will...

| | |
|---|---|
| <ul style="list-style-type: none"> Put the same toy in front of your baby, changing your baby's position or location, and also changing the position of the toy Cross one leg over the other and roll your baby over from back to side or tummy | <ul style="list-style-type: none"> Learn to explore a toy in different ways given his own or the toy's physical position Experience the sensation of flipping between two major positions of his body |
|---|---|

FINE MOTOR at 4 months

| Typical skills | Emerging skills |
|--|--|
| <ul style="list-style-type: none"> Relaxes with hands mostly open, not in fists as before Reaches for objects when supported in sitting position, and then brings them to mouth Uses mitten grasp, i.e., fingers close on open palm with thumb sticking out Glances from one object to another and looks at toys placed nearby Tries to swipe at objects, but still inaccurate; may look from object to hand, and back to object; often misses, but can grab it sometimes | <ul style="list-style-type: none"> Claps hands Can bring hands together though hands may meet below, beyond or in front of object Waves a rattle placed in his hand |

FINE MOTOR at 4 months

Typical skills

Emerging skills



Comfort

If you...



Your baby will...

- Let your baby play with your fingers while breast- or bottle-feeding
- Show your baby one toy at a time

- Enjoy the intimacy of touch at such times
- Be able to focus and explore without feeling rushed



Play

If you...



Your baby will...

- Hold toys out for your baby to grab
- Sit on the floor with your baby on his back, between your legs; as you sing, gently pull your baby up to a sitting position

- Practice the skill of looking, reaching and touching many times
- Strengthen his arm, back and abdominal muscles in this face-to-face game



Teach

If you...



Your baby will...

- Label each toy your baby holds and plays with
- Praise your baby's successes with descriptive phrases, for example, "Great reaching"

- Learn the names for objects over time
- Begin to learn what she is good at

Your Baby at 5 Months

The fifth month of life sets the stage for more interactive developmental growth. You will notice your baby starting to:

- Sit, if supported, to view her world.
- Start to connect eyes and fingers. Cooperate in reaching and grasping toys.

- Make sounds and interrupt conversations when he wants attention.
- Display an awareness and wariness with strangers.
- Babble double consonants such as baba, dada, mama.

SOCIAL SKILLS at 5 months

Typical skills

Emerging skills

- Makes sounds and interrupts conversations when he wants attention
- Smiles and vocalizes to her mirror image
- Distinguishes familiar and unfamiliar adults
- Shows anticipation, waves and raises arms to be picked up
- Tries to get close to someone near crib
- Frolics happily when played with; plays with rattle, pats bottle or breast

- Observes adult's facial expressions intently
- Bangs playfully on mirror image
- Learns how to tease



Comfort

If you...







Your baby will...

- Smile at others when you are out and encourage your baby to smile too
- Respond to the sounds your baby makes

- Learn that the world is generally a friendly place
- Learn that he can use his voice to get your attention



SOCIAL SKILLS at 5 months



| Typical skills | Emerging skills |
|---|--|
|  Play | |
| If you... |  |
| Your baby will... | |
| <ul style="list-style-type: none"> • Sit or hold your baby in front of a mirror and make faces • Talk to your baby during mirror play | <ul style="list-style-type: none"> • Love to look at your face and her own • Begin to talk back to her image and yours |



| | |
|--|--|
|  Teach | |
| If you... |  |
| Your baby will... | |
| <ul style="list-style-type: none"> • Hold out your hands and ask your baby if he wants to be lifted up—remember that he won't answer, but if his hands go up you know you're right! • Create a book of pictures for your baby with familiar people | <ul style="list-style-type: none"> • Begin to learn the meaning of social gestures • Learn about and become more familiar with the people in her world |

EMOTIONAL SKILLS at 5 months

| Typical skills | Emerging skills |
|---|--|
| <ul style="list-style-type: none"> • Displays awareness and wariness of strangers • Expresses anger when can't get desired effect • Clings to parent when held • Shows fear, anger and disgust • Pushes away when he doesn't like what you're doing to him, for example, wiping his nose | <ul style="list-style-type: none"> • Smiles, laughs, squeals when happy; grunts when angry • Is content to play by himself for a while with a few toys either in the crib or playpen • Shows strong dislikes and likes about food |

| | |
|---|---|
|  Comfort | |
| If you... |  |
| Your baby will... | |
| <ul style="list-style-type: none"> • Describe the different emotions your baby shows during the day • Reassure your baby when he clings to you or acts fearful around strangers | <ul style="list-style-type: none"> • Begin to learn about different emotions • Feel safe and secure with you when others are around |

| | |
|--|---|
|  Play | |
| If you... |  |
| Your baby will... | |
| <ul style="list-style-type: none"> • Use feeding, bathing and changing as a time to play, adding gentle tickles and finger plays • Sing action songs such as "If You're Happy and You Know It" to demonstrate different emotions | <ul style="list-style-type: none"> • Respond to your emotions • Seek more of your attention • Begin to become familiar with different emotions |

| | |
|--|--|
|  Teach | |
| If you... |  |
| Your baby will... | |
| <ul style="list-style-type: none"> • Read a book showing pictures of people with different faces; look at each page leisurely and describe the emotions in each picture • Talk about the different expressions you and your baby see on other people | <ul style="list-style-type: none"> • Learn about different expressions • Learn that people show different emotions |

LANGUAGE SKILLS at 5 months

| Typical skills | Emerging skills |
|--|---|
| <ul style="list-style-type: none"> • Watches your mouth, listens to your voice, then experiments with her own sounds • Tries to imitate sing-song quality of voice (inflections) • Babbles double consonants (baba, dada, mama) • Makes “raspberry” sound—tongue out and blowing • Looks up when she hears her own name | <ul style="list-style-type: none"> • Touches your hand to restart activity • Responds to her own name |



Comfort

If you...



Your baby will...

| | |
|---|--|
| <ul style="list-style-type: none"> • Use her name in songs, “Where is Priya, where is Priya, Where are you....There you are, There you are and how do you do?” | <ul style="list-style-type: none"> • Begin to respond more and more to her name |
|---|--|



Play

If you...



Your baby will...

| | |
|--|--|
| <ul style="list-style-type: none"> • Use different or funny voices when telling stories | <ul style="list-style-type: none"> • Notice different voice inflections |
|--|--|



Teach

If you...



Your baby will...

| | |
|--|--|
| <ul style="list-style-type: none"> • Repeat the same songs and finger plays | <ul style="list-style-type: none"> • Begin to imitate the sounds as she hears |
|--|--|

INTELLECTUAL SKILLS at 5 months

| Typical skills | Emerging skills |
|---|--|
| <ul style="list-style-type: none"> • Experiments with the concept of cause and effect, e.g., Cries more deliberately; waits to see if anyone is coming and then cries again • Turns head deliberately to sound or to follow vanishing object, e.g., leans over to look for something if dropped • Wants to touch, hold, turn, shake and taste everything • Remembers her own actions in the immediate past • Tries to maintain interesting changes he can make in his environment through repetitive actions | <ul style="list-style-type: none"> • Reaches for a second object with purpose • Works toward a desired, but out of reach, object |



Comfort

If you...



Your baby will...

| | |
|--|---|
| <ul style="list-style-type: none"> • Respond to the range of emotions she shows to get your attention | <ul style="list-style-type: none"> • Begin to learn she is a separate person from you • Feel safe knowing you will respond to her needs |
|--|---|



Play



If you...



Your baby will...



| | |
|---|--|
| <ul style="list-style-type: none"> • Let your child experience different textures by touch, smell, or taste • Move out from behind to either side of your baby to encourage him to find you in different places | <ul style="list-style-type: none"> • Begin to learn about different textures and which ones he likes and dislikes • Learn that even when he can't see you, you still exist |
|---|--|



INTELLECTUAL SKILLS at 5 months



| Typical skills | Emerging skills |
|---|--|
|  Teach If you...  Your baby will... | |
| <ul style="list-style-type: none"> • Give your baby toys that require her to work for a particular action, e.g., a noise-maker | <ul style="list-style-type: none"> • Learn that her actions can affect things—the start of cause and effect |

GROSS MOTOR at 5 months

| Typical skills | Emerging skills |
|---|---|
| <ul style="list-style-type: none"> • Brings feet to mouth and sucks on toes • Moves by either rocking, rolling or pivoting around in a circle on his stomach • Sits supported for long periods (30 min) with a firm back • When held in standing position, stamps feet and jumps up and down, bearing almost all weight on legs shoulders • Rolls from stomach to back; on tummy, pushes on hands and draws up knees | <ul style="list-style-type: none"> • Rolls over from back to stomach • Starts to learn to sit unsupported leaning on arms in front of him |

| | |
|---|--|
|  Comfort If you...  Your baby will... | |
| <ul style="list-style-type: none"> • Create safe spaces with pillows • Kiss your baby on each cheek and on his neck, arms, legs, feet | <ul style="list-style-type: none"> • Learn to explore his new-found abilities safely • Move various parts of his body as they are kissed, and learn where they are |

| | |
|---|---|
|  Play If you...  Your baby will... | |
| <ul style="list-style-type: none"> • Hold your baby in a standing position on your lap • Create games with songs that move your baby's limbs and torso | <ul style="list-style-type: none"> • Enjoy practicing weight bearing with his legs • Practice shifting from lying, to sitting, to standing with your assistance |

| | |
|--|---|
|  Teach If you...  Your baby will... | |
| <ul style="list-style-type: none"> • Lie your baby over a tubular pillow with her arms extended; let her reach for a toy while you rock her gently back and forth • Place baby in your lap; blow bubbles within easy reach of her arms or legs | <ul style="list-style-type: none"> • Strengthen her back, hips and arms in preparation for crawling • Be encouraged to reach for and burst the bubbles, much to her delight |

FINE MOTOR at 5 months

| Typical skills | Emerging skills |
|--|---|
| <ul style="list-style-type: none"> • Eyes and fingers co-operate in grasping and manipulation and can reach target with good aim • Drops and picks up objects • Grasps object with partial thumb and forefinger • Holds bottle with one or two hands • Grabs or waves object with either hand | <ul style="list-style-type: none"> • Transfers objects from hand to hand • Bangs objects on table • Grasps and holds two objects at once |

FINE MOTOR at 5 months

Typical skills

Emerging skills



Comfort

If you...



Your baby will...

- Provide familiar soft toys in play spaces that are easy to reach and grasp
- Practice passing objects back and forth

- Be more confident about grasping things
- Develop the fine motor skill of picking up and letting go, gaining more and more confidence with each attempt



Play

If you...



Your baby will...

- Help him play finger games and sing songs that use finger play
- Offer your baby a number of different toys to hold and explore

- Feel more confident about what his fingers can and can't do
- Develop the ability to grasp things of differing shapes and sizes



Teach

If you...



Your baby will...

- Use an old plastic container or the top of a table as a drum
- Make a noise maker for your baby to hold, play with and pass from hand to hand

- Learn that hands are not just for holding things—they can help you make noise
- Have fun learning to pass things from one hand to another with confidence

Your Baby at 6 Months

Approaching the half-year mark, your baby is becoming an active member of the family. At this stage he will:

- Roll from stomach to back and over again.

- Use hands to bang and splash objects.
- Prefer to play with people, especially games like 'peek-a-boo.'
- Vocalize both pleasure and displeasure.
- Study objects for a long time, even turning them upside down to get another view.

SOCIAL SKILLS at 6 months

Typical skills

Emerging skills

- Prefers play with people, especially co-operative games—"peek-a-boo", "come and get me", "go and find"
- Tries to imitate some facial expressions
- Smiles at and enjoys patting mirror image; differentiates self from mirror image
- Distinguishes adults from children; smiles at and reaches out to pat children who are new to him
- Demonstrates delightful openness and friendliness

- Is able to copy some facial expressions
- Starts to cooperate in games with others, e.g., ball games, building blocks, etc.



Comfort

If you...



Your baby will...

- Call out to your baby in a fun voice from another room
- Read to your baby at any time

- Begin to call out to you or get your attention when she hears your voice
- Enjoy the quiet one-on-one time

SOCIAL SKILLS at 6 months

| | |
|----------------|-----------------|
| Typical skills | Emerging skills |
|----------------|-----------------|



Play

If you...



Your baby will...

- | | |
|--|--|
| <ul style="list-style-type: none"> Follow your baby's lead instead of deciding what to play Play peek-a-boo with your baby | <ul style="list-style-type: none"> Like to interact and connect with you and others Begin to understand that things don't disappear when they are out of sight |
|--|--|



Teach

If you...



Your baby will...

- | | |
|--|---|
| <ul style="list-style-type: none"> Arrange time for your baby to be with other babies with you present all the time Sit with your baby in front of a mirror and point to her saying her name; then point to yourself saying "mommy" or "daddy" | <ul style="list-style-type: none"> Become comfortable with other babies Feel secure with new faces in the room Begin to see himself as separate from you |
|--|---|

EMOTIONAL SKILLS at 6 months

| | |
|----------------|-----------------|
| Typical skills | Emerging skills |
|----------------|-----------------|

- | | |
|--|--|
| <ul style="list-style-type: none"> Vocalizes pleasure and displeasure, i.e., squeals with delight and grunts with anger Responds sometimes to the emotional tones of parents' voices Begins to quiet down on his own after getting upset Displays strong likes/dislikes about food Can be content to play in crib/playpen for a while with one or two toys Begins to communicate discomfort with strangers | <ul style="list-style-type: none"> Distinguishes self as separate from parent Demonstrates stranger anxiety Expresses nervousness or anxiety when separated from parent Shows attachment to special toy or object and uses it to provide comfort in the absence of someone familiar, e.g., may have a special toy that always goes to bed with him |
|--|--|



Comfort

If you...



Your baby will...

- | | |
|---|--|
| <ul style="list-style-type: none"> Watch to see which behaviour helps your baby soothe himself and encourage it Respond to your baby's squeals of delight with happy sounds of your own | <ul style="list-style-type: none"> Realize what comforts him Learn to cope with his emotions Use his blanket or toy to feel safe and secure especially when you are unable to provide comfort |
|---|--|



Play

If you...



Your baby will...

- | | |
|--|---|
| <ul style="list-style-type: none"> Use daily routines like feeding and bathing as a time to play; add tickles, peek-a-boo or finger plays Recognize baby's reluctance to play with strangers and not force him to do what doesn't want to do | <ul style="list-style-type: none"> Feel loved because you are responding to him Squeal some more to engage you in a conversation Feel reassured about what to expect at these times Respond to your emotions Seek your attention more Learn that you recognize and respect her feelings |
|--|---|



Teach

If you...



Your baby will...

- | | |
|---|---|
| <ul style="list-style-type: none"> When you have to go out, leave your baby with the same person Create a routine for times when you have to be away from your baby | <ul style="list-style-type: none"> Learn that others he is familiar with can also comfort him Look to the people he knows for support and comfort |
|---|---|

LANGUAGE SKILLS at 6 months

| Typical skills | Emerging skills |
|--|---|
| <ul style="list-style-type: none"> • Makes some vowel-consonant sounds using such consonants as f, v, th, s, sh, sz, m and n • Has a ‘conversation’ by babbling with family members • Begins to understand some words by tone of voice, intonations and a look on your face • Turns when he hears his name to show understanding | <ul style="list-style-type: none"> • Waves in response to “bye-bye” • Listens to own voice sounds and those of others |



Comfort

If you...



Your baby will...

| | |
|--|---|
| <ul style="list-style-type: none"> • Encourage your baby to repeat an action by laughing and clapping | <ul style="list-style-type: none"> • Love the sense of approval and will repeat an action that pleases you |
|--|---|



Play

If you...



Your baby will...

| | |
|---|--|
| <ul style="list-style-type: none"> • Babble with baby! When he “talks” to you, answer with what you think he may be saying | <ul style="list-style-type: none"> • Start to learn that the noises he makes have meaning |
|---|--|



Teach

If you...



Your baby will...

| | |
|---|---|
| <ul style="list-style-type: none"> • Use words that incorporate the sounds that your baby can make | <ul style="list-style-type: none"> • Start to learn that different sounds can go together to make other sounds |
|---|---|

INTELLECTUAL SKILLS at 6 months

| Typical skills | Emerging skills |
|---|---|
| <ul style="list-style-type: none"> • Looks at and studies things for a long time; turns objects upside down to get another view of them (example, lifts cup by handles) • Looks for family members or pet when the name is called. • Picks things up, shakes them, listens to sounds they make when dropped; senses the relationship between her hands and objects • Follows path of fast moving object with eyes | <ul style="list-style-type: none"> • Enjoys peek-a-boo more as she understands things are still there when they are out of sight • Realizes he can move things, e.g., slides toy or object across surface • Demonstrates early problem solving, e.g., holds one block, reaches for a second; looks at third block trying to figure out how to grab it • Rotates objects to find their functional side |



Comfort

If you...



Your baby will...

| | |
|--|---|
| <ul style="list-style-type: none"> • Provide a variety of containers for your baby during bath time | <ul style="list-style-type: none"> • Obtain sensory pleasure and relaxation from water play while practicing motor control and problem solving |
|--|---|



Play



If you...



Your baby will...



| | |
|---|--|
| <ul style="list-style-type: none"> • Show your baby a favourite toy and partially hide it under a scarf • Completely hide an object under a container while your baby is watching | <ul style="list-style-type: none"> • Discover how objects disappear and reappear • Practice searching for hidden objects |
|---|--|



INTELLECTUAL SKILLS at 6 months



| Typical skills | Emerging skills |
|--|--|
|  Teach | |
| If you... |  |
| Your baby will... | |
| <ul style="list-style-type: none"> • Give your baby cause and effect toys; choose toys that make noise or change when squeezed, shaken or rolled • Give your baby balls to roll and blocks to stack and knock over | <ul style="list-style-type: none"> • Learn that she can make things happen • See and hear the results of her actions • Explore how objects move in space • Learn that he can make things happen, for example, when he knocks over a tower of blocks it makes a noise |

GROSS MOTOR at 6 months

| Typical skills | Emerging skills |
|---|---|
| <ul style="list-style-type: none"> • Rolls from back to stomach, stomach to back • Sits by himself with support either leaning forward on arms or propped up against a pillow; sits well in a chair • Pulls himself up from lying on his back when you grasp his hands • Bears large amount of weight on legs and bounces when held in standing position • On tummy, lifts and extends legs high; may get up on hands and knees in crouch position, to move forward or backward or rock back and forth | <ul style="list-style-type: none"> • Uses protective extension, i.e., arms extended out front or to the side • Holds weight on one hand when on stomach • Goes from sitting to lying on tummy • Creeps forward on tummy |

| | |
|---|---|
|  Comfort | |
| If you... |  |
| Your baby will... | |
| <ul style="list-style-type: none"> • Give your baby lots of praise for each effort to roll over or get onto her knees • Lie on your back with baby next to you in the same position; reach over and holding your baby’s hand, gently encourage her to roll over; imitate the action yourself and praise her efforts | <ul style="list-style-type: none"> • Feel good about your positive reaction and try to do it again • Feel safe and secure in attempting to roll over by herself |

| | |
|--|--|
|  Play | |
| If you... |  |
| Your baby will... | |
| <ul style="list-style-type: none"> • Sit your baby on the floor propped by pillows • Prop your baby in a sitting position; face your baby and sing simple songs like “Row, row, row your boat” | <ul style="list-style-type: none"> • Begin to see the world from a different view • Begin to feel confident about sitting with you so close by |

| | |
|---|---|
|  Teach | |
| If you... |  |
| Your baby will... | |
| <ul style="list-style-type: none"> • Lay your baby on a soft area on the floor encouraging him to roll over by placing a favourite toy nearby • Play “This Piggy Went to Market” on each foot with exaggerated facial expressions | <ul style="list-style-type: none"> • Begin to see that he can move in new and exciting ways • Enjoy the physical sensation of toes being wiggled and anticipate the tickling at the end |

FINE MOTOR at 6 months

| Typical skills | Emerging skills |
|--|--|
| <ul style="list-style-type: none"> Reaches for objects with one hand; picks things up with a raking motion; still usually holds things in the palm of her hand (example, holds a block skilfully) Uses hands to grasp, bang and splash, for example, hold bottle, bang spoon on table Rotates wrist to turn objects as way of exploring Puts hand on breast or bottle while drinking and may pat gently; pats and pulls at hair, glasses and face Follows a moving object with her eyes Transfer objects from one hand to the other while still bringing hands or toy to mouth | <ul style="list-style-type: none"> Drinks from a sippy cup with help Attempts to feed self |



Comfort

If you...



Your baby will...

| | |
|---|--|
| <ul style="list-style-type: none"> Offer different kinds of water toys your child can reach for, handle and put in his mouth | <ul style="list-style-type: none"> Enjoy practicing eye-hand coordination skills while splashing in the tub |
|---|--|



Play

If you...



Your baby will...

| | |
|---|---|
| <ul style="list-style-type: none"> Fill a large plastic container with household objects (not small enough to fit into baby's mouth); show her how to take things out and put them back in | <ul style="list-style-type: none"> Learn how to grasp an item and move it in space |
|---|---|



Teach

If you...



Your baby will...

| | |
|---|--|
| <ul style="list-style-type: none"> During meal times let your baby hold an use a sippy cup or utensil Suspend a large nerf ball in a mesh bag within reaching distance and show your baby how to hit the ball with either hands or feet | <ul style="list-style-type: none"> Learn that he can do things just like you Develop the grasp needed to hold smaller objects such as spoons Learn to make objects move by using either her hands or feet |
|---|--|

The Amazing World of Your Baby: An Overview of Baby's Development at 7–18 Months

Infancy is a very exciting time. You and your baby are discovering each other and your baby is discovering the world. She's learning and doing more and more, but she still depends on you for everything. As you spend time with her, you will come to know her likes and dislikes, her style of learning and her personality. In short, you'll discover a whole new person.

By the end of the first year your baby will be an active learner, increasingly using her gross and fine motor skills. As her coordination improves, her curiosity will prompt her to find out what different objects can do, and what she

can make them do. Although she shows signs of independence, such as trying to feed herself, the security of your presence is still vital to help her discover her world with confidence. She learns by doing things over and over and likes it when you repeat familiar songs, finger plays, stories and games. She will also respond to her name by turning and looking when you call, and will babble sounds that are her words for certain things.

The last part of infancy is a time when great strides are made in motor skills like walking, climbing, stooping, even dancing. Her dexterity is amazing. She'll stack a few blocks, play with shape-form puzzles, and even scribble with a large crayon. She is truly becoming a social creature and loves to be the centre of attention. And though she enjoys being with other children, she

is not ready to share or play with them. This is also the time your child will start putting sounds together to make words, point with her index finger to let you know what she wants and begin to respond to simple requests such as “Come” or “Go get...”. She is ready to move to the next stage—toddlerhood.

Your Baby at 7–9 Months

The second half of the first year shows some remarkable new abilities. At this stage you will notice your baby will begin to:

- Move either by crawling, bum shuffling, or pivoting on the tummy
- Use her first and second fingers with her thumb—even feed herself a cracker.
- Copy actions he sees others do, such as waving bye-bye
- Clearly attach herself to familiar caregivers and want to stay close
- Show intention when exploring objects to understand what they do or sounds they make

SOCIAL SKILLS – 7–9 months

| Typical skills | Emerging skills |
|--|---|
| <ul style="list-style-type: none"> • Plays social games such as peek-a-boo, pat-a-cake, so-big, bye-bye and ball games • Holds hands over eyes, trying to get someone to play peek-a-boo • Shows desire to be included in social interaction by showing off to adults; performs for home audience and repeats act if applauded • Resists pressure to do something he doesn’t want to do, for example, no longer automatically accepts feeding and will push spoon away • Copies actions he sees others do • Intentionally points to things he wants • Shouts for attention; breaks into the conversation with his voice signalling emphasis and emotion | <ul style="list-style-type: none"> • Demonstrates sense of control of his environment, e.g., extends toy to show you, but won’t give it to you • Learns to protect self and possessions • Tests parental reactions during feeding and bedtime • Able to concentrate other people’s actions, e.g., likes to watch people scribbling on paper • Shows persistence and may refuse to allow himself to be distracted |



Comfort

If you...



Your baby will...

| | |
|--|---|
| <ul style="list-style-type: none"> • Sing a song about looking for your baby, for example, “Where is Marco, where is Marco, where are you? There you are, there you are and how do you do?” • Use a soothing voice and a hug and explain how to take turns if your baby gets upset playing with others | <ul style="list-style-type: none"> • Begin to develop a sense of himself separate from you • Feel secure knowing that this hide-and-seek game always ends with you being reunited • Be reassured that you are there to help with his emotions when others are around |
|--|---|



Play



If you...



Your baby will...



| | |
|---|--|
| <ul style="list-style-type: none"> • Play time for your baby to be with other babies • Follow your baby’s lead instead of always deciding what game to play | <ul style="list-style-type: none"> • Enjoy spending time with other babies • Try to communicate to them using sounds or gestures • Enjoy the sense that she has control over her actions and wishes |
|---|--|



SOCIAL SKILLS – 7–9 months

| Typical skills | Emerging skills |
|--|--|
|  Teach | |
| If you... |  Your baby will... |
| <ul style="list-style-type: none"> • Go slowly with your baby; don't force him to go to someone she doesn't know or isn't sure of • Play, and invite others to play, peek-a-boo with your baby | <ul style="list-style-type: none"> • Understand he can warm up to a stranger and approach others on his terms, e.g., he may bring out lots of toys so the attention is on the other person and not on him • Understand that you and others are still there even when you can't be seen |

EMOTIONAL SKILLS – 7–9 months

| Typical skills | Emerging skills |
|---|--|
| <ul style="list-style-type: none"> • Feels strongly about what she does or does not want to do • Laughs because she has discovered she can laugh whenever she wants • Looks worried when she hears a loud noise, such as a balloon popping or the vacuum running or when someone speaks in a very stern voice • Displays fear of separation, i.e., is clearly attached to familiar caregivers, follows and wants to stay close to them • Expresses fright, i.e., is frightened by new experiences, new people and will fuss or cry if you look or behave differently | <ul style="list-style-type: none"> • Shows clear like or dislike for certain people, objects or places • May be more sensitive to other children and will cry if they cry • Begins to evaluate people's moods and motives |

| | |
|---|--|
|  Comfort | |
| If you... |  Your baby will... |
| <ul style="list-style-type: none"> • Watch to see what behaviour helps your baby soothe himself, and encourage it • Make sure you or someone familiar always responds to your baby's "calls" for help and attention | <ul style="list-style-type: none"> • Realize what comforts him • Learn to cope with his emotions in his own way, for example, using a special blanket or toy to feel safe and secure if you are unable to provide comfort • Learn that she can depend on you • Learn that others can provide emotional support too |

| | |
|--|---|
|  Play | |
| If you... |  Your baby will... |
| <ul style="list-style-type: none"> • Play some exciting, physical games that energize your baby, without making him anxious • Play one-to-one games like showing baby his eyes, nose and mouth in a mirror | <ul style="list-style-type: none"> • Learn how to become excited, and to calm down again • Trust that you and others won't push him beyond his limits • Enjoy spending time with you • Show his feelings by making faces and body movements |

| | |
|--|--|
|  Teach | |
| If you... |  Your baby will... |

EMOTIONAL SKILLS – 7–9 months

| Typical skills | Emerging skills |
|--|--|
| <ul style="list-style-type: none"> • Tell your baby about the routine, for example, “I need to change your diaper; let’s take a toy for you to play with while we do this” • Create routines for all regular activities, like changing, bedtime, feeding or playtime | <ul style="list-style-type: none"> • Feel safe, secure and respected as an individual • Begin to learn what’s happening next; this helps control her emotional reactions |

LANGUAGE SKILLS – 7–9 months

| Typical skills | Emerging skills |
|--|---|
| <ul style="list-style-type: none"> • Says several sounds like ma, mu, da, di, and ba all in one breath as well as multi-syllabic babbling, e.g., da-da-da or ga-ga-ga • Recognizes some words; shows excitement when she hears “bottle” or some other familiar word; looks toward mommy when asked, “Where’s Mommy?” • Can do simple things when asked, for example, “Show me the ball” or “Wave bye-bye” • Turns to listen when she hears familiar sounds like the telephone or her name • Uses special words meaningfully, example, dada and mama as specific names | <ul style="list-style-type: none"> • Shows understanding of words through appropriate behaviour or gesture • Labels an object in imitation of its sound, example, train—choo-choo or dog—woof • Has adult intonation when babbling • Listens selectively to familiar words and begins to recognize some • Knows what ‘no-no’ means |



Comfort

If you...



Your baby will...

| | |
|--|--|
| <ul style="list-style-type: none"> • Copy your baby’s actions, e.g., clap if he claps | <ul style="list-style-type: none"> • Feel his actions are important • Want to try other actions to get you to do the same thing • Start to take turns |
|--|--|



Play

If you...



Your baby will...

| | |
|---|---|
| <ul style="list-style-type: none"> • Use baby’s name in familiar songs for example, “Farmer Brown” becomes “Farmer Shiv” | <ul style="list-style-type: none"> • Recognize her name and feel pleasure hearing it in a song • Try to imitate you singing the song • Practice using her name |
|---|---|



Teach

If you...



Your baby will...

| | |
|---|--|
| <ul style="list-style-type: none"> • Respond to your baby’s babbling sounds by making the same kinds of noises | <ul style="list-style-type: none"> • Know that you are interested in what he says • Feel encouraged to babble on |
|---|--|

INTELLECTUAL SKILLS – 7–9 months

| Typical skills | Emerging skills |
|--|--|
| <ul style="list-style-type: none"> • Recognizes size of objects by reaching for small object with finger and thumb and large object with both hands • Distinguishes near and far objects and space • When exploring objects, demonstrates understanding of what they do or what sounds they make, e.g., she bangs a block on the floor, shakes a noise maker harder, purposefully pushes buttons on toy, or hits a rubber toy to make it squeak • Searches for an object when it is taken away but only in the place where it first appeared • Continues to experiment with things she can do with one side of her body, then the other • Understands meaning of ‘in’ and ‘out’, demonstrated by dropping several large beads in a cup or bowl, dumping them out, and repeating the game over and over | <ul style="list-style-type: none"> • Shows problem solving by using another object to get the one she wants, e.g., pulling a string horizontally to pull toy closer or holds onto two objects and reaches for a third • Realizes size differences between objects • Begins experimenting with familiar behaviours, e.g., imitating people when they’re out of sight and earshot; will imitate a new gesture • Starts to combine known bits of behaviour in new ways • May associate picture of baby with herself, and make a sound of recognition |



Comfort

If you...



Your baby will...

| | |
|---|---|
| <ul style="list-style-type: none"> • Help him calm down when he is upset | <ul style="list-style-type: none"> • Be better able to soothe and calm himself over time |
|---|---|



Play

If you...



Your baby will...

| | |
|---|---|
| <ul style="list-style-type: none"> • Play a game in which you and your baby copy each other’s simple actions like clapping, shaking a toy, or blowing a kiss | <ul style="list-style-type: none"> • Learn how to watch and copy an action • Learn that she can make an adult follow her lead |
|---|---|



Teach

If you...



Your baby will...

| | |
|---|--|
| <ul style="list-style-type: none"> • Give your baby different objects to play with in the bath, e.g., different sized containers | <ul style="list-style-type: none"> • Enjoy the relaxing feel of the water while learning about volume, quantity and other mathematical concepts |
|---|--|

GROSS MOTOR – 7–9 months

| Typical skills | Emerging skills |
|--|---|
| <ul style="list-style-type: none"> • Balances himself while sitting; sits alone steadily for longer periods without holding on; sits and bounces on his buttocks • Pushes up on hands and knees and rocks back and forth; sits up by pushing up from crawl position with arms at side • Crawls with an object in one or both hands; may also move by “bum” shuffling or turning in circles on stomach • Helps out when you pull him to stand; sometimes pulls himself up using furniture; stands firmly on his legs when held in standing position | <ul style="list-style-type: none"> • Makes stepping movements • Stands holding on to your hands; held standing, puts one foot in front of the other • Uses protective extension of arms to keep from falling backwards • Lowers himself to sitting from standing, holding on to supports • Crawls up stairs • Takes side step holding on to furniture (called cruising) |

GROSS MOTOR – 7–9 months

| Typical skills | Emerging skills |
|----------------|-----------------|
|----------------|-----------------|



Comfort

If you...



Your baby will...

| | |
|---|---|
| <ul style="list-style-type: none"> • Play on the floor and put some distance between you and your baby; encourage her to move toward you • Holding your baby’s hands, go for a walk | <ul style="list-style-type: none"> • Start to explore her environment more actively • Know that she can reach you even when there is some space between you |
|---|---|



Play

If you...



Your baby will...

| | |
|---|---|
| <ul style="list-style-type: none"> • Get down to his level and play hide-and-seek in a safe, small area of the house • Put objects a bit out of reach but don’t frustrate him | <ul style="list-style-type: none"> • Gain confidence in her legs and know she is safe trying something new because you’re right there • Begin to feel more independent while feeling loved, safe and secure as he always finds you • Be encouraged to exert new independence and reward herself by getting object without help |
|---|---|



Teach

If you...



Your baby will...

| | |
|---|---|
| <ul style="list-style-type: none"> • Sit your baby on the floor near steady, firm furniture so she can pull herself up onto her feet (make sure corners of furniture are protected) • Safely support your baby under the arms to help her to climb up a few steps | <ul style="list-style-type: none"> • Learn to pull herself up to standing position • Learn to use her body in a new way • Know she is safe because you are right there |
|---|---|

FINE MOTOR – 7–9 months

| Typical skills | Emerging skills |
|----------------|-----------------|
|----------------|-----------------|

| | |
|--|---|
| <ul style="list-style-type: none"> • Grasp is more refined; progresses from holding things in palm to using thumb, first and second fingers • Rakes at tiny objects and picks up shoe laces, cereal or crumbs with thumb and forefinger • Drops objects unintentionally and then looks for them • Feeds self some finger foods such as a cookie or cracker • Picks up, holds and manipulates an object, in each hand simultaneously; bangs objects together at centre of his body • Explores objects by grabbing, shaking, sliding and banging | <ul style="list-style-type: none"> • Removes pegs from pegboard • Is able to throw objects • Builds tower of two blocks • With index finger, pokes fingers into holes or anything that looks interesting • Takes objects out of container purposefully • Releases objects voluntarily |
|--|---|



Comfort

If you...



Your baby will...

| | |
|---|---|
| <ul style="list-style-type: none"> • Provide finger foods for snacks and meals • Roll the ball back and forth on the floor with your baby in sitting position | <ul style="list-style-type: none"> • Begin to feel independent as he starts to feed himself • Learn how two people can enjoy a turn-taking game |
|---|---|

FINE MOTOR – 7–9 months

| Typical skills | Emerging skills |
|----------------|-----------------|
|----------------|-----------------|



Play

If you...



Your baby will...

| | |
|--|--|
| <ul style="list-style-type: none"> • Create noise makers using plastic bottles that your baby can grasp and shake (see Activity Centre) • Use finger plays with your baby such as the “Finger Family” (see Activity Centre, songs) | <ul style="list-style-type: none"> • Learn that her actions cause things to happen • Learn to control finger movements |
|--|--|



Teach

If you...



Your baby will...

| | |
|--|---|
| <ul style="list-style-type: none"> • Give your child a container and objects to pick up and place into the container • Give your child blocks to stack up and knock over | <ul style="list-style-type: none"> • Further develop his ability to grasp and release objects • Explore how objects can be moved in space • Experience the effects on her motor skills |
|--|---|

Your Baby at 10–12 Months

The last months of your baby’s first year are a time full of wonderful new accomplishments. Now your baby will start to:

- Walk while holding onto furniture.
- Pinch fingers neatly to pick up the smallest items.

- Repeat sounds or gestures if laughed at.
- Display affection with hugs, kisses and pats.
- Understand simple sentences and requests like ‘Where’s your shoe?’
- Realize that things are still there, even when they are out of sight.

SOCIAL SKILLS – 10–12 months

| Typical skills | Emerging skills |
|----------------|-----------------|
|----------------|-----------------|

| | |
|--|--|
| <ul style="list-style-type: none"> • Knows when parent approves or disapproves of behaviour • Tries to help when being dressed, for example, by putting arms out for sleeves or feet for shoes • Loves to shake head and say ‘no’ even when he means ‘yes’ • Imitates adult movements and movements and play of other children • Repeats sounds or gestures if laughed at • Distinguishes self from others | <ul style="list-style-type: none"> • “Dances” to music • Shows familiarity with rituals and routines of the day; knows what comes next • Experiments with ways to get attention; enjoys being centre of attention • Responds to requests, e.g., generally gives up toys on request |
|--|--|



Comfort

If you...



Your baby will...

| | |
|--|---|
| <ul style="list-style-type: none"> • Describe feelings; put words to your baby’s expressions, for example, when your baby is crying, say “Ling is feeling sad,” and respond appropriately • Create a routine for daily events and talk about it before it starts and as it is happening, example, “It will be bath time soon,” then let him help to get things ready | <ul style="list-style-type: none"> • Feel you are responding to his feelings • Begin to recognize some of the words used to describe feelings • Feel comforted by your response • Feel safe and secure because he knows what’s happening next |
|--|---|

SOCIAL SKILLS – 10–12 months

Typical skills

Emerging skills



Play

If you...



Your baby will...

- Look at family photos and talk about what the people in the pictures are doing
- Provide a safe place where your baby can crawl and explore

- Start to put names with people's faces
- Try to say some of the names
- Communicate his interest in objects around him by gazing, reaching or pointing



Teach

If you...



Your baby will...

- Talk to your baby about upcoming events, for example, mommy's or daddy's return to work from parental leave

- Learn about what is happening and how that affects her

EMOTIONAL SKILLS – 10–12 months

Typical skills

Emerging skills

- Is able to seek comfort when upset, i.e., reaches up to be held
- Expresses many emotions and recognizes them in others, e.g., sad, happy, mad, scared, hurt, discomfort
- Feels guilty when he does something wrong
- Will communicate his need to be in constant sight and hearing of an adult
- Displays affection in hugs, kisses, pats and smiles

- Negativism increases; refuses eating a meal, new foods; resists napping; may have tantrums
- Displays independent behaviour; resists adult control
- Communicates specific preferences for certain people and toys, e.g., crying, laughing
- Able to communicate discomfort when fearful or stressed; may express new fears and insecurity with situations he was fine with before



Comfort

If you...



Your baby will...

- Turn everyday routines into playful moments by adding tickles, giggles and fun interactions
- Ask your baby for hugs and kisses

- Feel loved
- Look forward to daily routines because she enjoys fun times with you
- Feel very loved
- Be encouraged to respond to happy actions



Play

If you...



Your baby will...

- Provide opportunities to play with other babies

- Enjoy the company of other babies
- Try out ways to communicate and engage with other babies



Teach

If you...



Your baby will...

- Look at magazines or books with pictures of people expressing different emotions; talk about how that person is feeling; be sure to use common emotions such as happy, sad and mad

- Begin to label emotions
- Enjoy looking at books

LANGUAGE SKILLS – 10–12 months

| Typical skills | Emerging skills |
|---|--|
| <ul style="list-style-type: none"> • Understands simple sentences, questions and requests, for example, ‘Give the book to me,’ ‘Find your ball’, ‘Where’s your shoe?’ • Learns words and appropriate gestures like saying ‘no’ and shaking his head, saying ‘bye-bye’ and waving, also exclamations such as ‘oh-oh!’ • Starts to anticipate when a surprise happens in a song • Take turns making sounds with you | <ul style="list-style-type: none"> • Responds to simple verbal requests • Uses expressive vocabulary, 2–8 words, like ‘no’, ‘baby’, ‘bye-bye’, ‘hi’ and words that imitate sounds of objects, i.e., bow wow • Uses a single word to express a whole thought • May not talk as much while mastering walking |



Comfort

If you...



Your baby will...

| | |
|--|---|
| <ul style="list-style-type: none"> • Sing familiar songs as often as possible | <ul style="list-style-type: none"> • Attempt to imitate the words or actions |
|--|---|



Play

If you...



Your baby will...

| | |
|---|--|
| <ul style="list-style-type: none"> • Encourage your baby to make music and dance with shakers, pots and pans | <ul style="list-style-type: none"> • Love making noise, hearing rhythm and moving her body in time to music |
|---|--|



Teach

If you...



Your baby will...

| | |
|---|---|
| <ul style="list-style-type: none"> • Label everything in your baby’s world | <ul style="list-style-type: none"> • Learn the names of common objects |
|---|---|

INTELLECTUAL SKILLS – 10–12 months

| Typical skills | Emerging skills |
|---|--|
| <ul style="list-style-type: none"> • Searches for object if he knows it is hidden, e.g., lifts inverted cup, looks in box for toy or unwraps toy • Tries out new actions for same goal; modifies old ones through trial and error • Associates actions and sounds with things for example, meows for kitten, points up when he sees a bird • Is aware of his own actions and some of their implications; compares same action done with both sides of his body • Develops stronger memory skills | <ul style="list-style-type: none"> • Enjoys looking at pictures in books • Points to correct parts of the body when asked where they are • Knows that smaller objects fit in larger ones • Searches for hidden object, whether he remembers it was hidden or he hasn’t seen it hidden • Able to match shapes, e.g., places a cylindrical object in a matching hole in a container • Repeats an action that gets a reaction, such as knocking over blocks |



Comfort

If you...



Your baby will...

| | |
|--|---|
| <ul style="list-style-type: none"> • Use encouraging words such as “good for you” | <ul style="list-style-type: none"> • Develop feelings of self-confidence, independence and a sense of power and satisfaction |
|--|---|



Play



If you...



Your baby will...



| | |
|--|---|
| <ul style="list-style-type: none"> • Play a game in which you and your baby take turns doing simple actions, e.g., clapping, blowing a kiss | <ul style="list-style-type: none"> • Learn to watch and copy an action • Learn that she can make an adult follow her lead |
|--|---|



INTELLECTUAL SKILLS – 10–12 months



| Typical skills | Emerging skills |
|---|---|
|  Teach | |
| If you... |  Your baby will... |
| <ul style="list-style-type: none"> • Provide a variety of interesting objects and boxes or containers for baby to explore, e.g., cereal boxes, yogurt containers, sponges, etc. • Attach a toy by an elastic to your baby’s highchair | <ul style="list-style-type: none"> • Explore the objects and begin to have an understanding of functions and dimensions (size and shape) • Begin to look for the object when he throws it off the tray; learn he can get it back by pulling on the string |

GROSS MOTOR – 10–12 months

| Typical skills | Emerging skills |
|--|---|
| <ul style="list-style-type: none"> • Turns in a circle when sitting—twists to pick up objects • Stands by flexing knees, pushing off from squat • Walks while holding on to furniture • Walks when you hold both hands • Crawls up stairs • Crawls on the floor expertly | <ul style="list-style-type: none"> • Walks with one hand held • Squats down, stoops, bends over, then gets up • Crawls up and down stairs • Walks alone 2 or 3 steps • Plops down when moves from standing to sitting position |

| | |
|---|--|
|  Comfort | |
| If you... |  Your baby will... |
| <ul style="list-style-type: none"> • Provide lots of encouragement when baby tries to stand holding onto furniture • Go for walks in the park or yard and give your baby the chance to practice walking with your support | <ul style="list-style-type: none"> • Be motivated to keep on trying • Feel more confident about taking steps and feel secure with this new way of moving |

| | |
|--|--|
|  Play | |
| If you... |  Your baby will... |
| <ul style="list-style-type: none"> • Roll a ball back and forth between you and your baby • While playing on the floor, place some of his favourite toys around him far enough away so he has to reach to get them; praise him when he is successful | <ul style="list-style-type: none"> • Learn to coordinate eye and hand movements for bigger actions such as pushing, pulling, throwing • Learn to move confidently in different directions from the sitting position while reaching for objects of interest |

| | |
|--|--|
|  Teach | |
| If you... |  Your baby will... |
| <ul style="list-style-type: none"> • Supporting your baby from behind or by holding her hand, practice going up a few steps • Once your baby can pull himself up holding onto furniture, encourage him to hold on with one hand; urge him to let go once he’s comfortable; position yourself close by in case he falls | <ul style="list-style-type: none"> • Learn to crawl up steps with a sense of security knowing you are there if she falls • Feel your physical and emotional support as he practices standing freely and learns that if he falls he can get right back up |

FINE MOTOR – 10–12 months

| Typical skills | Emerging skills |
|--|--|
| <ul style="list-style-type: none"> • Uses neat pincer grasp (tips of index finger and thumb) to pick up small items • Puts objects in and takes them out of container • Points, pokes, touches and pries with extended index finger • Places one block on top of another without balancing • Voluntarily releases objects to another person on request • Holds spoon but needs help with its use | <ul style="list-style-type: none"> • Uses both hands freely—may show preference for one • Pulls off socks, hats • Holds crayons, makes marks • Builds tower using two cubes • Points with index finger • Feeds self with spoon and drinks from a cup |



Comfort

If you...



Your baby will...

| | |
|--|--|
| <ul style="list-style-type: none"> • Place finger foods on your baby’s plate or tray and show her how to pick them up • In a safe place on the floor, use soft building blocks to make a tower; show her how to pick up one block and place it on top of another | <ul style="list-style-type: none"> • Feel more confident and encouraged to use her fingers to pick up the food • Learn about what is involved in stacking objects • Feel confident about how to pick up and let go of objects |
|--|--|



Play

If you...



Your baby will...

| | |
|---|---|
| <ul style="list-style-type: none"> • Create a safe space in the kitchen with lots of different sized plastic containers and bowls • Together with your baby, sing songs and fingerplay that encourage him to move his fingers | <ul style="list-style-type: none"> • Enjoy putting things inside of one another and seeing how they fit • Learn to move his fingers with greater control • Feel loved and secured playing with you |
|---|---|



Teach

If you...



Your baby will...

| | |
|---|--|
| <ul style="list-style-type: none"> • Introduce your baby to cause and effect toys that require her to do something to hear noise or see action | <ul style="list-style-type: none"> • Learn that she can control things in her environment |
|---|--|

Your Child Between 13 and 18 Months

Your baby’s second year of life brings new skills for a different perspective on the world around her. At this stage your baby will begin to:

- Push and pull toys while walking.



- Turn pages of a book.
- Show a sense of humour.
- Identify herself in the mirror or photograph.
- Realize that things are still there, even when they are out of sight.



SOCIAL SKILLS 13–18 months



| Typical skills | Emerging skills |
|--|---|
| <ul style="list-style-type: none"> • Points to show you something • Understands far more words than can speak, e.g., can point to at least three different body parts when asked, “Where’s your mouth?” • Uses “no” correctly, often with a shake of the head • Uses five or more words to express needs, desires or expressions such as “all gone” • Tries to sing songs | <ul style="list-style-type: none"> • Names pictures in a book • Imitates animal sounds • Uses own name to refer to self • Follows simple directions without gestures, e.g., “Come, show me, go get, etc.” |

SOCIAL SKILLS 13–18 months

| Typical skills | Emerging skills |
|----------------|-----------------|
|----------------|-----------------|

| | | | |
|--|-----------------------------|---|---|
|  | Comfort If you... |  | Your baby will... |
| <ul style="list-style-type: none"> Use your child’s relaxed bath time to name parts of her body | | | <ul style="list-style-type: none"> Learn to point to different parts of the body by name |



| | | | |
|--|--------------------------|---|--|
|  | Play If you... |  | Your baby will... |
| <ul style="list-style-type: none"> When dressing your child, hold up his socks and say, “Socks go on your feet. Show me your feet.” Repeat using other clothes and body parts | | | <ul style="list-style-type: none"> Practice matching words to the different parts of his body as well as developing a positive sense of self and body image |



| | | | |
|---|---------------------------|---|---|
|  | Teach If you... |  | Your baby will... |
| <ul style="list-style-type: none"> Count things together in books and find the same objects in your home | | | <ul style="list-style-type: none"> Match real objects with those that she sees as two-dimensional in print |

EMOTIONAL SKILLS – 13–18 months



| Typical skills | Emerging skills |
|----------------|-----------------|
|----------------|-----------------|

| | |
|---|--|
| <ul style="list-style-type: none"> Is more confident, exploring and trying new things, taking risks when a trusted adult is present or has provided reassurance Shows particular interest in a music tape, special picture books or fish in a tank Identifies self in mirror or photograph; becomes more of an individual Hugs and kisses parents and other very familiar people and pets Enjoys being the centre of attention | <ul style="list-style-type: none"> Shows jealousy when attention is given to other family members Shows frustration easily Displays a sense of ownership over toys and people |
|---|--|

| | | | |
|---|-----------------------------|---|--|
|  | Comfort If you... |  | Your baby will... |
| <ul style="list-style-type: none"> Encourage your child to safely explore his surroundings, e.g., cupboards Give your child many opportunities to feel successful, e.g., play a game that he has initiated or allow him to take off his shoes | | | <ul style="list-style-type: none"> Explore his environment in a self-directed way Develop a sense of competence and feeling that he can influence others |



| | | | |
|---|--------------------------|---|---|
|  | Play If you... |  | Your baby will... |
| <ul style="list-style-type: none"> Use stories, songs or toys (teddies) to explore feelings Provide opportunities for your child to play on her own | | | <ul style="list-style-type: none"> Express emotion in response to what she sees or hears Learn to be self-reliant for small periods of time |



EMOTIONAL SKILLS – 13–18 months



| Typical skills | Emerging skills |
|---|--|
|  Teach If you...  Your baby will... | |
| <ul style="list-style-type: none"> • Teach your child simple words to express his feelings, e.g., “I’m sad, I’m tired” • Inform him when a routine will be different and what will be happening | <ul style="list-style-type: none"> • Learn to connect words to how he feels • Become better prepared to deal with any changes and lessen his anxiety |

LANGUAGE SKILLS 13–18 months

| Typical skills | Emerging skills |
|--|--|
| <ul style="list-style-type: none"> • Begins to show sense of humour • Plays best on her own; doesn’t want to share toys, shouting, “Mine, mine” or fights with another child over who gets to use a specific toy • Enjoys imitating adult task, example, dusting, sweeping floors, setting the table, raking lawn, etc. • Strongly resists limits you set • Looks at you when you are talking or playing together | <ul style="list-style-type: none"> • May be able to cooperate at times but may not respond quickly or will do the opposite of the request • Plays alongside and parallel to another child • Tries to dress/undress himself, e.g., pull up pants, undo Velcro shoe fasteners |

| | |
|---|---|
|  Comfort If you...  Your baby will... | |
| <ul style="list-style-type: none"> • Have good-bye routines when you and family members leave each other • Give your child the opportunity to partake in some daily chores, e.g. emptying the laundry basket, putting food in cupboards | <ul style="list-style-type: none"> • Be comforted by these routines which mean that people always come back • Enjoy imitating an adult task while feeling a sense of independence |

| | |
|--|---|
|  Play If you...  Your baby will... | |
| <ul style="list-style-type: none"> • Provide regular opportunities for your child to play with other children her age • Introduce make-believe toys such as dolls with accompanying props, e.g., small bottle, blanket, cradle or stroller | <ul style="list-style-type: none"> • Begin to learn the give and take that comes with being in a social group • Enjoy recreating familiar actions she has experienced herself |

| | |
|---|---|
|  Teach If you...  Your baby will... | |
| <ul style="list-style-type: none"> • Share a toy with your child, taking turns with it • Use “Yes” and “No” to clearly set limits and explain why; always respond warmly | <ul style="list-style-type: none"> • Begin to learn what’s expected when he plays with others • Begin to understand what actions are acceptable or not acceptable |

INTELLECTUAL SKILLS – 13–18 months

| Typical skills | Emerging skills |
|---|--|
| <ul style="list-style-type: none"> • Realizes things exist when they are out of sight • Shows understanding of some colours and shapes, e.g., matches circles and squares on a form board • Identifies pictures when requested, e.g., “Show me” or “Where’s the ___?” • Gains new understanding of the world around him while exploring the environment by looking for something to fit in holes; mix, fill, pile and dump sand at the sand table; stack, knock over or restack a set of boxes, blocks • Shows increased memory skills | <ul style="list-style-type: none"> • Groups similar things, such as socks, shoes • Engages in imaginative play during daily routines such as feeding, putting to bed or bathing dolls • Uses playdough and paints |



Comfort

If you...



Your baby will...

| | |
|---|---|
| <ul style="list-style-type: none"> • Read board books and look at pictures with your child | <ul style="list-style-type: none"> • Learn to point to different parts of the body by name |
|---|---|



Play

If you...



Your baby will...

| | |
|---|---|
| <ul style="list-style-type: none"> • Watch your child’s cues to learn the things he likes to play with | <ul style="list-style-type: none"> • Take the lead in playing or doing things she enjoys |
|---|---|



Teach

If you...



Your baby will...

| | |
|---|--|
| <ul style="list-style-type: none"> • Offer a toy with wheels that can be pulled by a string; encourage her to watch what happens when she pulls the string | <ul style="list-style-type: none"> • Begin to understand cause and effect |
|---|--|

GROSS MOTOR – 13–18 months

| Typical skills | Emerging skills |
|---|---|
| <ul style="list-style-type: none"> • Walks alone • Crawls or walks upstairs one step at a time holding onto banister or hand • Pushes and pulls toys while walking • Squats to pick up toy without falling • Climbs on things by himself, for example, chairs, sofas, tables or out of cribs, high chairs, strollers | <ul style="list-style-type: none"> • Walks down stairs holding rail—both feet on step • Tries to kick a ball • Likes to ride toys • Likes to run, but falls and bumps into things • Walks backward |



Comfort

If you...



Your baby will...

| | |
|---|--|
| <ul style="list-style-type: none"> • Stay close and supervise your child in the park • Safety proof the house | <ul style="list-style-type: none"> • Feel safe while exploring and testing out new motor skills • Feel confident playing and exploring at home |
|---|--|

GROSS MOTOR – 13–18 months

| Typical skills | Emerging skills |
|----------------|-----------------|
|----------------|-----------------|



Play

If you...



Your baby will...

| | |
|--|---|
| <ul style="list-style-type: none"> • Take your child to the park or playground often • Play favourite music/songs and encourage her to move to the music | <ul style="list-style-type: none"> • Take every opportunity to practice walking, climbing, jumping and running skills • Have fun swaying legs, body, arms and head to different rhythms |
|--|---|



Teach

If you...



Your baby will...

| | |
|--|---|
| <ul style="list-style-type: none"> • Arrange an obstacle course in a room so she can crawl through a box, under a chair, over a big pillow, etc. • Offer your child balls of different sizes | <ul style="list-style-type: none"> • Learn how to move her body through space • Feel the difference in weight; learn how to hold each one (one hand or two), to throw or roll the balls |
|--|---|

FINE MOTOR – 13–18 months

| Typical skills | Emerging skills |
|----------------|-----------------|
|----------------|-----------------|

| | |
|---|---|
| <ul style="list-style-type: none"> • Releases object to other person on request or gesture • Picks up and eats finger foods, e.g., raisin, cheerio, cracker, etc. • Turns container upside down to get an item out • Puts pegs into a pegboard • Turns pages of a book • Stacks three or more blocks • Scribbles with a big crayon | <ul style="list-style-type: none"> • Feeds self with spoon and fork • Throws ball forward • Begins to unlatch, unscrew, open and take apart • Squeezes, pokes, and pats playdough • Copies simple lines drawn on paper |
|---|---|



Comfort

If you...



Your baby will...

| | |
|--|--|
| <ul style="list-style-type: none"> • Give your child the opportunity to feed himself finger foods at meal times • Spend time reading picture books with your child | <ul style="list-style-type: none"> • Practice independent, self-help skills and be proud of newly emerging abilities • Use small muscles in his fingers to turn the pages and set the pace of your time together |
|--|--|



Play

If you...



Your baby will...

| | |
|--|--|
| <ul style="list-style-type: none"> • Offer your child plastic bowls she can either stack or put one inside the other • Provide big crayons and lots of paper | <ul style="list-style-type: none"> • Practice independent, self-help skills and be proud of newly emerging abilities • Use small muscles in his fingers to turn the pages and set the pace of your time together |
|--|--|



Teach

If you...



Your baby will...

| | |
|--|--|
| <ul style="list-style-type: none"> • Provide pots and lids to encourage finding matching sets • Help your child to solve a simple jigsaw puzzle with one or two large pieces | <ul style="list-style-type: none"> • Enjoy making noise with the pots and lids while beginning to appreciate different sizes of objects • Explore how things fit together using his new fine motor abilities |
|--|--|

The Remarkable World of Your Toddler: An Overview of Your Toddler’s Development at 19–24 Months

The toddler stage is a hugely exciting time, as parents begin to get a real sense of their child’s personality, especially with their toddler learning to do so many things. Your child will try to be independent but will still be a bit scared of it all. At this stage, it’s common for him to cling to you 1 min, afraid you will leave, and then want nothing to do with you the next. These sudden shifts of emotions, tantrums and bouts of helplessness are all part of his becoming his own person.

By 24 months, many toddlers play on their own, use their new motor skills to run, kick balls, jump and climb. They also can tackle fine motor

tasks such as large puzzles, taking lids off jars, using a fork, pulling off shoes and socks and building bigger and better block towers. Language is exploding at this time, even though his favourite word is “No!” When he talks, you should be able to understand him about half the time. And more and more, he will express his feelings, interests and needs in words.

Your Toddler Between 19 and 24 Months

Your toddler is entering a new and exciting stage of life. In this first stage, he will start to:

- Kick a ball.
- Take off shoes, socks and hats.
- Show ownership or possession of objects.
- Show fear, but is able to be settled down.
- Use two word sentences such as ‘More juice.’

SOCIAL SKILLS 19–24 months

| Typical skills | Emerging skills |
|---|--|
| <ul style="list-style-type: none"> • Enjoys playing alone for a few minutes, e.g., building blocks, drawing, looking at books • Shows ownership or possession of objects and cannot share easily • Says ‘no’ and likes to do things without help • Helps with simple household chores | <ul style="list-style-type: none"> • Distinguishes herself as a separate person, contrasts herself with others • Begins to be toilet trained • Puts on simple clothing without help |



Comfort

If you...



Your baby will...

- Use everyday routines (e.g., walks, meal times) as a time to talk about family and friends
- Follow your child’s lead rather than direct the play; suggest things, but let your child decide what she wants to do

- Learn the words to use when talking about feelings
- Feel comforted and supported to see there are ways to deal with her emotions



Play

If you...




Your baby will...

- Look at photos of family events so your child can find himself and identify family members
- Set up a water play activity with another playmate; give them dolls, sponges, and towels


- Begin to associate certain emotions with behaviours
- Begin to see what can make others sad, happy, angry, etc.


SOCIAL SKILLS 19–24 months


| Typical skills | Emerging skills |
|---|--|
|  Teach | |
| If you... | Your baby will... |
| <ul style="list-style-type: none"> • Prepare your child ahead of time for new social events, e.g., “At playgroup we will sing songs and listen to stories” • Let your child help with chores, e.g., wiping spills, putting clothes in drawers | <ul style="list-style-type: none"> • Know he can rely on you to help him cope with his emotions • Begin to develop some strategies to deal with his emotions |

EMOTIONAL SKILLS – 19–24 months

| Typical skills | Emerging skills |
|--|--|
| <ul style="list-style-type: none"> • Beginning to develop a range of emotions; is subject to mood swings and tantrums; shows some aggressive tendencies, e.g., biting and hitting • Shows concern for others • Shows fears, but can be settled down • Is pulled between the need to show independence and still being dependent for certain things • Still cautious around unfamiliar adults i.e. allows self to be drawn into play with a new adult as long as a familiar person is nearby | <ul style="list-style-type: none"> • Uses words such as “NO” a lot • Shares a piece of food • Familiar with routines and the order of the day; is unhappy about any changes in routine and likes to do things the same way each day • Develops a sense of comfort or fear with different experiences and objects, e.g., fear of the dark |

| | |
|---|--|
|  Comfort | |
| If you... | Your baby will... |
| <ul style="list-style-type: none"> • Recognize and name your child’s emotions, e.g., “Your crying tells me you are sad” • Suggest ways to deal with her feelings, e.g., “When you feel angry, come and get a grown-up for help” | <ul style="list-style-type: none"> • Learn the words to use when talking about feelings • Feel comforted and supported to see there are ways to deal with her emotions |

| | |
|--|---|
|  Play | |
| If you... | Your baby will... |
| <ul style="list-style-type: none"> • Sing songs that use emotion words, e.g., “If you’re happy and you know it, clap your hands” • Read stories that explore different emotions and discuss them simply from the character’s perspective | <ul style="list-style-type: none"> • Begin to associate certain emotions with behaviours • Begin to see what can make other sad, happy, angry, etc. |

| | |
|--|--|
|  Teach | |
| If you... | Your baby will... |
| <ul style="list-style-type: none"> • Notice when your child is frustrated and step in to help him deal with his emotions • Offer your child different choices to help him cope with his feelings | <ul style="list-style-type: none"> • Know he can rely on you to help him cope with his emotions • Begin to develop some strategies to deal with his emotions |

LANGUAGE SKILLS – 19–24 months

| Typical skills | Emerging skills |
|---|--|
| <ul style="list-style-type: none"> • Uses two word sentences, e.g., “more juice” or “want cookie” • Asks for help using words or actions • Jabbers in run-on flow of words while talking to stuffed animals or self • Names some pictures in a book • Imitates new words and phrases, e.g., “Go bye-bye” and “Mommy’s car” | <ul style="list-style-type: none"> • Sings simple songs with correct words and actions • Is more articulate; many more words are understood by others outside the family • Starts to use plurals • Uses past tense Imitates spontaneously or repeats new words |



Comfort

If you...



Your baby will...

| | |
|---|--|
| <ul style="list-style-type: none"> • Read books to your child that reflect her reality, e.g., starting child care, going to the doctor, playing with another child | <ul style="list-style-type: none"> • Begin to recognize common events and situations in printed materials |
|---|--|



Play

If you...



Your baby will...

| | |
|--|---|
| <ul style="list-style-type: none"> • Count fingers, toes, eyes, ears, mouth and nose during bath or play time | <ul style="list-style-type: none"> • Develop a strong sense of physical self, and learn numbers and words for body parts |
|--|---|



Teach

If you...



Your baby will...

| | |
|---|--|
| <ul style="list-style-type: none"> • Point out familiar sounds when walking or playing outside, e.g., car horns, dogs barking or fire truck sirens | <ul style="list-style-type: none"> • Begin to distinguish different sounds and learn the names for them |
|---|--|

INTELLECTUAL SKILLS – 19–24 months

| Typical skills | Emerging skills |
|--|--|
| <ul style="list-style-type: none"> • Understands how familiar objects are used, e.g., spoon for eating, cup for drinking, ball for throwing, hammer for banging, etc. • Understands the passing of time and the meaning of “not now” and “when we go home” • Recognizes and names familiar people in photos • Busy mastering existing skills which leads to the emergence of new ones • Shows increased memory for details and routines, e.g., says “hot” when reaching for a coffee cup; holds up seat belt in car seat to indicate it needs to be secured; remembers where objects go | <ul style="list-style-type: none"> • Explores one-to-one correspondence • Has a sense of more than one • Has intense curiosity to investigate any new person, object or sound • Understands two-part requests, e.g., “Go to the shelf and bring over the blocks” |



Comfort

If you...



Your baby will...

| | |
|---|---|
| <ul style="list-style-type: none"> • Follow your child’s lead in play, allowing her to be the director of the activities | <ul style="list-style-type: none"> • Begin to develop a sense of control about what she does and feel that you value her efforts |
|---|---|

INTELLECTUAL SKILLS – 19–24 months

| Typical skills | Emerging skills |
|----------------|-----------------|
|----------------|-----------------|



Play

If you...



Your baby will...

- | | |
|---|--|
| <ul style="list-style-type: none"> Count fingers, toes, eyes, ears, mouth and nose during bath or play time Provide different size containers for water and sand play | <ul style="list-style-type: none"> Develop a strong sense of physical self Explore relationships of size in objects as well as the concept of empty and full |
|---|--|



Teach

If you...



Your baby will...

- | | |
|--|--|
| <ul style="list-style-type: none"> Offer experiences that allow him to use his skills but challenge him a bit, e.g., if he can stack three blocks, add a fourth | <ul style="list-style-type: none"> Feel confident enough to try to overcome the challenge |
|--|--|

FINE MOTOR – 19–24 months

| Typical skills | Emerging skills |
|----------------|-----------------|
|----------------|-----------------|

- | | |
|---|---|
| <ul style="list-style-type: none"> Takes lids off jars Fits cups and boxes inside each other (nesting) Takes off shoes, hat and socks Strings large beads, using one hand to slide the bead while the other hand holds the string Raises and drinks from a cup then replaces it on table | <ul style="list-style-type: none"> Opens doors by turning knobs Imitates horizontal or circular strokes with a crayon Snips with scissors Folds paper in half |
|---|---|



Comfort

If you...



Your baby will...

- | | |
|---|--|
| <ul style="list-style-type: none"> Allow your child to undress as much as she is capable of Provide lots of containers during bath time | <ul style="list-style-type: none"> Feel independent while practicing eye-hand coordination Enjoy the sensory pleasure of pouring water in and out of containers repeatedly |
|---|--|



Play

If you...



Your baby will...

- | | |
|---|--|
| <ul style="list-style-type: none"> Provide large beads or buttons with a shoelace or string for beading Offer simple form boards or shape sorters (no more than three shapes) | <ul style="list-style-type: none"> Practice the fine motor coordination sequence required for inserting, threading and pulling Use his eyes and hands to practice distinguishing differences of shapes, such as circles, squares and triangles |
|---|--|



Teach

If you...



Your baby will...

- | | |
|---|---|
| <ul style="list-style-type: none"> Help your child make pictures using stickers; talk to her about what she is doing Invite your child to open and close few plastic containers in your kitchen | <ul style="list-style-type: none"> Practice the two step process of peeling/lifting the sticker off and placing it somewhere on the paper Use fine motor skills to put on lids Display very preliminary use of trial and error to find solutions |
|---|---|

GROSS MOTOR – 19–24 months

| Typical skills | Emerging skills |
|---|--|
| <ul style="list-style-type: none"> • Rides on small wheeled toys • Carries a large toy while walking • Kicks a ball • Squats while playing • Walks backwards or sideways pulling a toy • Backs into chair to sit down | <ul style="list-style-type: none"> • Walks on tip-toes • Throws and retrieves objects • Jumps in place with both feet • Catches a large ball |

**Comfort**

If you...



Your baby will...

| | |
|--|--|
| <ul style="list-style-type: none"> • Provide child-sized furniture • Provide child-sized versions of adult things, e.g., soccer ball | <ul style="list-style-type: none"> • Feel more in control if he can sit in a small chair and at a small table to do his activities • Feel like he can do really important things with his body |
|--|--|

**Play**

If you...



Your baby will...

| | |
|---|--|
| <ul style="list-style-type: none"> • Provide your child with toys that allow her to push and pedal with her feet • Pretend you are at the zoo and ask your child to move like animals, e.g., hop like a frog, squat like a bird, jump like a rabbit | <ul style="list-style-type: none"> • Practice climbing on and off ride toys and learn to coordinate her eyes, feet and hands • Practice and refine new motor abilities |
|---|--|

**Teach**

If you...



Your baby will...

| | |
|---|--|
| <ul style="list-style-type: none"> • Describe your child's movements and actions as he climbs the stairs, jumps over an object or crawls under a chair • Play different kinds of music for your child to dance to (e.g., march, rock 'n' roll, waltz) | <ul style="list-style-type: none"> • Learn to label his own actions and begin to understand words related to position (i.e. up/down, over/under, through) • Respond creatively by inventing his own movements and physically interpret the mood and speed of music |
|---|--|

The Remarkable World of Your Toddler: An Overview of Your Toddler's Development at 25–36 Months

The toddler stage is a hugely exciting time, as parents begin to get a real sense of their child's personality, especially with their toddler learning to do so many things. Your child will try to be independent but will still be a bit scared of it all. At this stage, it's common for him to cling to you 1 min, afraid you will leave, and then want nothing to do with you the next. These sudden shifts of emotions, tantrums and bouts of help-

lessness are all part of his becoming his own person.

In the final phase of toddlerhood, your child's mental abilities show dramatic growth. He explores the more abstract concepts of shapes, colours, size and quantity by playing with puzzles, paints, water and sand, and, of course, books. He may be able to match objects, sort clothing, count and tell the difference between "one" and "many." Although he is more sociable now and enjoys playing with other children, he is still not great at sharing or cooperating. These days, your toddler is spending a lot of his time building confidence and self-esteem, ready to enter the world of the preschooler.

Your Toddler Between 25 and 30 Months

As she starts into her third year, you will notice some dramatic achievements. For example, your toddler will start to:

- Walk upstairs and downstairs alone, with both feet on one step.

- Scribble, clutching the crayon in her whole hand.
- Show she can be attached to a cuddly or favourite toy.
- Express feelings through language and pretend play.
- Better understand the similarities and differences of shapes and sizes

SOCIAL SKILLS 25–30 months

| Typical skills | Emerging skills |
|--|---|
| <ul style="list-style-type: none"> • Establishes self as separate from parents, saying, “No! Me do it!” • Displays shyness around strangers and in outside situations • Likes to play near other children but not yet able to play co-operatively • May pull hair, hit or bite other children when frustrated • Becomes aware of gender differences | <ul style="list-style-type: none"> • Helps put things away • Approaches new person after you have talked to them • Begins to show more readiness for co-operative play • Is more able to wait patiently for needs to be met by others • Knows own gender, and that of others |



Comfort

If you...



Your baby will...

- Praise everyday experiences and encourage positive behaviour
- Provide safe opportunities to assert independence
- Read stories to your toddler about ways people care about each other

- Know you notice her and develop a feeling of self worth
- Know she is a separate person but that you are there to help her if needed
- Begin to understand the actions that go with caring and how to get along with others



Play

If you...



Your baby will...

- Provide opportunities to go to the park and play in the sand with other children
- Invite one peer over to play for a short time
- Encourage your toddler to play with his dolls and pour them drinks

- Feel a sense of belonging in a group
- Begin to develop social skills and become more able to play with others one on one
- Begin to practice caring for the needs of another



Teach

If you...



Your baby will...

- Share a quiet activity together, such as reading a book
- When conflicts occur, explain how her behaviour makes the other person feel
- Encourage taking turns adding ingredients when making playdough together

- Feel valued because you made time for her
- Begin to learn positive ways to interact with other children and to problem-solve
- Develop important social skills while doing a soothing and enjoyable activity

EMOTIONAL SKILLS – 25–30 months

| Typical skills | Emerging skills |
|---|--|
| <ul style="list-style-type: none"> • Moves back and forth between wanting independence and needing security of parents • Can still be attached to a cuddly or favourite toy • Demands his own way much of the time • Needs an ordered, predictable routine (e.g., when saying good-bye to parent in the morning) • Expresses feelings through language and pretend play (e.g., roaring like an angry lion) | <ul style="list-style-type: none"> • Separates more easily from parents • Responds to other children's feelings and begins to show empathy • May develop sudden fears • Displays frustration and tantrums if he is not understood • Becomes less upset by limits and discipline |

**Comfort****If you...****Your baby will...**

| | |
|--|--|
| <ul style="list-style-type: none"> • Model coping with emotions, such as talking through frustrating problems with your toddler, using words like, "This makes me feel sad/happy" • Move your toddler to a quieter place when he is having difficulty coping with his emotions | <ul style="list-style-type: none"> • Feel comfortable expressing his feelings • Be more likely to recognize emotions in other children and adults • Learn strategies for dealing with emotions • Learn more acceptable coping skills |
|--|--|

**Play****If you...****Your baby will...**

| | |
|---|---|
| <ul style="list-style-type: none"> • Provide the chance for pretend play with dolls and teddies in order to experiment with emotions • Give your toddler many opportunities to "do it myself;" offer times to practice getting dressed or helping with household tasks • Read books that illustrate how children or animals experience a range of emotions like jealousy, anger, affection | <ul style="list-style-type: none"> • Express different emotions through toys • Begin to understand that he is a separate person from you • Develop the ability to understand another person's emotions and what might have caused them |
|---|---|







**Teach****If you...****Your baby will...**

| | |
|---|--|
| <ul style="list-style-type: none"> • Encourage your toddler to understand how others may feel in situations • Help her understand how her behaviour may have an impact on others • Watch education programs on television and point out the kinds of emotions characters are feeling | <ul style="list-style-type: none"> • Begin to develop empathy and sympathy • Begin to be aware of the feelings others may have • Begin to understand how other children might feel in certain situations • Enjoy being with you and talking about an imaginary character |
|---|--|





LANGUAGE SKILLS – 25–30 months

| Typical skills | Emerging skills |
|---|---|
| <ul style="list-style-type: none"> • Uses "self-centred" pronouns like 'I', 'me', 'mine', 'you' • Puts together simple, two-word sentences • Answers simple questions like, "What's your name?", and performs simple tasks when asked to • Enjoys looking at books and talking about the pictures • Sings parts of songs | <ul style="list-style-type: none"> • Is able to use words that describe things, e.g., big, dirty, wet, hot • Participates more in conversations and stories • Is able to provide more information about self (e.g., name, gender, age) and understands two-step directions • Can recite a few simple nursery rhymes • Using plurals in a general way (e.g., foos not feet) |

LANGUAGE SKILLS – 25–30 months

| Typical skills | Emerging skills |
|---|---|
|  Comfort If you...  Your baby will... | |
| <ul style="list-style-type: none"> • Provide opportunities for your toddler to talk about things that he finds interesting | <ul style="list-style-type: none"> • Know that you are interested in what he has to say and will want to converse with you |
|  Play If you...  Your baby will... | |
| <ul style="list-style-type: none"> • Let your toddler fill in the blanks while singing a song | <ul style="list-style-type: none"> • Enjoy singing important words on her own |
|  Teach If you...  Your baby will... | |
| <ul style="list-style-type: none"> • Keep expanding language by adding more new words and descriptions about events in your toddler’s day | <ul style="list-style-type: none"> • Develop confidence in the use of many words and feel secure enough to try new words |

INTELLECTUAL SKILLS – 25–30 months

| Typical skills | Emerging skills |
|---|--|
| <ul style="list-style-type: none"> • Engages in simple pretend play with others • Matches shapes, pictures, some colours • Can better understand the similarities and differences of shapes and sizes • Becomes aware of verbal sequence of numbers • Shows increased attention span, staying with activities longer | <ul style="list-style-type: none"> • Sorts groups of objects into sets • Completes simple puzzles • Combines toys and games in more complex ways (e.g., uses playdough in dramatic play) • Begins to understand the concept of future time, e.g., ‘soon’, ‘in a long time’, but not past, e.g., ‘yesterday’ • Begins to understand one-to-one actions, e.g., one plate per person |
|  Comfort If you...  Your baby will... | |
| <ul style="list-style-type: none"> • Incorporate numbers and counting into daily routines, such as tidying up toys or putting away tin cans • Make playdough with your toddler | <ul style="list-style-type: none"> • Begin to understand that numbers are a part of his everyday environment • Observe how dry ingredients change in texture through the process of cooking |
|  Play If you...  Your baby will... | |
| <ul style="list-style-type: none"> • Incorporate counting into child-initiated activities, such as block building, for example, “Let’s count how many blocks you used in your tower” • Provide different sized jars and lids and, together, find out which ones match | <ul style="list-style-type: none"> • Begin to recognize and correctly repeat numbers; may only count to 4 with confidence • Enjoy working with you to solve problems |

INTELLECTUAL SKILLS – 25–30 months

Typical skills

Emerging skills

**Teach****If you...****Your baby will...**

- Offer experiences for your toddler to sort objects, for example, all the puzzles in this box, crayons in this tin
- Play with playdough using different tools, cookie cutters, rollers and so on

- Experiment with sorting, such as the big blocks in one pile, little blocks in another
- Compare the different sizes and shapes of objects he creates

FINE MOTOR – 25–30 months

Typical skills

Emerging skills

- Scribbles, holding the crayon in whole hand
- Imitates drawing vertical and horizontal lines
- Builds a tower of five or more blocks
- Strings beads, picking them up with thumb and forefinger
- Removes lids from jars, rotating wrist

- Begins to use thumb and fingertips when holding crayon
- Imitates drawing a cross, copies a circle
- Folds paper
- Uses small scissors to snip paper
- Removes clothing already unbuttoned; pulls up zipper

**Comfort****If you...****Your baby will...**

- Praise your toddler's drawing efforts and describe the markings you see
- Provide your toddler with chances to practice dressing skills, helping with buttons and zippers
- Make playdough with your toddler and create different shapes together

- Know you are interested in his creations and feel encouraged to draw more
- Develop confidence in his ability to dress himself
- Enjoy the soothing feeling as he squeezes, pinches, rolls, pats and shapes the dough

**Play****If you...****Your baby will...**

- Make necklaces together using beads, cut up straws, bits of paper with holes punched in them
- Supply your toddler with costumes for pretend play including hats, shoes, coats, pants
- Provide many art materials including markers, crayons, paint and chalk

- Strengthen her ability to pick things up using thumb and forefingers (pincer grasp)
- Practice dressing skills as she engages in an imaginative activity
- Become more able to control these materials as she scribbles and copies lines and shapes

**Teach****If you...****Your baby will...**

- Provide your child with tongs and various items to sort onto different plates
- Provide puzzles of different sizes and colours, and different numbers of pieces
- Invite your toddler to help with simple cooking jobs like ripping lettuce or stirring with a spoon

- Practice the grasp he will be using to cut with scissors
- Learn to use his grasping skills, problem-solve and complete tasks he started
- See how his growing skills can be used to help other people

GROSS MOTOR – 25–30 months

| Typical skills | Emerging skills |
|---|---|
| <ul style="list-style-type: none"> • Walks backward and sideways • Walks upstairs and downstairs alone, both feet on one step • Runs without falling • Jumps in place, both feet off the floor • Climbs on a riding toy and makes it go using both feet at the same time | <ul style="list-style-type: none"> • Walks on narrow balance beam • Walks upstairs and downstairs, alternating feet, holding the handrail • Runs, avoiding obstacles • Jumps forward • Pedals a tricycle |



Comfort

If you...



Your baby will...

| | |
|---|--|
| <ul style="list-style-type: none"> • Join in pretend play and move with your toddler, jumping like mother and baby frogs, slithering like daddy and baby snakes • Praise your toddler’s efforts when she runs at the park or goes down the slide • Do knee bounces like “To Market, To Market” | <ul style="list-style-type: none"> • Know that you enjoy playing with her and will be able to practice different actions by using his imagination • Develop confidence in her ability to test her physical abilities • Enjoy being cuddled while you bounce and giggle together |
|---|--|



Play

If you...



Your baby will...

| | |
|--|--|
| <ul style="list-style-type: none"> • Play different music and encourage your toddler to explore different movements like jumping, rolling, stretching, marching and walking • Set up some plastic bottles for bowling pins so your toddler can knock them down with a ball • Play “Sleeping bunnies,” substituting different actions and creatures like birds, horses and elephants | <ul style="list-style-type: none"> • Make comparisons between each movement and learn to match them to different music styles, speeds • Be able to practice coordinating arm movements and aiming a ball • Be able to explore different movements like flying, galloping and stomping |
|--|--|



Teach

If you...



Your baby will...

| | |
|--|---|
| <ul style="list-style-type: none"> • Play simple movement games where your toddler can stop and go, change directions, move quickly or slowly • Sing songs like “If you’re happy and you know it,” naming body parts and doing different actions • Demonstrate different movements like marching, bending, stretching and | <ul style="list-style-type: none"> • Learn several concepts through movement like stop/go, fast/slow, backward/forward, up/down • Be able to label his body parts and learn that shoulders shrug, feet stomp, hands clap, knees bend and hips twist • Feel encouraged to explore new physical skills by following your example |
|--|---|

Your Toddler Between 31 and 36 Months

The last half of your child’s third year is full of exciting developmental gains. At this stage you will notice your toddler beginning to:

- Run without falling.

- Remove lids from jars, rotating her wrist.
- Enjoy playing near other children, but he is not yet able to play co-operatively.
- Enjoy looking at books and talking about the pictures.
- Match shapes, pictures, and some colours.

SOCIAL SKILLS – 30–36 months

| Typical skills | Emerging skills |
|--|---|
| <ul style="list-style-type: none"> Expresses affection openly Uses social conventions like ‘please’, ‘thank you’ and greetings Plays alongside others comfortably Is more able to play co-operatively and take turns Plays make-believe games | <ul style="list-style-type: none"> Imitates adult behaviours, for example, shopping in make-believe grocery store; creates an imaginary friend to talk to Is comfortable around new adults Helps other children to do things Develops pro-social skills like turn-taking, sharing, using words to resolve conflicts |



Comfort

If you...



Your baby will...

| | |
|---|--|
| <ul style="list-style-type: none"> Introduce your toddler to familiar neighbours and community workers Demonstrate affection with hugs and loving words Acknowledge his positive behaviours, for example, “The way you shared was so polite” | <ul style="list-style-type: none"> Learn to recognize people and feel safe with them Learn how to show affection appropriately Know his behaviour was appropriate and be motivated to repeat it |
|---|--|



Play

If you...



Your baby will...

| | |
|---|---|
| <ul style="list-style-type: none"> Provide many dramatic play props like food containers, play money, a basket Invite two of your child’s friends over for a cooking or craft activity Encourage your child to wash plastic dolls by providing a small basin of water and cloths | <ul style="list-style-type: none"> Recreate her experiences in pretend play situations (e.g., shopping) Be able to practice his social skills as she shares art materials or takes turns adding ingredients Practice caregiving and nurturing skills with others |
|---|---|



Teach

If you...



Your baby will...

| | |
|--|---|
| <ul style="list-style-type: none"> Plan shopping excursions with your toddler, including list-making, looking at flyers Provide puppets and dolls for dramatic play Play simple turn-taking games like “I Spy With My Little Eye” | <ul style="list-style-type: none"> Model these actions in his pretend play Learn about language skills and imagination Practice waiting his turn while developing his observation skills |
|--|---|

EMOTIONAL SKILLS – 30–36 months

| Typical skills | Emerging skills |
|--|--|
| <ul style="list-style-type: none"> Objects to major changes in routines Recognizes and responds to other children’s feelings Becomes more comfortable with new people Wants independence but may fear new experiences Desires approval and needs praise | <ul style="list-style-type: none"> Explains feelings when asked about them Is more able to understand the feelings of other children, and talk about them Gets excited about activities she may have done, e.g., baking cookies May stamp feet when frustrated May request certain stories to help resolve fears, e.g., of monsters |



Comfort

If you...



Your baby will...

| | |
|--|---|
| <ul style="list-style-type: none"> Try to maintain regular routines and let your toddler know when a change is coming Praise your child’s emerging abilities and independent efforts Acknowledge his feelings and talk about them | <ul style="list-style-type: none"> Feel a sense of security and predictability Become more self-assured and feel more encouraged to try things Learn to understand his own feelings and respond appropriately to those of others |
|--|---|

EMOTIONAL SKILLS – 30–36 months

| Typical skills | Emerging skills |
|----------------|-----------------|
|----------------|-----------------|



Play

If you...



Your baby will...

| | |
|--|--|
| <ul style="list-style-type: none"> • Sing the song “If you’re happy and you know it, clap your hands,” substituting different feelings and actions (grumpy/stamp feet) • Find people pictures showing different emotions; talk about the person’s feelings and why they might feel that way • Encourage your child to do small excursions with other familiar caregivers, e.g., going to the park | <ul style="list-style-type: none"> • Learn to label different emotions and explore how people express their feelings • Begin to think about what causes people to have different feelings and recognize words that match emotions • Become more comfortable being away from her parents |
|--|--|



Teach

If you...



Your baby will...

| | |
|---|--|
| <ul style="list-style-type: none"> • Read books with your child about different feelings • Create a picture chart of his day (e.g., showing breakfast time, nap time) • Do his favourite activities with him | <ul style="list-style-type: none"> • Have a chance to ask about emotions and learn about his own • Have a comforting reminder of his routine and learn about the sequence of events • Feel proud to demonstrate his abilities |
|---|--|

LANGUAGE SKILLS – 30–36 months

| Typical skills | Emerging skills |
|----------------|-----------------|
|----------------|-----------------|

| | |
|---|--|
| <ul style="list-style-type: none"> • Uses “self-centred” pronouns like ‘I’, ‘me’, ‘mine’, ‘you’ • Puts together simple, two-word sentences • Answers simple questions like, “What’s your name?”, and performs simple tasks when asked to • Enjoys looking at books and talking about the pictures • Sings parts of songs | <ul style="list-style-type: none"> • Is able to use words that describe things, e.g., big, dirty, wet, hot • Participates more in conversations and stories • Is able to provide more information about self (e.g., name, gender, age) and understands two-step directions • Can recite a few simple nursery rhymes • Using plurals in a general way (e.g., fooms not feet) |
|---|--|



Comfort

If you...



Your baby will...

| | |
|---|---|
| <ul style="list-style-type: none"> • Provide opportunities for your toddler to talk about things that he finds interesting | <ul style="list-style-type: none"> • Know that you are interested in what he has to say and will want to converse with you |
|---|---|



Play

If you...



Your baby will...

| | |
|--|--|
| <ul style="list-style-type: none"> • Let your toddler fill in the blanks while singing a song | <ul style="list-style-type: none"> • Enjoy singing important words on her own |
|--|--|



Teach

If you...



Your baby will...

| | |
|--|---|
| <ul style="list-style-type: none"> • Keep expanding language by adding more new words and descriptions about events in your toddler’s day | <ul style="list-style-type: none"> • Develop confidence in the use of many words and feel secure enough to try new words |
|--|---|

INTELLECTUAL SKILLS – 30–36 months

| Typical skills | Emerging skills |
|--|---|
| <ul style="list-style-type: none"> • Develops size comparisons, using language like ‘bigger’, ‘smaller’, ‘really little’ • Tries to dramatize thoughts and ideas (e.g., pretends to be a dinosaur) • Counts three objects • Matches similar pictures and objects, sorts different ones • Enjoys creative movement | <ul style="list-style-type: none"> • Separates small objects from large ones • Understands different forms of measurement for weight, height and length • Makes a plan before taking action (e.g., searches for needed felt board pieces) • Notices changes in nature (e.g., when a seed he planted sprouts) • Uses words associated with an understanding of time (e.g. sleep time) • Pretends to be community helpers |



Comfort

If you...



Your baby will...

| | |
|--|---|
| <ul style="list-style-type: none"> • Use laundry routines as an opportunity to describe and sort family members’ clothing | <ul style="list-style-type: none"> • Learn number concepts and counting in a playful way |
|--|---|



Play

If you...



Your baby will...

| | |
|---|---|
| <ul style="list-style-type: none"> • Introduce the concept of first, second, third in simple games, asking, “Who is first? Who comes second?” • Provide simple puzzles with three to six pieces | <ul style="list-style-type: none"> • Begin to recognize that numbers are used in different ways • Gain confidence in his ability to put things together |
|---|---|



Teach

If you...



Your baby will...

| | |
|--|---|
| <ul style="list-style-type: none"> • Keep expanding language by adding more new words and descriptions about events in your toddler’s day | <ul style="list-style-type: none"> • Develop confidence in the use of many words and feel secure enough to try new words |
|--|---|

FINE MOTOR – 30–36 months

| Typical skills | Emerging skills |
|---|--|
| <ul style="list-style-type: none"> • Holds pencil in writing position • Imitates drawing a cross, circles, dots, small lines, swirls • Cuts paper with scissors, but may not be able to cut along straight lines • Turns pages of book one at a time • Turns rotating handles, doorknobs | <ul style="list-style-type: none"> • Experiments with pencils, crayons and markers, using an adult-like grasp • Draws squiggles and says that’s her name • Participates in songs and finger plays • Plays with different manipulative toys, e.g., connecting straws and snap blocks • Puts on and takes off clothes |



Comfort

If you...



Your baby will...

| | |
|--|--|
| <ul style="list-style-type: none"> • Do simple finger plays like “This Little Piggy” with your child • Compliment your child’s drawing skills, and comment on how “grown up” he is • Read your child’s favourite book to him and put him in charge of turning the pages | <ul style="list-style-type: none"> • Enjoy having his fingers played with as he pretends they are “piggies” • Feel proud of his abilities and creations and want to make more and show them off • Learn to love looking at books because of the time spent reading with you |
|--|--|

FINE MOTOR – 30–36 months

| | |
|----------------|-----------------|
| Typical skills | Emerging skills |
|----------------|-----------------|



Play

If you...



Your baby will...

| | |
|--|--|
| <ul style="list-style-type: none"> • Provide different things to write and draw with (e.g., pencils, markers, crayons, chalk) • Supply your child with board books to read to her dolls and teddy bears • Help your child cut out small pieces of paper to use as tickets for a puppet show | <ul style="list-style-type: none"> • Be encouraged to use different things to colour with and express herself • Use page turning skills as she develops her early literacy skills • Learn that cutting paper helps with other projects she is doing |
|--|--|



Teach

If you...



Your baby will...

| | |
|--|--|
| <ul style="list-style-type: none"> • Provide different kinds of dress up clothes with snaps, buttons, zippers • Make greeting cards with your child, and together, print special messages • Role model reading and writing in front of your child | <ul style="list-style-type: none"> • Practice self-help skills at his own pace through creative play • Use skills like cutting, folding and drawing to express his ideas and feelings • See reading and writing as useful and want to do them too |
|--|--|

GROSS MOTOR – 30–36 months

| | |
|----------------|-----------------|
| Typical skills | Emerging skills |
|----------------|-----------------|

| | |
|---|---|
| <ul style="list-style-type: none"> • Participates in group activities that include running, galloping, crawling, rolling over and twirling around • Walks on balance beam, alternating feet a few steps • Runs, avoiding obstacles • Climbs up the ladder of a slide or other play equipment • Pedals a tricycle | <ul style="list-style-type: none"> • Walks on balance beam a few steps, going forward and backward • Rides tricycle, steering well and using pedals • Kicks ball with increasing accuracy • Throws ball overhand with fairly accurate aim • Participates in circle games involving many players, such as ‘The Hokey Pokey’ |
|---|---|



Comfort

If you...



Your baby will...

| | |
|---|---|
| <ul style="list-style-type: none"> • Encourage your child as she attempts more challenging skills • Count out loud how many stairs she manages independently and offer praise • Set up a big target for your child to throw a ball at or a big box to kick a ball into | <ul style="list-style-type: none"> • Develop confidence in her physical abilities and be open to trying new activities • Know you are noticing her and gain self-confidence • Feel successful every time she hits the target or gets the ball in |
|---|---|



Play

If you...



Your baby will...

| | |
|--|--|
| <ul style="list-style-type: none"> • Participate in physical activities with your toddler by playing tag or rolling down a hill • Play music and provide him with colourful scarves to move and dance with • Demonstrate movements like galloping and twirling by playing “Follow the Leader” | <ul style="list-style-type: none"> • Enjoy the interaction and know that it is fun to exercise because of your example • Explore the different actions he can do with his body and be inspired by the music • Learn different possibilities for movement by observing and trying them out |
|--|--|

GROSS MOTOR – 30–36 months

Typical skills

Emerging skills



Teach

If you...



Your baby will...

- Show your child pictures of different animals, e.g., birds, turtles, fish, and say, “Show me how you move like a fish!”
- Talk about safety rules and explain how to use playground equipment carefully
- Create a simple obstacle course with blocks and hoops

- Demonstrate her understanding of how animals move through her own creative movement
- Practice Learn to take her time and be cautious when playing at the park
- Begin to understand concepts like going over and around, in and out

The Busy World of Your Preschooler: An Overview of Your Preschooler’s Development at 36–48 Months

Your preschooler is a pretty capable person by now. In her third year, your child shows more self-esteem, confidence, optimism and enjoyment of daily activities. She is becoming her own person and standing up for what she wants. She is quite an accomplished negotiator and tries to make things go her way. Your child will have endless questions about how things work and why things happen. Language development is still on the fast track and most 3-year olds will have a vocabulary of over 700 words. Three-year olds are better at understanding and following simple rules and controlling their impulses. Toilet training is usually completed (with the exception of night time for some). She is quite adept on the playground, climbing up and sliding down equipment, and has good control over her fine motor skills. At the end of the third year she may have started using safe scissors, copying letters and even printing some letters of her name.

Four-year olds are more even-tempered and cooperative with parents though they still stand up for what they want. A 4-year old is full of energy and loves testing her body with climbing, jumping, skipping and even pedalling a tricycle. She can now focus for longer periods on activities like cutting and pasting, drawing and creating interesting projects. Her imagination is developing with make-believe play and she enjoys playing out situations that are familiar in her life.

Your Preschooler Between 36 and 48 Months

Your child has a very active time ahead of her. At this stage your preschooler will:

- Climb, slide and swing on playground equipment.
- Handle child’s scissors and cut out simple designs.
- Enjoy playing with other children and socialize well.
- Become less self-centred and more able to understand feelings and point of view of others.
- Start to count objects.

SOCIAL SKILLS – 36–48 months

Typical skills



Emerging skills



- Enjoys playing with other children and socializes well
- More able to take turns, share, co-operate
- Greets familiar adults and says ‘please’ and ‘thank you’
- Imitates mom or dad in play
- Likes to talk and carry on conversations



- Participates in interactive games like ‘London Bridge’ and ‘Farmer in the Dell’
- Enjoys games with rules
- Complies with requests from parents more often
- Seeks adult approval
- Enjoys dramatic play with others

SOCIAL SKILLS – 36–48 months

| Typical skills | Emerging skills |
|----------------|-----------------|
|----------------|-----------------|

| | | | | |
|---|----------------|--|---|--------------------------|
|  | Comfort | If you... |  | Your baby will... |
| <ul style="list-style-type: none"> • Give your preschooler a special responsibility, like watering the garden • Be available to your preschooler and ready to talk to her when needed • Tell your child what she does well | | <ul style="list-style-type: none"> • Feel that she has a special and important role in the family • Know that you are interested in her activities and feel secure • Be encouraged to take on more activities independently | | |



| | | | | |
|--|-------------|--|---|--------------------------|
|  | Play | If you... |  | Your baby will... |
| <ul style="list-style-type: none"> • Provide opportunities for your child to play with other preschoolers • Spend time playing simple games that require turn-taking, e.g., simple card games like Go Fish • Praise turn-taking during everyday routines, e.g., waiting for his turn to take a bath | | <ul style="list-style-type: none"> • Develop his ability to share and take turns • Enjoy playing with you and begin to understand games with rules • Begin to practice turn-taking, even in everyday events | | |

| | | | | |
|--|--------------|--|---|--------------------------|
|  | Teach | If you... |  | Your baby will... |
| <ul style="list-style-type: none"> • Ask your preschooler about her day, e.g., “What was one special thing you did?” • Explain to your preschooler reasons behind your requests • Model using words like ‘please’ and ‘thank you’ | | <ul style="list-style-type: none"> • Want to talk to you more often about her experiences • Have a better understanding of routines, rules and limits • Learn positive ways to interact with others and use these appropriately | | |

EMOTIONAL SKILLS – 36–48 months

| Typical skills | Emerging skills |
|----------------|-----------------|
|----------------|-----------------|

| | |
|---|---|
| <ul style="list-style-type: none"> • Experiences a broad range of feelings, e.g., jealousy, excitement, fear, happiness, anger • Expresses needs with words, e.g., “I’m tired” • Is more able to express anger verbally rather than physically • Is becoming less egocentric and more able to understand feelings and point of view of others • Is less upset by limits and discipline | <ul style="list-style-type: none"> • Continually grows in independence and self-esteem • Expands pretend play into rich, connected themes • Is more even tempered and co-operative with parents • Shows empathy, e.g., for a friend who is upset • May show attachment to one playmate |
|---|---|

| | | | | |
|--|----------------|--|---|--------------------------|
|  | Comfort | If you... |  | Your baby will... |
| <ul style="list-style-type: none"> • Model coping with emotions • Help your preschooler deal with tantrums by talking to her about what makes her feel better when she is angry or sad • Explore books that talk about emotions | | <ul style="list-style-type: none"> • Learn acceptable ways to cope • Feel supported when experiencing negative emotions • Begin to develop the ability to empathize with others | | |

EMOTIONAL SKILLS – 36–48 months

| Typical skills | Emerging skills |
|----------------|-----------------|
|----------------|-----------------|



Play

If you...



Your baby will...

| | |
|---|---|
| <ul style="list-style-type: none"> • Arrange special play dates with his friends • Provide opportunities for him to make choices about play activities • Help him set small goals he can achieve during play or other activities | <ul style="list-style-type: none"> • Feel supported in his social needs • Develop a sense of mastery and positive self-esteem in areas he likes • Develop the ability to complete a task or activity |
|---|---|



Teach

If you...



Your baby will...

| | |
|--|--|
| <ul style="list-style-type: none"> • Engage in activities that make your preschooler happy, e.g., reading books, doing puzzles • Provide her with some tasks that require some concentration • Give her some responsibility during daily routines, e.g., choosing her clothes and getting dressed | <ul style="list-style-type: none"> • Feel respected when you engage in her favourite activity • Learn to persevere on a task for a period of time • Develop confidence in her ability to be responsible |
|--|--|

LANGUAGE SKILLS – 36–48 months

| Typical skills | Emerging skills |
|----------------|-----------------|
|----------------|-----------------|

| | |
|--|---|
| <ul style="list-style-type: none"> • Enjoys books, simple songs, nursery rhymes, nonsense words and stories • Uses a vocabulary of about 900 words • Uses sentences with five words • Uses plurals and pronouns, e.g., ‘I, you and me’ • Understands position words, such as ‘in’, ‘out’, ‘behind’, ‘in front of’ | <ul style="list-style-type: none"> • Asks and answers ‘who, what, where, why, when, how’ questions • Can follow a three-part command • Recognizes some letters and words • Uses regular past tense forms, but may add ‘ed’ to some words (e.g., eat-ed) • Understands “It’s time to” |
|--|---|



Comfort

If you...



Your baby will...

| | |
|---|---|
| <ul style="list-style-type: none"> • Read your preschooler his favourite books before bed • Talk to your preschooler about events or people that make him feel happy, sad, or angry | <ul style="list-style-type: none"> • Use words and sentences he has memorized to participate actively in the experience • Start to categorize and sort the emotions and responses of others |
|---|---|



Play

If you...



Your baby will...

| | |
|--|--|
| <ul style="list-style-type: none"> • Have your preschooler “show and tell” their favourite people, places and things • Sing the alphabet song • “I SPY” alphabets (e.g. “I spy the letter A”) | <ul style="list-style-type: none"> • Enhance the descriptive vocabulary to describe their surroundings • Learn the letters and order of the alphabet • Learn to recognize letters of the alphabet |
|--|--|



Teach

If you...



Your baby will...

| | |
|--|--|
| <ul style="list-style-type: none"> • Ask your preschooler to tell you about the stories that go with the pictures she has drawn | <ul style="list-style-type: none"> • Begin to understand how writing can represent her thoughts and ideas |
|--|--|

INTELLECTUAL SKILLS – 36–48 months

| Typical skills | Emerging skills |
|---|---|
| <ul style="list-style-type: none"> • Enjoys dramatic play and role playing; play is becoming more realistic, e.g., school, fire station, shop • Classifies objects by purpose, e.g., ‘to play with’, ‘to wear’ • Understands the order of daily routines • Sorts objects by colour and size • Counts objects | <ul style="list-style-type: none"> • Sorts and classifies objects by characteristics • Understands ideas like opposites • Understands different forms of measurement, such as weight, height and length • Attaches words to numbers, for example, when you say the word ‘three’, it means three things • Understands time intervals better, e.g., today, tomorrow, yesterday |



Comfort

If you...



Your baby will...

| | |
|--|--|
| <ul style="list-style-type: none"> • Introduce the concepts of sorting and classifying in daily routines, e.g., “Your socks go in this drawer and your shirts in the other” | <ul style="list-style-type: none"> • Begin to understand that similar items can be sorted into groups |
|--|--|



Play

If you...



Your baby will...

| | |
|--|--|
| <ul style="list-style-type: none"> • Play guessing games that encourage her to think about functional relationships, e.g., “What do you draw with?” • Put measuring cups and spoons in the bath tub so your preschooler can practice measuring • Provide hard and soft craft materials such as feathers, cotton balls, strings, popsicle sticks and beads; have your preschooler create a picture and talk about the different textures and why some are soft or hard | <ul style="list-style-type: none"> • Use her memory instead of relying on concrete objects • Begin to understand that measurement can take different forms, e.g., “We can measure how tall you are and how much a cup of water is” • Begin to understand the concept of opposites |
|--|--|



Teach

If you...



Your baby will...

| | |
|--|---|
| <ul style="list-style-type: none"> • Use coloured beads or buttons in play as an opportunity to explore different patterns, shapes and sequences • Include your preschooler in cooking activities and use these to explore measurement | <ul style="list-style-type: none"> • Begin to recognize patterns and shapes, understand how sequences are made up of patterns • Understand how quantity, numbers and measurement all relate |
|--|---|

FINE MOTOR – 36–48 months

| Typical skills | Emerging skills |
|---|---|
| <ul style="list-style-type: none"> • Builds a tower of using blocks • Handles scissors and cuts out simple designs • Holds pencil with thumb and forefinger in adult-like grasp • Draws a house, and people with two to four body parts • Can button large buttons | <ul style="list-style-type: none"> • Carries liquid in a cup, with some spillage • Puts on shoes, but not yet able to tie laces • Prints some capital letters • Dresses and undresses without assistance • Cuts out and pastes simple shapes |

FINE MOTOR – 36–48 months

Typical skills

Emerging skills

**Comfort****If you...****Your baby will...**

- Encourage your child to draw pictures of his home and all the people who live in it
- Praise your child's increasing ability to dress and undress independently
- Give your child the opportunity to help with bringing cups and dishes to the table

- Feel secure and understand his special role in the family
- Feel capable and motivated to practice these skills with less and less help
- Gain pride in his growing ability to carry things and to be responsible for a task

**Play****If you...****Your baby will...**

- Provide your preschooler with a box of mixed beads or buttons that she can sort by colour or shape in an egg carton
- Give her a broad selection of arts and crafts materials for drawing, cutting and pasting
- Provide dolls with clothing that have buttons, zippers, snaps, laces

- Engage her small motor skills in sorting different materials according to their characteristics
- Strengthen her pincer grasp (thumb and forefinger) while creating drawings and collages
- Practice skills necessary for dressing herself through dramatic play

**Teach****If you...****Your baby will...**

- Use peg boards, connecting blocks and other building materials to explore different patterns, shapes and sequences
- Give your child different magazines and small scissors to cut out his favourite pictures for making a collage
- Provide your child with small building blocks or drawing materials that use small motor skills

- Physically create patterns and shapes and learn to label and identify them
- Enhance decision-making and categorize pictures as people, animals, food, vehicles while improving her cutting skills
- Understand that his hands can represent thoughts and ideas through constructing and drawing

GROSS MOTOR – 36–48 months

Typical skills

Emerging skills

- Runs several steps with alternating arm movements
- Catches, bounces and throws a ball easily
- Climbs, slides and swings on playground equipment
- Gets up from squatting position without any help
- Gallops, runs, walks, wiggles, and tip-toes with other classmates

- Catches a large ball with arms extended
- Gallops, runs, walks and tip toes as part of a group activity
- Jumps off the ground with a two-footed jump
- Turns somersaults
- Stands on one foot with momentary balance

**Comfort****If you...****Your baby will...**

- Praise your child's developing skills e.g., "You are so good at catching the ball"
- Put on your child's favourite music and explore different movements together
- Be available to help your child try more challenging skills, e.g., using the slide independently

- Become more confident in her abilities and want to repeat the activity
- Love spending time with you and enjoy being able to show you how many ways she can move
- Feel secure and develop the confidence to try more challenging activities on her own

GROSS MOTOR – 36–48 months

Typical skills

Emerging skills



Play

If you...



Your baby will...

- Encourage your child to move like different animals, e.g., jump like a frog, swim like a fish, wiggle like a worm, gallop like a horse
- Turn nursery rhymes into movement activities, prompting him to do the actions, e.g., jumping over a candlestick or over the moon!
- Invite your child’s peers over and teach them a simple game like ‘London Bridge’

- Practice a variety of physical actions while using his imagination
- Develop literacy skills as he creates movements for role playing
- Practice social skills like turn-taking while he plays a fun, movement game



Teach

If you...



Your baby will...

- Explore yoga stretches with your child, e.g., cat, dog, rabbit, snake, candle and rag doll
- Set up a simple obstacle course using hoops, a table, cones, balance board, etc.
- Play simple games like ‘Simon Says,’ and suggest different actions for your child to try, e.g., “Simon says jump three times! Simon says do one somersault!”

- Learn to move her body in ways that are both relaxing and imaginative as she pretends to be different animals and things
- Develop an understanding of concepts like over, under, around, up and down as she navigates the obstacles
- Develop listening and counting skills while she demonstrates her growing physical capabilities

The Busy World of Your Preschooler: An Overview of Your Preschooler’s Development at 48–60 Months

Your preschooler is a pretty capable person by now. Four-year olds are more even-tempered and cooperative with parents though they still stand up for what they want. A 4-year old is full of energy and loves testing her body with climbing, jumping, skipping and even pedalling a tricycle. She can now focus for longer periods on activities like cutting and pasting, drawing and creating interesting projects. Her imagination is developing with make-believe play and she enjoys playing out situations that are familiar in her life.

By the fifth year, your child is embracing life fully. She is learning to cope with frustration and to understand rules. With the emergence of a conscience, she adopts rules, accepting them as her own. She is much better at taking turns and playing cooperatively, as well as planning and problem solving with others. Now your child can

speak almost like an adult, using correct grammar 90% of the time. She uses language to describe objects, events and sort out the past, present and future. By the end of the year, your 5-year old knows “left” from “right”, can identify colours, shapes and sizes and can copy patterns and sequences. She is ready to conquer new worlds—*like school!*

Your Preschooler Between 48 and 60 Months

The fifth year of your child’s life signals the end of early childhood. As she prepares to enter a new world of school and friends, she will begin to:

- Start running, then stop and change direction smoothly.
- Draw a person with head, arms, legs and trunk.
- Begin to grasp the concept of sharing.
- Use pretend play to gain control of frustrating and frightening experiences.
- Tell long stories about her own experiences.

SOCIAL SKILLS – 48–60 months

| Typical skills | Emerging skills |
|--|--|
| <ul style="list-style-type: none"> Plays games with simple rules Shows attachment to one playmate Shows interest in gender differences, and may undress with other children Enjoys dramatic play with other children Begins to grasp the concept of sharing | <ul style="list-style-type: none"> Explains rules of a game/activity to others Plays cooperatively in a group of 2–3 children Apologizes for actions he didn't mean to do Shows an understanding of right and wrong Listens while others are speaking |



Comfort

If you...



Your baby will...

| | |
|--|--|
| <ul style="list-style-type: none"> Provide opportunities for your child to create her own stories, either by drawing them or by telling them to others Tell her how proud you are of her abilities whenever you catch her doing something well | <ul style="list-style-type: none"> Start to create her own stories Feel proud of what's she's done, and have a strong sense of her strengths and abilities |
|--|--|



Play

If you...



Your baby will...

| | |
|---|--|
| <ul style="list-style-type: none"> Encourage more sophisticated pretend play by providing props, e.g., restaurant, grocery store, doctor's visit Provide many opportunities for social interactions with other preschoolers | <ul style="list-style-type: none"> Engage more in problem solving, making decisions and conversation Strengthen social skills while playing with peers |
|---|--|



Teach

If you...



Your baby will...

| | |
|--|--|
| <ul style="list-style-type: none"> Encourage your child not to give up on games or tasks when he plays with others Create the opportunity for your child to play with younger children | <ul style="list-style-type: none"> Learn to persist at a task, especially when others are counting on him Feel a sense of leadership |
|--|--|

EMOTIONAL SKILLS – 48–60 months

| Typical skills | Emerging skills |
|---|--|
| <ul style="list-style-type: none"> Uses pretend play to gain control of frustrating and frightening experiences Experiences positive self-esteem, feels good about himself and takes pride in his accomplishments Complies with requests from parents more often Concentrates and works alone for up to 20–30 min Keeps going on a difficult task for longer periods | <ul style="list-style-type: none"> Shows a desire to fit into home routines Shows ability to reflect on himself and his actions e.g., "What I said wasn't nice" Experiences and understands positive and negative feelings about another person Is able to distinguish fantasy from reality Starts to show more interest in taking care of himself alone, e.g. cleaning room, bathroom needs, bathing |



Comfort

If you...



Your baby will...

| | |
|--|---|
| <ul style="list-style-type: none"> Monitor and put a name to things that may cause your child's experiences to be negative Give your child the chance to develop his strengths and talents | <ul style="list-style-type: none"> Experience lower stress levels and feel your parental support Learn to feel capable in different areas, e.g., sports, music, drawing |
|--|---|

EMOTIONAL SKILLS – 48–60 months

| Typical skills | Emerging skills |
|----------------|-----------------|
|----------------|-----------------|



Play

If you...



Your baby will...

- | | |
|---|--|
| <ul style="list-style-type: none"> • Provide crayons, paper and markers and encourage your child to draw and talk about her pictures and events • Create a stage where your child can act out situations and emotions by herself or using puppets | <ul style="list-style-type: none"> • Use her creativity to express emotions and talk about feelings in relation to events • Identify and talk about feelings in an imaginative way |
|---|--|



Teach

If you...



Your baby will...

- | | |
|---|---|
| <ul style="list-style-type: none"> • Show and coach your child on how to handle emotions and feelings • Support your child when he wants to try new things or take risks in social situations | <ul style="list-style-type: none"> • Learn how to express anger and frustration safely • Learn that wanting to try out new things is ok and can bring success |
|---|---|

LANGUAGE SKILLS – 48–60 months

| Typical skills | Emerging skills |
|----------------|-----------------|
|----------------|-----------------|

- | | |
|--|---|
| <ul style="list-style-type: none"> • Plays with words in silly rhymes • Loves to recite and chant jingles and rhymes • Talks about imaginary situations • Uses new and unfamiliar words • Tells long stories about own past experiences • Uses an average vocabulary of 1500 words | <ul style="list-style-type: none"> • Asks “how”, “why” questions and listens closely to explanations • Uses ‘yesterday’ and ‘tomorrow’ correctly, incorporating past, present and future tenses of verbs • Says most speech sounds accurately but may have difficulty with some sounds e.g. “th” and “s” • Shows interest in written words and letters, e.g., reads own name and some words |
|--|---|



Comfort

If you...



Your baby will...

- | | |
|---|--|
| <ul style="list-style-type: none"> • Encourage your child to talk by asking open-ended questions, e.g., “How come...?” or “Why do you think...?” | <ul style="list-style-type: none"> • Enjoy special shared time while using his imagination and building his vocabulary and comprehension skills |
|---|--|



Play

If you...



Your baby will...

- | | |
|--|--|
| <ul style="list-style-type: none"> • Give your child simple problems to solve, e.g., “how many different ways can you make a sound with your body (fingers, feet, mouth, etc.)” | <ul style="list-style-type: none"> • Learn to identify things that are the same and different |
|--|--|



Teach

If you...



Your baby will...

- | | |
|--|--|
| <ul style="list-style-type: none"> • Point out words that he sees around him every day, e.g., Stop sign, labels on milk or cereal boxes, “Keep dogs on leash” | <ul style="list-style-type: none"> • Begin to understand how writing can represent her thoughts and ideas |
|--|--|

INTELLECTUAL SKILLS – 48–60 months

| Typical skills | Emerging skills |
|--|---|
| <ul style="list-style-type: none"> • Understands how to sort and classify objects by characteristics • Enjoys games that require matching items • Recognizes and identifies bigger, biggest, smaller and smallest • Identifies and names different colours • Replicates patterns, sequences and order • Understands the order of numbers | <ul style="list-style-type: none"> • Understands concepts of texture, weight, position and space • Understands different forms of measurement for weight, height and length • Plans and builds with simple tools |



Comfort

If you...



Your baby will...

| | |
|--|--|
| <ul style="list-style-type: none"> • Tell your child stories without pictures | <ul style="list-style-type: none"> • Practice reasoning skills as he thinks about the relationship between cause and effect |
|--|--|



Play

If you...



Your baby will...

| | |
|---|--|
| <ul style="list-style-type: none"> • Create a matching card game based on your child’s interests, e.g., vehicles, dinosaurs, etc | <ul style="list-style-type: none"> • Use his creativity to think things out and stretch his imagination |
|---|--|



Teach

If you...



Your baby will...

| | |
|--|--|
| <ul style="list-style-type: none"> • Use household objects/food to do simple addition and subtraction, e.g., “If you have three apples and eat one, how many are left?” | <ul style="list-style-type: none"> • Begin to understand concepts of “more” and “less” and explore basic math |
|--|--|

FINE MOTOR SKILLS – 48–60 months

| Typical skills | Emerging skills |
|---|--|
| <ul style="list-style-type: none"> • Draws person with features including head, arms, legs and trunk • Cuts and pastes using art materials • Paints with a large brush on large paper • Manipulates clay, playdough • Draws lines, simple shapes and a few letters • Dresses and undresses with little help | <ul style="list-style-type: none"> • Carries a cup without spilling what’s in it • Cuts on a line or cuts out simple shapes along an outline with scissors • Strings small beads to make a necklace • Prints recognizable numbers, letters and words, including her own name |



Comfort

If you...



Your baby will...

| | |
|--|--|
| <ul style="list-style-type: none"> • Give your child sensory materials to play with like sand or water along with different sized containers, sieves and utensils • Make play dough for your child, scented with spices (vanilla, mint) and food colouring | <ul style="list-style-type: none"> • Enjoy the pleasurable feelings of the materials while learning about volume • Learn about the sense of smell and how colours are made while manipulating the dough to make shapes |
|--|--|



Play



If you...



Your baby will...



| | |
|---|---|
| <ul style="list-style-type: none"> • Make pencils, crayons and chalk available often • Offer a variety of arts and crafts materials for your child to make anything she wishes, e.g., boxes, glue, ribbons, tubes, yarn, scissors, tape, etc. | <ul style="list-style-type: none"> • Get used to colouring, drawing pictures or exploring letters and numbers • Use her imagination and fine motor skills to make her own creations |
|---|---|



FINE MOTOR SKILLS – 48–60 months



| Typical skills | Emerging skills |
|--|--|
|  Teach If you...  Your baby will... | |
| <ul style="list-style-type: none"> • Use peg boards, connecting blocks and other building materials to explore different patterns, shapes and sequences • Give your child different magazines and safe scissors to cut out his favourite pictures for making a collage • Provide your child with small building blocks or drawing materials that use small motor skills | <ul style="list-style-type: none"> • Physically create patterns and shapes and learn to label and identify them • Enhance decision-making and categorize pictures as people, animals, food, vehicles while improving her cutting skills • Understand that his hands can represent thoughts and ideas through constructing and drawing |

GROSS MOTOR – 48–60 months

| Typical skills | Emerging skills |
|---|--|
| <ul style="list-style-type: none"> • Rides a tricycle without bumping into things • Bounces, throws and catches a large ball • Starts, stops and changes direction smoothly when running • Climbs playground equipment without any difficulty • Jumps forwards and backwards for short distances | <ul style="list-style-type: none"> • Walks up and down stairs, alternating feet without support • Jumps down from half metre high • Skips for a distance • Kicks a soccer ball • Hops on one foot |

| | |
|---|---|
|  Comfort If you...  Your baby will... | |
| <ul style="list-style-type: none"> • Support your child’s exploration and curiosity about her physical environment • Supervise play and safety, i.e., helmets for bike riding, care when throwing balls to others, etc. | <ul style="list-style-type: none"> • Use her motor skills to discover new concepts of physical characteristics of things • Enjoy mastering skills without worry of injury |

| | |
|--|---|
|  Play If you...  Your baby will... | |
| <ul style="list-style-type: none"> • Take your child on a “bike hike” around the park or neighbourhood • Arrange for playmates to come over to play outdoor games, e.g., hide and seek, tag | <ul style="list-style-type: none"> • Enjoy exploring his area and learning about places and people • Practice motor coordination skills while learning games with rules |

| | |
|--|--|
|  Teach If you...  Your baby will... | |
| <ul style="list-style-type: none"> • Teach safety rules for walking or riding on streets, e.g., always stop at the curb before crossing the street; never ride on the road, etc. • Teach your child that when playing certain games, someone wins and someone loses; help your child understand how to win and lose graciously | <ul style="list-style-type: none"> • Slowly learn how to manage safety; full mental capacity for these rules is absent before age 10 • Learn how to cope with disappointments as well as successes |

So What Derails Early Development?

As mentioned earlier, adversity early in life can derail development ultimately influencing developmental trajectory in the short term and long

term and also impacting both physical and mental health outcomes. For this reason, at the very least, when consulting with families where there is adversity (poverty, parental mental health challenges, substance use etc.), monitoring overall development can alert a physician to potential

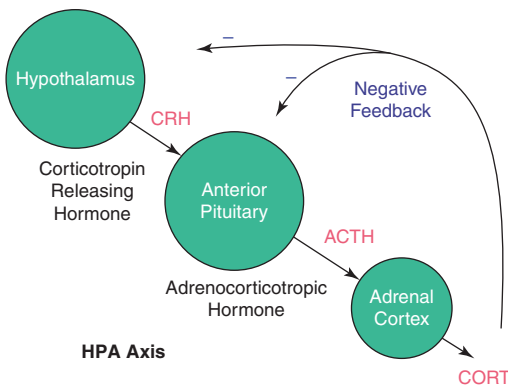
developmental challenges which, when recognized and responded to early can be minimized or overcome. It is important to understand that the absence of serve and return or the prolonged and frequent activation of the stress response system can have a devastating impact on a child’s outcomes across the lifespan.

Toxic Stress Derails Healthy Development

Hans Seyle, a physician in Prague in the early 1900s, was the first to use the term “stress” in a biological context, defining it as “the non-specific response of the body to any demand placed upon it”. Seyle further suggested that factors which alter or disrupt the body’s state of equilibrium or homeostasis lead to stress. Researchers such as Shonkoff et al have extensively studied the adverse effects of stress influencing the mental and cognitive function of young children not only in their life span but also their offspring and future generations (Shonkoff et al. 2012a, b).

The neural circuits for dealing with stress are particularly malleable (or “plastic”) during the fetal and early childhood periods. During such sensitive developmental periods, the brain architecture is particularly vulnerable to stress.

The stress response involves activation of the hypothalamic-pituitary-adrenocortical axis and the sympathetic-adrenomedullary system, which results in increased levels of stress hormones mainly cortisol and adrenaline (Danese and McEwen 2012, McEwen 2008, Glaser 2000). While transient increases in these stress hormones are protective and even essential for survival (positive stress), excessively high levels for prolonged periods can be quite harmful and toxic (McEwen 2005, 1998, 2008, McEwen and Seeman 1999) and can lead to a chronic “wear and tear” effect on multiple organ systems including the brain (McEwen 2005, 1998, McEwen and Seeman 1999). Chronic exposure to stressful experiences particularly affects the size as well as the neuronal architecture of the amygdala, hippocampus and the pre-frontal cortex leading to functional differences and deterioration in learning, memory, and aspects of executive functioning (Danese and McEwen 2012, Glaser 2000, McEwen 2008, McEwen and Gianaros 2010). Stress can cause physiologic disruptions that result in higher levels of stress-related chronic diseases. (Glaser 2000, Juster et al. 2010, McEwen 2008, Danese and McEwen 2012).



- Positive**
Brief increases in heart rate, mild elevations in stress hormone levels.
- Tolerable**
Serious, temporary stress responses, buffered by supportive relationships.
- Toxic**
Prolonged activation of stress response systems in the absence of protective relationships.

Image: National Scientific Council on the Developing Child, 2012 Toxic Stress: The Facts

Image: Basic hypothalamic–pituitary–adrenal axis summary (corticotropin-releasing hormone=CRH, adrenocorticotrophic hormone=ACTH). Original work from Jessica Malisch and Theodore Garland Feb. 25, 2004

When infants and toddlers experience positive or tolerable stress that is buffered by a supportive relationship the child learns how to cope with stress—resulting in what is referred to as a secure attachment. However, when the child’s stress response system is activated for a prolonged period without a supportive buffering relationship, this can become toxic stress which leads to the development of maladaptive coping strategies (Toxic Stress: The Facts).

Significant mental health problems can and do occur in young children. In some cases, these problems can have serious consequences for early learning, social competence, and lifelong health.

Infants Most at Risk

Any child lacking a supportive relationship to buffer the impact of a stressful and/or traumatic experience is vulnerable to a toxic stress response. At greater risk are those infants who are not living in a secure and stable home with a parent or caregiver who is consistently caring, supportive and responsive, are most vulnerable to experiencing the toxic stress response and consequently less than optimal brain development. These may be children with parents who suffer from substance abuse, poor mental health, experience poverty, experience violence or have themselves been victims of abuse and/or neglect and therefore may not understand the significance of their relationship with their baby and the need to respond to their baby consistently in a nurturing and caring manner. In a recent review of the data in Ontario, it was determined that the majority of cases referred for investigation involving infants, the main concern was parenting. In the United States, an estimated 1 in 7 children has experienced some form of neglect, physical or emotional abuse (National Scientific Council on the Developing Child 2010a, b). Those living in low income families are on average exposed to less and lower-quality parental responsiveness in conjunction to more frequent conflictive and punitive parenting behavior (Evans 2004, Dodge et al. 1994, McLoyd 1998). Furthermore, half of these children have witnessed violence, or are indirectly victims of violence themselves (National Scientific Council on the Developing

Child 2010a, b). These early stresses in a child’s environment prime the neurobiological stress system to respond to lower threshold stimuli that are normally not stressful, thereby increasing the risk of stress-related physical and mental illnesses (National Scientific Council on the Developing Child 2005, 2008). Maladaptive infant social behavior may reflect exposures to traumatic and uncompensated adverse childhood encounters including the absence of a responsive relationship.

When an infant has multiple aforementioned risk factors compounded in his or her environment, the chances of this child being identified with developmental deficit skyrockets. The fact that 90–100% of all toddlers with seven adverse childhood experience risk factors have impaired development is simply astonishing (Barth et al. 2007).

How Can This Information Change the Practice of Clinicians and Practitioners

Through research, we better understand the behaviors of infants and toddlers that can be indicative of poor social emotional development. Those in the health and social services areas need a working knowledge of early development to understand normal behavior vs. abnormal behavior. These professionals then need to understand the specific behaviors that may be indicative of vulnerability or a delay in development. There was a time when child welfare focused primarily on safety. Access to food and shelter, absence of broken bones or physical ailments meant a child was fine. Today, we know that in the case of infants and toddlers we must look beyond the obvious signs and observe behaviors and interactions with primary caregivers more closely. The absence of “normal” interactions should be a reason to observe more, ask questions and conduct developmental screening that includes a focus on social emotional development. Today’s clinician has access to easy to use screening tools that look at overall development and social emotional development as early as 3 months. Those systems caring for infants and toddlers can make some immediate changes.

1. Early screening for all children but at the very least those who are in vulnerable situations. In a recent pilot that screened children under 5 being served by child welfare using the Ages and Stages Questionnaire 3, it was found that 60% of children already had an established delay in one or more areas that had not been identified by any of the professionals involved. Those same children were also screened using the Ages and Stages Questionnaire Social Emotional. Of those screened over 50% (Kulkarni et al. 2015). Based on the results, the caregivers of those showing delays were provided with a Developmental Support Plan to respond to the child's needs.
2. Implementation of proven models of interventions such as the Nurse Family Partnership (Olds et al. 2013).
3. Integration of the new research on brain development, epigenetics and toxic stress response into undergraduate graduate training programs in the areas of health sciences, social work and education.

References

- Barth RP, et al. Developmental status and early intervention service needs of maltreated children. Washington, DC: U.S. Department of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation; 2007.
- Berger SL. The complex language of chromatin regulation during transcription. *Nature*. 2007;447(7143):407–12.
- Center on the Developing Child at Harvard University. The foundations of lifelong health are built in early childhood. 2010. <http://www.developingchild.harvard.edu>
- Center on the Developing Child Harvard University. Core concepts in the science of early childhood development: healthy development builds a strong foundation—for kids and for society. 2012. www.developingchild.harvard.edu
- Danese A, McEwen BS. Adverse childhood experiences, allostasis, allostatic load, and age-related disease. *Physiol Behav*. 2012;106(1):29–39.
- Denberg AE, Daneman D. Pascal's Wager: from science to policy on early childhood development. *Can J Public Health*. 2010;101(3):235–6.
- Dodge KA, Pettit GS, Bates JE. Socialization mediators of the relation between socioeconomic status and child conduct problems. *Child Dev*. 1994;65:649–65. <https://doi.org/10.1111/j.1467-8624.1994.tb00774.x>.
- Evans GW. The environment of childhood poverty. *Am Psychol*. 2004;59(2):77–92.
- Glaser D. Child abuse and neglect and the brain—a review. *J Child Psychol Psychiatry*. 2000;41:97–116. <https://doi.org/10.1111/1469-7610.00551>.
- Grantham-McGregor S, Cheung YB, Cueto S, Glewwe P, Richter L, Strupp B, International Child Development Steering Group. Developmental potential in the first 5 years for children in developing countries. *Lancet*. 2007;369:60–70.
- Juster RP, BS ME, Lupien SJ. Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neurosci Biobehav Rev*. 2010;35(1):2–16.
- Kouzarides T. Chromatin modifications and their function. *Cell*. 2007;128(4):693–705.
- Kulkarni C, Packard B & Paolozza C. Infant Mental Health and Family Law Initiative (FLI). Imprint The Newsletter of Infant Mental Health Promotion, The Hospital for Sick Children, Toronto. Issue 64, Summer 2015.
- McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med*. 1998;338(3):171–9.
- McEwen BS. Stressed or stressed out: what is the difference? *J Psychiatry Neurosci*. 2005;30(5):315–8.
- McEwen BS. Central effects of stress hormones in health and disease: understanding the protective and damaging effects of stress and stress mediators. *Eur J Pharmacol*. 2008;583(2–3):174–85. Epub 30 Jan 2008.
- McEwen BS, Gianaros PJ. Central role of the brain in stress and adaptation: links to socioeconomic status, health, and disease. *Ann N Y Acad Sci*. 2010;1186:190–222.
- McEwen BS, Seeman T. Protective and damaging effects of mediators of stress. Elaborating and testing the concepts of allostasis and allostatic load. *Ann N Y Acad Sci*. 1999;896:30–47.
- McLoyd VC. Socioeconomic disadvantage and child development. *Am Psychol*. 1998;53(2):185–204.
- Mellor J, Dudek P, Clynes D. A glimpse into the epigenetic landscape of gene regulation. *Curr Opin Genet Dev*. 2008;18(2):116–22. Epub 4 Mar 2008.
- National Scientific Council on the Developing Child. Excessive stress disrupts the architecture of the developing brain: Working Paper No. 3. 2005. www.developingchild.harvard.edu
- National Scientific Council on the Developing Child. Mental health problems in early childhood can impair learning and behavior for life: Working Paper No. 6. 2008. www.developingchild.harvard.edu
- National Scientific Council on the Developing Child. Persistent fear and anxiety can affect young children's learning and development: Working Paper No. 9. 2010a. www.developingchild.harvard.edu
- National Scientific Council on the Developing Child. Early experiences can alter gene expression and affect long-term development: Working Paper No. 10. 2010b. www.developingchild.harvard.edu

- Olds D, Donelan-McCall N, O'Brien R, MacMillan H, Jack S, Jenkins T, Dunlap WP, O'Fallon M, Yost E, Thorland B, Pinto F, Gasbarro M, Baca P, Melnick A, Beeber L. Improving the nurse–family partnership in community practice. *Pediatrics*. 2013;132(Suppl 2):S110–7. <https://doi.org/10.1542/peds.2013-1021I>.
- Shonkoff JP, Garner AS, Committee on Psychosocial Aspects of Child and Family Health, Committee on Early Childhood, Adoption, and Dependent Care, Section on Developmental and Behavioral Pediatrics. The lifelong effects of early childhood adversity and toxic stress. *Pediatrics*. 2012a;129(1):e232–46. Epub 26 Dec 2011.
- Shonkoff JP, Richter L, van der Gaag J, Bhutta ZA. An integrated scientific framework for child survival and early childhood development. *Pediatrics*. 2012b;129(2):e460–72. Epub 4 Jan 2012.
- Zero to Three. Task force on infant mental health. Definition of infant mental health. 2002. www.zerotothree.org

Suggested Reading

- Center on the Developing Child at Harvard University. Maternal depression can undermine the development of young children: Working Paper No. 8. 2009. <http://www.developingchild.harvard.edu>
- Conti G, Hansman C, Heckman JJ, Novak MFX, Ruggiero A, Suomi SJ. Primate evidence on the late health effects of early-life adversity, NBER Working Paper No. 18002. April 2012, JEL No. I12, J13 www.developingchild.harvard.edu. Last updated 2012.
- Felitti VJ, Anda R. The relationship of adverse childhood experiences to adult medical disease, psychiatric disorders, and sexual behavior: implications for healthcare. In: Lanius R, Vermetten E, Pain C, editors. The hidden epidemic: the impact of early life trauma on health and disease. 2009. <http://www.unnaturalcauses.org/assets/uploads/file/ACE%20Study-Lanius.pdf>
- Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, Koss MP, Marks JS. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. *Am J Prev Med*. 1998;14(4):245–58.
- Fuller-Thomson E, Brennenstuhl S. Making a link between childhood physical abuse and cancer: results from a regional representative survey. *Cancer*. 2009;115(14):3341–50.
- Hertzman C. Making early childhood development a priority: lessons from Vancouver. The Canadian Centre for Policy Alternatives. 2004. www.policyalternatives.ca
- Liston C, Miller MM, Goldwater DS, Radley JJ, Rocher AB, Hof PR, Morrison JH, McEwen BS. Stress-induced alterations in prefrontal cortical dendritic morphology predict selective impairments in perceptual attentional set-shifting. *Journal of Neuroscience*. 2006;26(30):7870–4.
- Mustard JF. Early child development and experience-based brain development: the scientific underpinnings of the importance of early child development in a globalized world. Washington, DC: The Brookings Institution; 2006. Online publication: <http://www.brookings.edu/views/papers/200602mustard.htm>
- National Scientific Council on the Developing Child. Young children develop in an environment of relationships: Working Paper No. 1. 2004a. www.developingchild.harvard.edu
- National Scientific Council on the Developing Child. Children's emotional development is built into the architecture of their brains: Working Paper No. 2. 2004b. www.developingchild.harvard.edu
- National Scientific Council on the Developing Child. Early exposure to toxic substances damages brain architecture: Working Paper No. 4. 2006. www.developingchild.harvard.edu
- National Scientific Council on the Developing Child. The timing and quality of early experiences combine to shape brain architecture: Working Paper No. 5. 2007. www.developingchild.harvard.edu
- Seyle H. The stress of life. New York: McGraw-Hill; 1956.
- Stevens GD. Gradients in the health status and developmental risks of young children: the combined influences of multiple social risk factors. *Matern Child Health J*. 2006;10(2):187–99. Epub 29 Mar 2006.



Update in Development: Section B—Autism Spectrum Disorder

7

R.G. Smith and D. Samdup

Recently, a patient of mine who happens to be a very bright 10-year-old young man with an Autism Spectrum Disorder came into my office and sat down. Without asking me anything about my day, or what type of summer I was having he stated: “So Dr. Smith what can I teach you today? I know, tell me all the countries of the world in alphabetical order AND their capitals?” When I started to say that I could not do that, he quickly retorted: “Aren’t doctors supposed to be bright?” And he quickly reeled off to me every country and its capital (IN ALPHABETICAL ORDER), some of which I had never heard of! He then proceeded to ask me if I knew the distance of Mars from Earth! This very bright young man has one friend at school, who is also on the Autism Spectrum. He is often seen walking around at recess reenacting video games or speaking Japanese to himself, which he learned from watching Yu-Gi-Oh on the internet!

Then there is an 8-year-old nonverbal boy with ASD who can spin anything in my office (including chairs), but struggles in school and is highly disruptive because of this fixation and his tendency to run out of the classroom.

Finally, there is a 16-year-old young lady, who first spoke at age 6-years, who can now tell me the **day** of my birth seconds after I tell her my birthdate, then she tells me “Man you are old!”

Such is the nature of some of my days in my Autism Clinic!

What Is an Autism Spectrum Disorder?

The autism spectrum disorders (ASD’s) are a heterogeneous set of neurodevelopmental syndromes characterized by deficits in social communication and social interaction and the presence of restricted, repetitive behaviors. Social communication deficits include impairments in aspects of joint attention and social reciprocity, as well as challenges in the use of verbal and nonverbal communicative behaviors for social interaction. Restricted, repetitive behaviors, interests, or activities are manifested by stereotyped, repetitive speech, motor movement, or use of objects; inflexible adherence to routines; restricted interests; and hyper- and/or hypo-sensitivity to sensory input (American Speech-Language Hearing Association 2015). This results in the inability to engage in and benefit from many of the basic activities of life including but not restricted to conversing, learning, and engaging in meaningful and mutually beneficial relationships (Joseph et al. 2014).

R.G. Smith (✉) • D. Samdup
KidsInclusive Centre for Child and Youth
Development, Hotel Dieu Hospital, 166 Brock St.,
Kingston, ON K7L 5G2, Canada

Queen’s University, 99 University Ave.,
Kingston, ON K7L 3N6, Canada
e-mail: gs3@queensu.ca

The purpose of this update is to provide a review of current literature pertaining to some of the more useful and practical innovations in the field, based on recent publications as well as some consensus. We have also taken the liberty of inserting some practical key points in the update. These are intended to facilitate acquisition of salient historical points, as well as demystifying presentation of the diagnosis to parents and caregivers.

We will begin by giving a general overview and then select a few important and possibly controversial topics to discuss. Throughout the chapter, we will attempt to make things easy to understand, practical and as much as possible, evidence-based.

Prevalence Update

Prevalence is the actual number of cases alive, with the disease either during a certain period of time (period prevalence) or at a particular date in time (point prevalence). Incidence is the rate of new (or newly diagnosed) cases of the disease. It is generally reported as the number of new cases occurring within a period of time (e.g., per month, per year, etc.). Thus incidence gives information about the RISK of acquiring a disease, while prevalence gives an indication of how widespread a disease actually is. The prevalence data for autism spectrum disorders appears to be a rapidly moving target. Current estimates range from 1 in 45 to 1 in 68 from the Centers for Diseases Control and Prevention-CDC (2014) (Zablotsky et al. 2015). Despite this, certain aspects of the demographic characteristics have remained stable over time. For example, the male-to-female ratio appears to be quite stable with a mean ratio of about 4 to 5:1, ranging from approximately 1.5:1 to 16:1 depending on the cognitive level being looked at. Boys are far more represented in the “higher functioning” group. However, both sexes are found throughout the intellectual spectrum. It is suspected that with the somewhat stricter criteria for diagnosis of autism spectrum disorders in the DSM 5, there may be a slight reduction in the frequency of diagnosis of some types of autism spectrum

disorder, especially what used to be called pervasive developmental disorder, not otherwise specified (PDD-NOS) (Kullage et al. 2014; Smith et al. 2015).

Whether a true increase in autism spectrum disorders has resulted in the increase in ASD prevalence, or the latter is due to changes in community awareness, and identification patterns, is still not clear (Rice et al. 2012). However, these authors state that “disentangling the many potential reasons for ASD prevalence increases has been challenging. Understanding the relative contribution of multiple factors such as variation in study methods, changes in diagnostic and community identification, and potential changes in risk factors is an important priority for the ADDM network and for the CDC.” Fombonne (2003a, 2005) states that “surveys conducted in the 1960s and 1970s only dealt with autism disorder (as opposed to ASD) and with a rather narrow definition of autism... and not accounting for autism occurring in subjects who are not “mentally retarded” (intellectually disabled). The closest estimate of ASD prevalence available in the late 1970s was 20 per 10,000 in a survey from the United Kingdom that was limited to the severely impaired children with ASD”. He further stated that “rates of autism disorder in recent surveys have consistently been more than 10 per 10,000 whereas previous prevalence estimates ranged from 4 to 5 in 10,000” (Fombonne 2002). Therefore, he felt that from the available evidence it could be concluded that recent rates for both ASD and autistic disorder are 3–4 times higher than 30 years ago! Fombonne (2003b) concludes that the combination of the broadened definition (especially at the less severe end of the spectrum), possibly differences in methods for case finding, changes in referral patterns, availability of services, public and professional awareness, diagnostic concepts and practices, could all contribute to the apparent or real increase in prevalence.

As stated above, current data from the CDC, suggested that about **1 in 68** children have been identified with autism spectrum disorder (ASD) according to estimates from CDC’s Autism and Developmental Disabilities Monitoring (ADDM) Network. There was a sex differentiation with

approximately **1 in 42** boys being affected, and **1 in 189** girls living in the ADDM network communities being identified with an ASD. Worldwide, the prevalence seems to more closely approximate **1 in 100** (The Morbidity and Mortality Weekly Report 2014). The annual cost financially and otherwise to families and governments clearly is intimidating at the least!

What Causes Autism?

With the rapidly escalating prevalence of autism spectrum disorders, researchers worldwide are attempting to identify potential genetic and epigenetic factors that may play a role in causing this disorder.

Despite significant research documenting no link between the measles-mumps-rubella (MMR) vaccine and autism development, there persists a belief among parents that there is indeed a causal relationship, especially with regards to the regressive form. This has resulted in lower immunization rates in many countries.

Wakefield et al. (1998) in the *Lancet*, initially claimed an association between the autistic diagnosis and the presence of lymphoid hyperplasia and measles antibodies, in a since retracted publication which led to an unwarranted hype about the possible causal relationship between the measles vaccine and the development of regressive autism.

The recent publication in *JAMA* (Jain et al. 2015), where they looked at 95,727 children with older siblings, 994 (1.04%) were diagnosed with ASD, and 1929 (2.02%) had an older sibling with ASD. Of those with older siblings with ASD, 6.9% had ASD versus 0.9% who had unaffected siblings. These children were all privately insured in the United States of America. They concluded that there was no association between MMR vaccine receipt and ASD even among children already at higher risk for ASD! Taylor et al. (1999) in 1999 published similar findings in the *Lancet*, as did Madsen et al. (2002). Doja and Roberts (2006) did a literature review, and a Cochrane review (Demicheli et al. 2012) was published in 2012 on the subject, all of which found no support for any link. Anecdotally, and

sadly, many of us have seen parents who opted not to immunize their second child after the first was diagnosed with the regressive form of ASD, only to have the second child subsequently be diagnosed. With increasing reports of outbreaks of measles in particular in various parts of the United States (CDC data; Centres for Disease Control and Prevention 2016), this raises new concerns about the health and well-being of these children. Measles can be a devastating disease causing serious pneumonias and other respiratory morbidities, but is also known to potentially cause a profound and progressive (but thankfully rare) neurological disorder called subacute sclerosing panencephalitis (SSPE). Accumulating data from various different sources, including genetic, neuropathological, electrophysiological, and even infant eye gaze preference studies, have suggested that the developmental pathways for autism are created much earlier than clinical symptoms are manifest—informing both the timing and the types of environmental exposures on which research should focus (Pierce et al. 2016).

Xiang and colleagues utilizing the large Kaiser-Permanente database, found that early onset (<26 weeks gestation) gestational diabetes increased the risk of ASD diagnosis (Xiang et al. 2015). Numerous studies have identified antenatal maternal stress as a possible “epigenetic” factor in autism spectrum disorders (Talge et al. 2007; Babenko et al. 2015; Grossi et al. 2016; Crawford 2015; Matelski L, Van de Water J 2016; Walder et al. 2014; Kinney et al. 2008). Severe maternal stress in pregnancy has been associated with lower cognitive and language abilities in childhood (Buss et al. 2010). King et al. (2012) reviewed the impact of natural disasters on neurodevelopmental disorders including autism using the Québec ice storm and Louisiana hurricane studies which revealed not only a “stress severity impact” but also a timing (gestation) impact. It appears that 5–6 months gestation is a particularly vulnerable period especially based on the Louisiana study (King et al. 2012). Beversdorf et al. (2005) suggested that pathological changes in the cerebellum in autism are thought to correspond to an event before 30–32 weeks gestation. In a retrospective study of 434 mothers of children with autism compared to 191 surveys to mothers

of children with Down syndrome, the researchers found a higher incidence of prenatal stressors in autism at 21–32 weeks gestation, with a peak at 25–28 weeks. Autoimmune disorders have also been associated with ASD (Sweeten et al. 2003; Molloy et al. 2006).

A relatively new (and somewhat controversial) area of interest involves the so-called “gut dysbiosis” phenomenon. GI symptoms are frequently reported in ASD and include constipation, diarrhea, food allergies/intolerance and abdominal pain. Rosenfeld (2015) reviewed the research re microbiome disturbances and autism spectrum disorders and the so-called “microbiome-gut-brain axis”, and concluded that it was still premature to render definitive conclusions and establish causation but recommended further research. De Angelis et al. (2015) found altered fecal microbiota and metabolomes in children with autistic disorder and PDD-NOS compared to healthy controls. Mayer et al. (2015) suggest a possible benefit of probiotic treatment in rodent models of autism. Clearly further studies are required before this can be recommended in humans. In a review O’Mahony et al. (2015), they reviewed the evidence on the role gut microbes could play in childhood disease generation, including autism. They concluded that “it must be appreciated that there are complex relationships between host genetics, microbial interactions, and environmental factors that determine the risk of disease development. However, key developmental windows exist in the prenatal and postnatal periods that allow the microbiota to influence essential modulatory systems and vice versa”. Potential areas for intervention or prevention were suggested. The higher prevalence of ASD in extremely premature infants adds further intrigue to the stress related hypothesis as well as the gut dysbiosis theories (Groer et al. 2015). It may be that for probiotics to have a role in prevention, they must be used EARLY in life, especially in high-risk infants (e.g., premature infants, and siblings of children with ASD, or perhaps even pregnant mothers). **Thus far, however, there is NO evidence of proven preventative or therapeutic benefit from probiotics use in other than possibly GI related issues.**

A Further Word About Risk-Factors

A number of factors have been identified as potential risk factors for ASD:

- Increased parental age (fathers ≥ 50 years; mothers 40–49 years AND < 20 years; there was a joint effect of maternal and paternal age with increasing risk of ASD for couples with increasing differences in parental ages) (Lord and Bishop 2015).
- Both short and long inter-pregnancy intervals (IPIs) have recently been found to be associated with an increased risk of autism spectrum disorders (Sandin et al. 2016). Compared with children born to women with IPIs of ≥ 36 months, children born to women with IPIs of < 12 months had a significantly increased risk of any ASD (pooled adjusted odds ratio [OR] 1.90, 95% confidence interval [CI] 1.16–3.09). This was less significant for long IPIs (Sandin et al. 2016).

Genetics

Autism spectrum disorder (ASD) is clearly a highly heritable condition (Agudelo et al. 2016). A number of authors (Packer 2016; Sandin et al. 2014) summarize by stating that a range of epidemiologic studies have supported the notion that ASD is multifactorial, with strong contributions from additive genetic and non-shared environmental risk factors. A very important recent finding was that de novo copy number variants (CNVs) are strongly associated with ASD risk (Sebat et al. 2007). To date at least 65 autism risk genes have been identified with several others showing strong potential (Packer 2016). It appears as if the future task of identifying the relationship between genotype and phenotype could be quite complex and challenging. Listing genes already identified as being significant is beyond the scope of this update. We strongly recommend the excellent review by Packer (2016) for this purpose. A recent study published in Nature Medicine (Yuen et al. 2015) and looking at quartet families with autism spectrum

disorder (two or more affected siblings with ASD) revealed that some 69.4% of the affected siblings carry different ASD-relevant mutations. These siblings with discordant mutations seemed to demonstrate more clinical variability than those who shared a risk variant. The authors concluded that there appears to be substantial genetic heterogeneity in ASD, necessitating the use of whole-genome sequencing (WGS) to delineate all the susceptibility variants in research and clinical diagnostics.

It is also very clear that a number of genetic syndromes have a higher than normal association with the development of autism spectrum disorder. These include DiGeorge syndrome (~20%), 22Q duplication, Angelman, Trisomy 21 (~8%), Fragile X (25–40%), 15q11–13 deletion, Tuberous Sclerosis (60%), Cornelia de Lange and others. Recent reports suggest an association between autism spectrum disorders and fetal alcohol spectrum disorders (Varadinova and Boyadjieva 2015; Evrard 2010). In clinical practice many of us working with this population certainly see features of ASD in many children with FASD.

ADHD and ASD share environmental and biological risk factors. Individuals with both disorders are more severely impaired than those with only one. There is strong evidence for genetic overlap between ADHD and ASD, demonstrating that rather than being an artifact of diagnosis, comorbidity is rooted in shared genetic risk factors (Antshel et al. 2013; Visser et al. 2016). A substantial minority of youth with ADHD demonstrate traits of autism spectrum disorder (15–25%), and interestingly, ADHD is one of the most common comorbidities in children with ASD (40–70%). Van der Meer et al. (2012) question whether autism spectrum disorder and ADHD represent different manifestations of one overarching disorder. A large number of copy number variants and chromosome abnormalities confer risks for ADHD and ASD (please refer to Van der Meer et al. (2012) for more details about this important and interesting phenomenon). In another great review by Craig et al. (2016) they reviewed the similarities and differences in executive dysfunction in these disorders. The ASD + ADHD

group appeared to share impairment in both flexibility and planning with the ASD group, while it shared the response inhibition deficit with the ADHD group. Conversely, deficit in attention, working memory, preparatory processes, fluency, and concept formation did not appear to be distinctive in discriminating from ASD, ADHD, or ASD + ADHD group. Miodovnik et al. (2015), found that approximately 20% of children (who) had initially been diagnosed with ADHD before ASD were diagnosed with ASD ~3 years (95% confidence interval 2.3–3.5) after children in whom ADHD was diagnosed at the same time or after ASD. The children with ADHD diagnosed first were nearly 30 times more likely to receive their ASD diagnosis after age 6 (95% confidence interval 11.2–77.8). The delay in ASD diagnosis was consistent across childhood and independent of ASD severity.

The recurrence risk after one child is diagnosed with ASD approximates 20% (19–27%) (Schaefer 2016; Zwaigenbaum et al. 2012).

A “New” Finding

- Although the literature is quantitatively limited, some recent publications suggest a possible association between gender identity disorder (GID), or gender dysphoria (GD) and ASD. Skagerberg et al. (2015), looked for an association between GD and autistic features using the Social Responsiveness Scale (SRS). Approximately 46% fell within the normal range on the SRS, and of those 2.8% had an ASD diagnosis. 27.1% fell within the mild/moderate range and of those 15.6% had an ASD diagnosis and 6.7% and ASD query. Twenty-seven percentage also fell within the severe range and of those 24.4% at an ASD diagnosis and 26.7% in ASD query. VanderLaan et al. (2015) identified that high birth weight was associated with both high gender nonconformity and autistic traits among GD children. Pasterski et al. (2014) found less consistent data in adults with gender dysphoria. Schalkwyk et al. (2015) suggested that perhaps a more complex approach

that attempts to understand gender in developmental terms is potentially more salient for both research and clinical purposes. They also suggest that the current understanding about the unique social development of individuals with ASD, may impact the process of gender identity formation and thus underline the need for such an approach. In our clinic, we have recently had 4 patients self-identify as “transgender” or gender dysphoria.

Assessment/Evaluation

Autism spectrum disorder can be diagnosed reliably by age 2 by an experienced professional (Lord et al. 2006). For many children <3 years, early intervention can improve outcomes, including core deficits of ASD (social attention), e.g., language and symptoms severity (Dawson et al. 2010; Kasari et al. 2010).

Primary care providers have the opportunity to conduct developmental surveillance during well-child visits and monitor for early signs of delays including autism spectrum disorder at each visits.

Diagnosing a child with ASD takes two steps: (1) Developmental screening and (2) Comprehensive diagnostic evaluation. The American Academy of Pediatrics (AAP) recommends screening all children for ASD at 18–24 months of age. The modified toddler checklist for autism M-CHAT is a modified screening tool which can be used for children 16–30 months old during the well-child visits. This is a 23 item parent questionnaire with the structured follow-up interview to clarify items endorsed by parents. Recently Robins et al. (2014), validated a newer version of this instrument, the modified checklist for autism in toddlers, revised with follow-up M-CHAT-R/F. The questionnaire was reduced to 20 items with three risk ranges. Children in the low risk range (0–2) did not require follow-up interview unless <24 months of age, where a repeat screening after the second birthday is required. Children in the medium risk range (3–7) required the follow-up interview to clarify the risk of ASD, if at least two items remain positive, then preference for diagnostic evaluation was indicated. Children

in the high risk range (8–20) were considered at sufficiently high risk to be referred directly for diagnostic assessment without the follow-up interview. The revised scoring increased the overall rate of ASD detection (67 versus 45 per 10,000 (Robins et al. 2014). The communication and symbolic behaviour scales infant toddler checklist CSBS-ITC, is a broad band screener to detect infants/toddlers (6–24 months) with communication delays including ASD from the general population. Positive and negative predictive value support the validity of the CSBS-ITC for children 9–24 months but not 6–9 months (Wetherby et al. 2008).

Historical Pearls

In trying to elicit a history consistent with an ASD diagnosis, it is sometimes difficult to be sure how to interpret the responses to our questions. Do parents REALLY understand what we are asking? Here are some ways to simplify this process:

- Does your child play **WITH** or **AMONG** other kids?
- Is your child a “**creature of habit?**”
- Is your child a “**stickler**” for rules?
- Does your child like to “**run**” the show?

The above are questions that many parents of kids with ASD can relate to. I am amazed at the different reaction I get when I ask, “Does your child play with other kids?” vs. “Does your child play WITH or AMONG other kids?”

A similar question would include “**HOW does** your child play with other kids?”

[Sidebars are great for calling out important points from your text or adding additional info for quick reference, such as a schedule.

They are typically placed on the left, right, top or bottom of the page. But you can easily drag them to any position you prefer.

When you’re ready to add your content, just click here and start typing.]

Children with positive ASD screens *and* clinician concern should be referred for further diagnostic assessment. Evaluation of ASD should include a comprehensive assessment by a team that has expertise in diagnosis and management. Since this is not always feasible, depending on the location or wait list, the diagnosis can be evaluated/confirmed by another pediatric specialist (psychologist, psychiatrist, neurologist, developmental pediatrician, general pediatrician) with expertise in ASD in collaboration with other team members (speech and language therapist, occupational therapist, teachers, etc).

Assessment includes a detailed neurodevelopmental history: current concerns, prenatal, perinatal, developmental history, medical, social and three generation family history (including mental-health history). Information and functioning in multiple settings e.g. home, school, after school programs and community by using rating scales, structured interviews and observations. For the parent interview, the ADI-R, though lengthy, has been established as a useful diagnostic tool in the assessment of ASD (Lord et al. 1994). Clinicians may decide to use other questionnaires if ADI-R is not feasible. The social communication questionnaire SCQ is the screening tool based on the ADI-R that can be used for children with a mental age over 2 years (Rutter and Barley 2003). Social Responsiveness Scale, second edition (SRS-2) is designed to identify social impairment that is seen in ASD and to differentiate it from social difficulties that occur in other disorders. It can be completed for children as young as 30 months to adulthood and takes about 15 min to complete (Constantino 2012). A useful tool for the evaluation of autism is the Autism Diagnostic Observation Schedule 2nd Edition (ADOS-2), which is a semi structured, standardized assessment of communication, social interaction, play and restricted and repetitive behaviours. Module 1–4 provide cut off scores for ASD and can be used in children as young as 31 months. The toddler module (12–30 months) of the ADOS provides ranges of concern reflecting the extent to which a child demonstrates behaviors associated with ASD (Lord and Rutter 2012).

Examination of the child should document growth parameters especially head circumference since children with ASD may have acceleration of head growth followed by stabilization (Courchesne et al. 2003). Look for dysmorphic features, neurocutaneous lesions and medical/genetic disorders that may co-exist with ASD e.g. Fragile X, tuberous sclerosis etc. (See also section “Genetic Disorders”.)

Consider if the child has other co-existing or co-morbid conditions e.g. intellectual disability, language delays, developmental coordination disorder, ADHD, anxiety, etc., and carry out appropriate assessments for identification.

Investigations

All children with ASD should have an audiological exam and lead screening (if there is history of pica, or live in a high-risk area). EEG is not recommended routinely except when there is suspicion of subclinical seizures or clinical seizures and/or history of developmental regression. There is no evidence to support the role of clinical neuroimaging in the diagnostic evaluation of autism (Filipek et al. 2000). It should be performed based on clinical suspicion of existing alternative diagnosis e.g. Tuberous sclerosis, or presence of microcephaly or extreme (≥ 4 SD) macrocephaly, or focal seizures (Anagnostou et al. 2014). If a metabolic etiology is suspected magnetic resonance spectroscopy should be considered with standard neuroimaging. Metabolic testing should be guided by clinical indicators (seizures, neuro-regression, extrapyramidal signs, severe intellectual disability, failure to thrive, etc.). Suspicion of a particular genetic disorder helps in the selection of the specific genetic investigation since many recognizable syndromes have documented association with ASD (e.g. Fragile X, Angelman syndrome, etc.—see earlier) Chromosomal microarray (CMA) is a first-tier test in place of karyotype and the diagnostic yield is nearly 30% in complex ASD (congenital anomalies, microcephaly, seizures, dysmorphic features). Other

testing should include DNA testing for Fragile X in males, MECP2 sequencing in females with ASD can be considered with intellectual disability, MECP2 duplication testing in males if phenotype is suggestive, and PTEN testing if head circumference is >2.5 SD above the mean (Schaefer et al. 2013; Anagnostou et al. 2014). Where available, whole-exome sequencing may also be considered (Tammimies K et al. 2015).

Other testing should be dictated by the circumstances or history, for example, in a child with ASD who has highly selective dietary intake, nutritional screening for iron, zinc and vitamin B12 and others, could be considered (with the assistance of a dietician).

Treatment Options for Autism Spectrum Disorders

An excellent summary of treatments found to be effective in the management of ASD is provided by Anagnostou et al. (2014) in their review.

In their review they very succinctly summarize the treatment of autism spectrum disorders by stating: “The goal of existing interventions is to facilitate the acquisition of skills, remove barriers to learning and improve functional skills and quality of life.”

Management is divided into **Behavioral** and **Biomedical** approaches.

Behavioral Interventions

Applied behavioral analysis (ABA) utilizing empirically derived basic learning principles, has been shown by many studies to produce meaningful and positive changes in behavior (Peters-Scheffer et al. 2011; Reichow et al. 2012) There are several models of ABA intervention all of which have some evidence to support their efficacy. There are still questions around timing, intensity and patient-selection for treatment to produce optimal effects, but in general it appears that early intervention is critical for this. A comprehensive review of this is provided in

the paper by Zwaigenbaum et al. (2015). Several important statements, based on the review of a range of studies, and expert opinion were compiled. These included the following:

- “Current best practices for interventions for children aged 3 years with suspected or confirmed ASD should include a combination of developmental and behavioral approaches and begin as early as possible.
- Current best practices for children aged 3 years with suspected or confirmed ASD should have active involvement of families and/or caregivers as part of the intervention.
- Interventions should enhance developmental progress and improve functioning related to both the core and associated features of ASD, including social communication, emotional/behavioral regulation, and adaptive behaviors.
- Intervention services should consider the sociocultural beliefs of the family and family dynamics and supports, as well as economic capability, in terms of both the delivery and assessment of factors that moderate outcomes.”

They also acknowledged the need to simultaneously address the comorbid conditions such as sleep disorders, gastrointestinal disorders (Bauman 2010), anxiety, and other maladaptive behaviors, in addition to seeking the assistance of occupational therapy and speech language pathology, when required.

Biomedical Interventions

Several studies have unsuccessfully attempted to identify pharmaceutical interventions which alter the core symptoms of ASD creating dysfunction. However, there are a number of studies now published which support the use of pharmacological agents to alleviate comorbidities affecting day-to-day functioning and quality of life of child and caregivers. These will be covered in more detail in the discussion of comorbidities later in this chapter. However, a few brief general points will be made here.

Perhaps the neuroleptics and stimulants have the most support for their use in the management of irritability/aggression. With the use of neuroleptics, the CAMESA guidelines should be carefully followed to monitor metabolic effects as well as potential hormonal impacts of their use (Pringsheim et al. 2011).

Comorbidities can significantly impact the quality of life of the child, caregivers at home and at school and therefore should be addressed, if it is possible to do this safely. The general premise is that it is often difficult to disentangle symptoms/comorbidities/ASD symptoms in every child. As a result, success in management is often not easily attained. For example, sleep disorders (see later discussion) are highly prevalent in the ASD population and can often result in irritable behavior, self-injurious behaviors, impaired focus, and hyperactive symptoms. In turn, sleep can be affected by anxiety, ADHD, medication use, etc. (Frye 2016). It is also important to recognize that children with ASD can also have medical problems, for example migraine headaches, which similarly can cause or exacerbate sensory and other issues. Sensory Integration Disorder (SID), now included in the DSM 5 as part of the ASD diagnosis also can significantly exacerbate other behaviors, and consultation with an occupational therapist competent with managing SID should be undertaken (McDonnell et al. 2015). Sensory disorders can affect a range of behaviors including feeding, sleep, attention, and can exacerbate as well as be exacerbated by anxiety. Management of GI issues, are beyond the scope of this update, but can be treated with the assistance of a gastroenterologist (Coury 2010). The Autism Treatment Network (Autism Speaks) also has excellent resources available for physician and parent use (The Autism treatment Network 2017).

Comorbidities in ASD

Comorbid conditions are common in ASD individuals though overlapping symptoms of ASD and other disorders often make diagnosis difficult.

Attention Deficit/Hyperactivity Disorder

ADHD occurs in 41–78% off children with ASD (Murray 2010). The DSM-IV did not allow the diagnosis of ASD and ADHD, however in the new DSM-5 this has been changed. It is important to consider the patient's ability to attend to both preferred and non-preferred activities since individuals with ASD may be able to focus for prolonged periods when engaged in preferred activities. ASD patients may be less responsive to methylphenidate than those with primary ADHD with a response rate of 50% and have a higher rate of side effects (e.g., irritability, self-injury, and stereotypy) (Mahajan et al. 2012; Reichow et al. 2013; Davis and Kollins 2012). Stimulants are recommended as first line choice in children with ASD and ADHD followed by atomoxetine and alpha agonists (guanfacine, clonidine) as second line and atypical antipsychotics as third line (Mahajan et al. 2012). Symptoms of ADHD can overshadow the symptoms of ASD, making diagnosis challenging. Children initially diagnosed with ADHD received their ASD diagnosis 3 years later than the children in whom ADHD was diagnosed at the same time or after ASD (Miodovnik et al. 2015). The coexistence of ADHD with ASD can significantly negatively impact the management and prognosis of ASD.

Irritability/Aggression (IA)

Approximately 20% of patients with ASD exhibit irritability/aggression at a moderate to severe range (Lecavalier 2006). Currently only two psychotropic medications, risperidone and aripiprazole, have been approved by the FDA for treatment of IA in individuals with ASD (Fung et al. 2016). Mood stabilizers such as Divalproex sodium (Hollander et al. 2010) and opioid antagonists (naltrexone) may decrease irritability in ASD but more clinical trials are required (Fung et al. 2016). Medication combined with behavioral intervention appears to be more effective for reducing aggressive behavior than medication alone (Dawson and Burner 2011). Novel treatments with glutamatergic

agents (amantadine, memantine, riluzole, NAC) are underway and encouraging results have been seen with N-acetylcysteine (NAC) when used as an adjunctive therapy to risperidone in decreasing irritability in children with ASD (Ji and Finding 2015).

Seizures

The prevalence of epilepsy in ASD varies from 5% to 38% and is related to underlying comorbid medical and intellectual disability. The risk of seizures and epilepsy increase with age. Every clinical seizure type has been noted in ASD. The prevalence of subclinical electrical discharges (SED) in ASD range from 30% to 61% in studies that have used long term EEG monitoring (Richard 2015). Studies have suggested that SED is common in childhood, while clinical seizures become increasingly prevalent with age (Parmeggiani and Barcia 2010). In individuals with ASD, the SED is multi-focal and includes temporal and frontal cortical areas and it has been suggested that SED may be associated with more severe speech and intellectual impairment in children with ASD (Richard 2015). Studies on individuals with SED but no ASD are associated with cognitive and behavior impairment which improve with antiepileptic medication (Pressler et al. 2005). Treatment of children with SED and ASD may be beneficial but further research is needed. Treating epilepsy in children with ASD follow the same principles as treatment of epilepsy in any individual.

Gastrointestinal (GI)

Gastrointestinal disorders are commonly associated with a subset of children with autism spectrum disorder. The prevalence of GI problems reported in children with autism spectrum disorder range from 9% to 91% depending on the definition used (Mannion and Leader 2014). The most common GI complaints in children with autism are constipation, diarrhea and gastroesophageal reflux and are treated in a standard manner. There is emerging evidence on GI dysfunction in ASD and the relationship of increased intestinal permeability, gut microbiome, immune function though scientific conclusions cannot be reached yet on

interventions (Coury et al. 2012). Available data do not support the use of casein-free, a gluten-free diet or combination diets as a primary treatment for children with ASD, but results have largely been controversial as to whether there is any role, in the absence of diagnosed sensitivity or frank celiac disorder (Buie et al. 2010). In a largest study of its kind, researchers did not find any links between autism and celiac disease, though there was a strong association between autism and presence of antibodies to gluten suggesting gluten sensitivity (Ludvigsson et al. 2013).

Anxiety

At least one anxiety disorder is seen in 39.6% of the youth with ASD (Van Steensel et al. 2011). There is now evidence that anxiety may be “underdiagnosed” in this population, and standard anxiety screening tools may under-diagnose anxiety in these patients (White SW et al. 2009). The range of prevalence of anxiety disorders in the latter review was 11-84%.

Treatment recommendations include psychoeducational coordination of care and modified cognitive behavior therapy, which has been clearly shown to be beneficial especially in high functioning patients with ASD. It should be noted that anxiety can often present as inattention and restlessness, and therefore can mimic features of ADHD. It can also present as a sleep disorder, affecting both sleep initiation and night awakening. Patients with anxiety and ASD can also present with self-injurious behaviors and aggression. Specific phobias such as elevators, insects, thunder and lightning, etc. are not unusual. SSRI's are frequently prescribed for anxiety in youth with ASD though there is limited evidence unlike in typically developing youth with anxiety. Children with ASD may respond to far lower dosages than would be typically expected. As such, a liquid formulation is preferred, as this allows for lower titration (Folstein and Carcache 2016). SSRI's should be prescribed cautiously in youths with ASD with close monitoring (Folstein and Carcache 2016; Vasa et al. 2016). Some research also suggests the use of buspirone, or mirtazapine if SSRI's fail (Politte et al. 2015). It is also important to inquire about a family history of the mood

or anxiety disorder in these children, as there is some evidence that a high proportion of children with ASD and a mood/anxiety disorder also have a parent with a mood/anxiety disorder (Mazefsky et al. 2008).

Sleep Problems

Sleep problems are common in autism spectrum disorder, with prevalence rates of 40–80% (Cohen et al. 2014; Cortesi et al. 2010). Sleep issues include increased sleep latency, frequent night waking, and shorter sleep duration (Cortesi et al. 2010). It is worth noting that sleep onset and night-waking problems are often associated with poor sleep hygiene or maladaptive sleep associations. Good sleepers with ASD showed fewer affective problems and better social interaction than ASD poor sleepers (Cohen et al. 2014; Marlow et al. 2006; Cortesi et al. 2010). The reasons for sleep difficulties in children with ASD are multifactorial: poor sleep hygiene, medical issues (GI, seizures), medications, psychiatric issues (anxiety, depression, ADHD), abnormal melatonin regulation among others. Management requires addressing any medical or psychiatric issues that may interfere with sleep. Behavioural intervention (including sleep hygiene) can be effective in decreasing sleep problems and should be tried first, before medication (Cortesi et al. 2010). Addressing sensory issues may facilitate sleep in some children (e.g. weighted blankets). Light therapy can be considered for children with ASD who present with circadian dysfunction (Cortesi et al. 2010). Melatonin has been shown to be effective in a subgroup of children with ASD by decreasing the onset and improving the duration of sleep (Goldman et al. 2014). Low ferritin levels have been found to be associated with sleep disturbances in both children and adults, notably periodic leg movements and ADHD and studies have been done in the ASD population as well (Dosman et al. 2007).

Developmental Coordination Disorder (DCD)/Dyspraxia

Numerous studies have described motor impairments (Dyspraxia/DCD) in the ASD population (Dziuk et al. 2007). Children with DCD struggle

with motor tasks like writing, dressing, self-care, and participating in sports, etc. This further negatively impacts social acceptance by peers. With the change to the DSM 5 a formal diagnosis of DCD can be made if the ASD individual meets the motor criteria, which is a change from the DSM IV-TR. Referral to a physiotherapist (PT) and occupational therapist (OT) is recommended in this scenario. Treatment modalities vary, depending on the areas of need (e.g. fine (FM) or gross motor skills, and presence of intellectual impairment). Generally, individual sports (e.g. swimming, or martial arts) are recommended for gross motor skills, and the OT will recommend FM adaptive devices, where applicable or computer software. For a great review of this topic please see Paquet et al. (2015).

Intellectual Disability (ID)

Intellectual Disability (IQ < 70) has been reported in 31% of children with ASD while 23% was in the borderline range (IQ 71–85) and 46% in the average or above range (IQ have increased >85) range. However, because of a variety of behavioral, language and mental health co-morbidities, getting an accurate assessment of intellectual functioning in children with ASD can be challenging. These individuals often “march to their own drum” and may not demonstrate their optimal abilities on queue. Children with IQ in the average to above range have increased in the last decade from 32% in 2002 to 46% in 2010. This shift in IQ may be attributed to a larger proportion of children with average to above average IQ being diagnosed with ASD (Buio 2014). As with all other co-morbidities, ID significantly impacts prognosis negatively. As noted earlier, all patients with ID warrant specific genetic, and possibly metabolic work-up.

Tics and Tourette Syndrome (TS)

Burd et al. (2009) studied 7288 participants from the Tourette Syndrome International Database Consortium Registry and found that 4.6% had a co-morbid autism spectrum disorder. Increased risk was noted in “male gender, no family history of tics/Tourette syndrome, and an increased number of comorbidities (P < 0.001)”. Interesting

questions surface about the similarities between the two conditions, namely complex tics versus stereotypies, and OCD versus repetitive behaviors among others. Ordering and arranging compulsions occur in TS while lining up toys, etc., is commonly noted in ASD. Hoarding behaviors occur in both. Therefore, the notion is growing that, instead of viewing TS, OCD, ADHD, and autism as separate but co-morbid disorders, these disorders should be seen as part of a spectrum of disorders with overlapping etiologies, converging in dysfunctional cortico-striatal circuitry underlying these disorders (Huisman-van Dijk et al. 2016). Systematic review in another study revealed that the co-occurrence of ASD and TS is around 4–5% and the co-occurrence of ASD and tic disorder (TD) ranges from 9% to 12%. The comorbidity prevalence rates vary according to the level of ASD severity (with comorbidity of high-functioning ASD and TS reaching 20%) (Kalyva et al. 2016).

Summary

ASD is a fascinating and complex neurodevelopmental disorder. Future research hopefully will help sort out whether in fact ASD is a disorder in its own right or part of a broader spectrum of disorders possibly involving ASD, ADHD, DCD and Tourette Syndrome. The impact of comorbidities not only complicates and negatively impacts treatment but adversely affects prognosis.

The possible associations between maternal stress and ASD and other neurodevelopmental disorders is intriguing to say the least. Probiotics and the concept of the gut-brain connection with the microbiome also needs further research.

The true cause of the rapidly rising prevalence of ASD is still not fully understood, but there appears to be an increasing role for higher functioning individuals with ASD in our increasingly technological society (viz Silicon Valley). Are epigenetic factors causing an evolutionary drive to make future generations more capable of coping with our inevitably technological world?

Exciting times are ahead as we endeavour to look into these fascinating questions.

References

- Agudelo A, Rosas-Bermudez A, et al. Birth spacing and risk of autism and other neurodevelopmental disabilities: a systematic review. *Pediatrics*. 2016;137(5):1–13.
- American Speech-Language Hearing Association Autism review; 2015. <http://www.asha.org/PRPSpecificTopic.aspx?folderid=8589935303§ion=Overview>
- Anagnostou A, Zwaigenbaum L, et al. Autism spectrum disorder: advances in evidence-based practice. *CMAJ*. 2014;186(7):509–19.
- Antshel MA, Zhang-James Y, et al. An update on the comorbidity of ADHD and ASD: a focus on clinical management. *Expert Rev Neurother*. 2013;16(3):279–93.
- Babenko O, Kovalchuk I, et al. stress-induced perinatal and transgenerational epigenetic programming of brain development and mental health. *Neurosci Biobehav Rev*. 2015;48:70–91.
- Bauman ML. Medical comorbidities in autism: challenges to diagnosis and treatment. *Neurotherapeutics*. 2010;7(3):320–7.
- Beversdorf DQ, Manning SE, et al. Timing of prenatal stressors and autism. *J Autism Dev Disord*. 2005;35(4):471–8.
- Buie T, Campbell DB, et al. Evaluation, diagnosis and treatment of gastrointestinal disorders in individuals with autism spectrum disorders: a consensus report. *Pediatrics*. 2010;125(1):S1–18.
- Buio J. Prevalence of autism spectrum disorders, among children aged eight years: autism and developmental disabilities monitoring network. *CDC*. 2014;63(SS02):1–12.
- Burd L, Li Q, et al. Tourette syndrome and co-morbid pervasive developmental disorder. *J Child Neurol*. 2009;24(2):170–5.
- Buss C, Davis EP, et al. High pregnancy anxiety during mid-gestation is associated with decreased gray matter density 6–8 year-old children. *Psychoneuroendocrinology*. 2010;35(1):141–53.
- Centres for Disease Control and Prevention 2016. <http://www.cdc.gov/measles/cases-outbreaks.html>.
- Cohen S, Conduit R, et al. The relationship between sleep and behaviour in autism spectrum disorders: a review. *J Neurodev Disord*. 2014;6(1):44.
- Constantino J. 2012. Social responsiveness scale, second edition (SRS-2). www.wpspublish.com
- Cortesi F, Giannotti F, et al. Sleep in children with autism spectrum disorder. *Sleep Med*. 2010;11(7):659–64.
- Courchesne E, Carper R, et al. Evidence of brain overgrowth in the first year of life and autism. *JAMA*. 2003;290(3):337–44.
- Coury D. Medical treatment of autism spectrum disorders. *Curr Opin Neurol*. 2010;23:131–6.

- Coury DL, Ashwood P, et al. Gastrointestinal conditions in children with autism spectrum disorders: developing a research agenda. *Pediatrics*. 2012;130(2):S160–8.
- Craig F, Margari F, et al. A review of executive function deficits in autism spectrum disorder and attention deficit hyperactivity disorder. *Neuropsychiatr Dis Treat*. 2016;12:1191–202.
- Crawford S. On the origins of autism: the quantitative threshold exposure hypothesis. *Med Hypotheses*. 2015;85:798–806.
- Davis NO, Kollins SH. Treatment of co-occurring attention deficit hyperactivity disorder and autism spectrum disorder. *Neurotherapeutics*. 2012;9:518–30.
- Dawson G, Burner K. Behavioural interventions in children and adolescents with autism spectrum disorders: a review of recent findings. *Curr Opin Pediatr*. 2011;23(6):616–20.
- Dawson G, Rogers S, et al. Randomized controlled trial of an intervention for toddlers with autism: the early start Denver model. *Pediatrics*. 2010;125(1):e17–23.
- De Angelis M, Francavilla R, et al. Autism spectrum disorders and intestinal microbiota. *Gut Microbes*. 2015;6(3):207–13.
- Demicheli V, Rivetti A, et al. Vaccines for measles mumps and rubella in children. *Cochrane Database Syst Rev*. 2012;2:CD004407.
- Doja A, Roberts W. Immunize stations in autism: a review of the literature. *Can J Neurol Sci*. 2006;33(4):341–6.
- Dosman CF, Brian JA, et al. Children with autism: effect of iron supplementation on sleep and ferritin. *Pediatr Neurol*. 2007;36(3):152–8.
- Dziuk MA, Gidley L, et al. Dyspraxia in autism associated with motor, social and communicative deficits. *Dev Med Child Neurol*. 2007;49(10):734–9.
- Evrard SG. Prenatal alcohol exposure as an etiological factor in neuropsychiatric diseases of childhood adolescence and adults. *Vertex*. 2010;21(92):260–5.
- Filipek PA, Accardo PJ, et al. Practice parameter: screening and diagnosis of autism. *Neurology*. 2000;55(4):468–79.
- Folstein SE, Carcache LM. Psychiatric comorbidity in autism spectrum disorder. In: CJ MD, editor. *Autism spectrum disorder*. Oxford University Press: Oxford; 2016.
- Fombonne E. Epidemiological trends in rates of autism. *Mol Psychiatry*. 2002;7(Suppl 2):S4–6.
- Fombonne E. Epidemiological surveys of autism and other pervasive developmental disorders: an update. *J Autism Dev Disord*. 2003a;33(3):365–82.
- Fombonne E. The prevalence of autism. *JAMA*. 2003b;289(1):87–9.
- Fombonne E. Epidemiology of autistic disorder and other pervasive developmental disorders. *J Clin Psychiatry*. 2005;66(suppl 10):3–8.
- Frye RE, Rossignol DA. Identification and treatment of pathophysiological comorbidities of autism spectrum disorders to achieve optimal outcomes. *Clin Med Insights Pediatr*. 2016;10:43–56.
- Fung LK, Mahajan R, et al. Pharmacological treatment of severe irritability and problem behaviours in autism: a systematic review and meta-analysis. *Pediatrics*. 2016;137(2):S124–35.
- Goldman SE, Adkins KW, et al. Melatonin in children with autism spectrum disorders: endogenous and pharmacokinetic profiles in relation to sleep. *J Autism Dev Disord*. 2014;44(10):2525–35.
- Groer MW, Gregory KE, et al. The very low birth weight infant microbiome and child health. *Birth Defects Res C Embryo Today*. 2015;105(4):252–64.
- Grossi E, Veggo F, et al. Pregnancy risk factors in autism: a pilot study with artificial neural networks. *Pediatr Res*. 2016;79(2):339–47.
- Hollander E, Chaplin W, et al. Divalproex sodium vs placebo for the treatment of irritability in children and adolescents with autism spectrum disorders. *Neuropsychopharmacology*. 2010;35(4):990–8.
- Huisman-van Dijk HM, van de Schoot R, et al. The relationship between tics, OC, ADHD and autism symptoms: a cross-disorder symptom analysis in Gilles de la Tourette syndrome patients and family-members. *Psychiatry Res*. 2016;237(2016):138–46.
- Jain A, Marshall J, et al. Autism occurrence by MMR vaccine status among US children with older siblings with and without autism. *Lancet*. 2015;313(15):1534–40.
- Ji N, Finding RL. An update of pharmacotherapy for autism spectrum disorder in children and adolescents. *Curr Opin Psychiatry*. 2015;28:91–101.
- Joseph L, Soorya L, Thurm A. *Autism spectrum disorder*. Cambridge, MA: Hogrefe and Huber Publishers; 2014.
- Kalya E, Kyriazi M, et al. A review of co-occurrence of autism spectrum disorder and Tourette syndrome. *Res Autism Spectr Disord*. 2016;24:39–51.
- Kasari C, Gulsrud AC, et al. Randomized controlled caregiver mediated joint engagement intervention for toddlers with autism. *J Autism Dev Disord*. 2010;40(9):1045–56.
- King S, Dancause K, et al. Using natural disasters to study the effects of prenatal maternal stress on child health and development. *Birth Defects Res C Embryo Today*. 2012;96(4):273–88.
- Kinney DK, Miller AM, et al. Autism prevalence following prenatal exposure to hurricanes and tropical storms in Louisiana. *J Autism Dev Disord*. 2008;38(3):481–8.
- Kullage KM, Smaldone AM, Cohn EG. How will DSM 5 affect autism diagnosis? A systematic literature review and meta-analysis. *J Autism Dev Disord*. 2014;44(8):1918–32.
- Lecavalier L. Behavioural and emotional problems in young people with pervasive developmental disorders: relative prevalence, effects of subject characteristics and empirical classification. *J Autism Dev Disord*. 2006;36(8):1101–14.
- Lord C, Bishop SL. Recent advances in autism research as reflected in DSM-V criteria for autism spectrum disorder. *Annu Rev Clin Psychol*. 2015;11:53–70.

- Lord C, Rutter M. 2012. Autism diagnostic observation schedule, second edition (ADOS-2). www.wpspublish.com
- Lord C, Rutter M, et al. Autism diagnostic interview revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord*. 1994;24(5):659–85.
- Lord C, Risi S, et al. Autism from 2 To 9 years of age. *Arch Gen Psychiatry*. 2006;63(6):694–701.
- Ludvigsson JF, et al. The nationwide study of the association between celiac disease and the risk of autism spectrum disorders. *JAMA Psychiat*. 2013;70(14):1224–30.
- Madsen KM, Hviid A, et al. A population-based study of measles, mumps, and rubella vaccination and autism. *N Engl J Med*. 2002;347(19):1477–82.
- Mahajan R, Bernal MP, et al. Clinical practice pathways for evaluation and medication choice for attention deficit/hyperactivity disorder symptoms in autism spectrum disorders. *Pediatrics*. 2012;m130(2):S125–38.
- Mannion A, Leader G. Gastrointestinal symptoms in autism spectrum disorder: a literature review. *Rev J Autism Dev Disord*. 2014;1:11–7.
- Marlow BW, Marzec ML, et al. Characterizing sleep in children with autism spectrum disorders: a multidimensional approach. *Sleep*. 2006;29(12):1563–71.
- Matelski L, Van de Water J. Risk factors in autism: thinking outside the brain. *J Autoimmun*. 2016;67:1–7.
- Mayer EA, Tillisch K, et al. Gut/brain axis and they microbiota. *J Clin Invest*. 2015;125(3):926–38.
- Mazefsky CA, Folstein EF, et al. Overrepresentation of mood and anxiety disorders in adults with autism and their first degree relatives: what does it mean? *Autism Res*. 2008;1(3):193–7.
- McDonnell A, McCreadie M, et al. The role of physiological arousal in the management of challenging behaviors in individuals with autism spectrum disorders. *Res Dev Disabil*. 2015;36:311–22.
- Miodovnik A, Harstad E, et al. Timing of diagnosis of attention deficit hyperactivity disorder and autism spectrum disorder. *Pediatrics*. 2015;136(4):e830–7.
- Molloy CA, Morrow AL, et al. Familial autoimmune thyroid disease as a risk factor for regression in children with autism spectrum disorder: a CPEA study. *J Autism Dev Disord*. 2006;36(3):317–24.
- Murray MJ. Attention deficit hyperactivity disorder in the context of autism spectrum disorders. *Curr Psychiatry Rep*. 2010;12(5):382–8.
- O'Mahony SM, Stilling RM, et al. The microbiome and childhood diseases: focus on brain-gut axis. *Birth Defects Res C Embryo Today*. 2015;105(4):296–313.
- Packer A. Neocortical neurogenesis and the etiology of autism spectrum disorder. *Neurosci Biobehav Rev*. 2016;64(2016):185–95.
- Paquet A, Olliac B, et al. Current knowledge of motor disorders in children with Autism Spectrum Disorders. *Child Neuropsychol*. 2015;29:1–32.
- Parneggiani A, Barcia G. Epilepsy and EEG paroxysmal abnormalities in autism spectrum disorder. *Brain and Development*. 2010;32(9):783–9.
- Pasterski V, Gilligan L, et al. Traits of autism spectrum disorders in adults with gender dysphoria. *Arch Sex Behav*. 2014;43:387–93.
- Peters-Scheffer N, Didden R, Korzilius H, et al. A meta-analytic study on the effectiveness of comprehensive ABA-based early intervention programs for children with autism spectrum disorders. *Res Autism Spectr Disord*. 2011;5:60–9.
- Pierce K, et al. Eye tracking reveals abnormal visual preference for geometric images as an early biomarker of an autism spectrum disorder subtype associated with increased symptom severity. *Biol Psychiatry*. 2016;79(8):657–66.
- Politte LC, Howe Y, et al. Evidence based treatments for autism spectrum disorder. *Curr Treat Options Psychiatry*. 2015;2:38–56.
- Pressler RM, Robinson RO, et al. Treatment of interictal epileptiform discharges can improve behaviour in children with behavioural problems and epilepsy. *J Pediatr*. 2005;146(1):112–7.
- Pringsheim T, Paniagiatopoulos C, Davidson J, et al. Evidence-based recommendations for monitoring safety of second-generation antipsychotics in children and youth. *Pediatr Child Health*. 2011;16(9):581–9. <http://comesguideline.org/>
- Reichow B, Barton EE, Boyd BA, et al. Early intensive behavioral intervention (EIBI) for young children with autism spectrum disorders (ASD). *Cochrane Database Syst Rev*. 2012;10:CD009260.
- Reichow B, Volkmar FR, et al. Systematic review and meta-analysis of pharmacological treatments of the symptoms of attention deficit/hyperactivity disorder in children with pervasive developmental disorders. *J Autism Dev Disord*. 2013;43(10):2435–41.
- Rice CE, Rosanoff M, Dawson G, Durkin MS, Croen LA, Singer A, Yeargin Allsopp M. Evaluating changes in the prevalence of the autism spectrum disorders (ASDs). *Public Health Rev*. 2012;34(2):1–22.
- Richard EF. Prevalence, significance of clinical characteristics of seizures, epilepsy and subclinical electrical activity in autism. *NAJ Med Sci*. 2015;8(3):113–22.
- Rk Y, Thiruvahindrapuram B, et al. Whole genome sequencing of quartet families with autism spectrum disorder. *Nat Med*. 2015;21(2):185–91.
- Robins DL, Casagrande K, et al. Validation off the modified checklist for autism in toddlers, revised with follow-up (M-CHAT-R/F). *Pediatrics*. 2014;133:37–45.
- Rosenfeld CS. Microbiome disturbances and autism spectrum disorders. *Drug Metab Dispos*. 2015;43(10):1557–71.
- Rutter M, Barley A. 2003. Social communication questionnaire. www.wpspublish.com
- Sandin S, Lichtenstein P, et al. The familial risk of autism. *JAMA*. 2014;311(17):1770–7.

- Sandin S, Schendel D, et al. Autism risk associated with parental age and with increasing difference in age between the parents. *Mol Psychiatry*. 2016;21(5):693–700.
- Schaefer GB. Clinical genetic aspects of ASD spectrum disorders. *Int J Mol Sci*. 2016;17(180):1–14.
- Schaefer GB, Mendelsohn NJ, et al. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revision. *Genet Med*. 2013;15(5):399–407.
- Schalkwyk V, et al. Gender identity and autism spectrum disorders. *Yale J Biol Med*. 2015;88:81–3.
- Sebat J, Lakshmi B, et al. Strong association of de novo copy number mutations with autism. *Science*. 2007;316(5823):445–9.
- Skagerberg D, Di Ceglie E, et al. Brief report: autistic features in children & adolescents with gender dysphoria. *J Autism Dev Disord*. 2015;45(8):2628–32.
- Smith I, Reichow B, Volkmar FR. The effects of DSM 5 criteria on number of individuals diagnosed with autism spectrum disorder: a systematic review. *J Autism Dev Disord*. 2015;45(8):2541–52.
- Sweeten TL, Bowyer SL, et al. Increased prevalence of familial autoimmunity in probands with pervasive developmental disorders. *Pediatrics*. 2003;112(5):e420–4.
- Talge NM, Neal C, et al. Antenatal maternal stress and long-term effects of child development: how and why? *J Child Psychol Psychiatry*. 2007;48(3–4):245–61.
- Tammimies K, Marshall CR, Walker S, Kaur G, Thiruvahindrapuram B, Lionel AC, Yuen RKC, Uddin M, Roberts W, Weksberg R, Woodbury-Smith M, Zwaigenbaum L, Anagnostou E, Wang Z, Wei J, Howe JL, Gazzellone MJ, Lau L, Sung WWL, Whitten K, Vardy C, Crosbie V, Tsang B, D'Abate L, Tong WWL, Luscombe S, Doyle T, Carter MT, Szatmari P, Stuckless S, Merico D, Stavropoulos DJ, Scherer SW, Fernandez BA. Molecular diagnostic yield of chromosomal microarray analysis and whole-exome sequencing in children with autism spectrum disorder. *JAMA*. 2015;314(9):895.
- Taylor B, Miller E, et al. Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association. *Lancet*. 1999;353(9169):2026–9.
- The Autism treatment Network Autism speaks. 2017 (<https://www.autismspeaks.org/family-services/tool-kits>).
- The Morbidity and Mortality Weekly Report (2014) The Morbidity and Mortality Weekly Report (MMWR) 63(SS02):1–21. <https://www.cdc.gov/mmwr/preview/mmwrhtml/ss6302a1.htm>.
- Van der Meer JM, Oerlemans AM, et al. Are autism spectrum disorder and attention deficit hyperactivity disorder different manifestations of one overarching disorder? Cognitive and symptom evidence from a clinical and population-based sample. *J Am Acad Child Adolesc Psychiatry*. 2012;51(11):1160–72.
- Van Steensel FJ, Bogels SM, et al. Anxiety disorders in children and adolescents with autism spectrum disorders: a meta-analysis. *Clin Child Fam Psychol Rev*. 2011;14(3):302–17.
- VanderLaan DP, Leef JH, et al. Autism spectrum disorder risk factors and autistic traits in gender dysphoric children. *J Autism Dev Disord*. 2015;45:1742–50.
- Varadinova M, Boyadjieva N. Epigenetic mechanisms: a possible link between autism spectrum disorders and fetal alcohol spectrum disorders. *Pharmacol Res*. 2015;102:71–80.
- Vasa RA, Mazurek MO, et al. Assessment and treatment of anxiety in youth with autism spectrum disorders. *Pediatrics*. 2016;137(2):S115–23.
- Visser JC, Rommelse NN, et al. Autism spectrum disorder and attention deficit hyperactivity disorder in early childhood: a review of unique and shared characteristics and developmental antecedents. *Neurosci Biobehav Rev*. 2016;65:229–63.
- Wakefield AJ, Murch SH, et al. Ileal-lymphoid-nodular hyperplasia, nonspecific colitis, and pervasive developmental disorder in children. *Lancet*. 1998;351(9103):637–41.
- Walder DJ, Laplante DP, et al. Prenatal maternal stress predicts autism traits in 6 ½ year old children: project ice storm. *Psychiatry Res*. 2014;219(2):353–60.
- Wetherby AM, Brosnan-Maddox S, et al. Validation of the infant toddler checklist as a broad band screener for autism spectrum disorders from 9 to 24 months of age. *Autism*. 2008;12(5):487–511.
- White SW, Oswald D, Ollendick T, Scahill L. Anxiety in children and adolescents with autism spectrum disorders. *Clin Psychol Rev*. 2009;29(3):216–29.
- Xiang AH, Wang X, et al. Association of maternal diabetes with autism in offspring. *JAMA*. 2015;313(14):1425–34.
- Zablotsky B, Black LI, et al. Estimated prevalence of autism and other developmental disabilities following questionnaire changes in the 2014 national health interview survey. *Natl Health Stat Rep*. 2015;87:1–20.
- Zwaigenbaum L, Bryson SE, et al. Sex differences in children with autism spectrum disorder identified within a high-risk infant cohort. *J Autism Dev Disord*. 2012;42:2585–96.
- Zwaigenbaum L, Bauman ML, et al. Early intervention for children with autism spectrum disorder under 3 years of age: recommendations for practice and research. *Pediatrics*. 2015;136:S60–81.



Update in Pediatric Emergency Medicine: Pediatric Resuscitation, Pediatric Sepsis, Interfacility Transport of the Pediatric Patient, Pain and sedation in the Emergency Department, Pediatric Trauma

Tania Principi, Deborah Schonfeld,
Laura Weingarten, Suzan Schneeweiss,
Daniel Rosenfeld, Genevieve Ernst,
Suzanne Schuh, and Dennis Scolnik

Resuscitation

Cardiopulmonary arrest in the pediatric population is infrequent and it is thus important that physicians who deal with children are comfortable managing the pediatric airway and using Pediatric Advanced Life Support (PALS) algorithms. With improved evidence and management of pediatric cardiac arrests, the rates of survival for pediatric in-hospital arrest have considerably improved over the last 10 years from 24% to 39% (Girotra et al. 2013).

T. Principi • D. Schonfeld, M.D., F.R.C.P.C.
S. Schneeweiss, M.D., M.Ed., F.R.C.P.C.
D. Rosenfeld • G. Ernst, M.D., F.R.C.P.C.
Department of Pediatrics, Division of Pediatric
Emergency Medicine, University of Toronto,
Toronto, Ontario, Canada
e-mail: tania.principi@sickkids.ca;
Deborah.schonfeld@sickkids.ca;
suzan.schneeweiss@sickkids.ca;
Daniel.rosenfeld@sickkids.ca;
Genevieve.ernst@sickkids.ca

L. Weingarten
Pediatric Emergency Physician and Assistant Clinical
Professor, Department of Pediatrics at McMaster
University, Hamilton, Canada
e-mail: laura.weingarten@gmail.com

Airway

The most common cause of pediatric cardiac arrest is usually respiratory distress leading to respiratory failure (Shaw and Bachur 2016). Tracheal intubation is the definitive method to secure the airway and should be considered when the patient is unable to oxygenate, ventilate, lacks respiratory drive and/or has lost his/her airway protective reflexes. Pediatric airway management can be challenging due to the following differences in anatomy compared to the adult airway:

S. Schuh, M.D., F.R.C.P.(C.), F.A.A.P. (✉)
Division of Paediatric Emergency Medicine,
Research Institute, Hospital for Sick Children,
University of Toronto, Toronto, ON, Canada
e-mail: suzanne.schuh@sickkids.ca

D. Scolnik, F.R.C.P.(C.), D.C.H., M.Sc.
Department of Paediatrics, Faculty of Medicine,
University of Toronto, Toronto, ON, Canada

Divisions of Paediatric Emergency Medicine
and Clinical Pharmacology and Toxicology,
The Hospital for Sick Children, Toronto, ON, Canada
e-mail: dennis.scolnik@sickkids.ca

Table 8.1 Suggested equipment for intubation

| |
|---|
| • Cardiac monitors with automated blood pressure measurements and continuous pulse oximetry |
| • Non-rebreather mask |
| • Bag-valve mask |
| • Functional suction device |
| • Functioning laryngoscope with various blades and sizes |
| • Endotracheal tubes with stylet, one size above and below desired tube size |
| • End-tidal CO ₂ detector: capnography or colorimetry |
| • 10 mL syringe |
| • Nasopharyngeal and oropharyngeal airway |
| • Tape to secure the tube |
| • Laryngeal mask airway |

larger occiput, large tongue in proportion to the oral airway, more anterior location of the vocal cords and floppy epiglottis (Singh and Frenkel 2013). Prior to intubation, all the necessary personnel and equipment must be readily accessible. Table 8.1 lists the necessary equipment for intubation; intravenous or intraosseous access should be obtained and all required medications drawn up prior to intubation.

Pre-oxygenation is important to minimize desaturation and to increase the safe apnea time during intubation. Ideally, the patient should be pre-oxygenated for at least 3 min (Weingart and Levitan 2012). If the patient is adequately breathing, oxygenation can be accomplished through a 100% non-rebreather mask with the rate of oxygen flow as high as possible. Bag Mask Ventilation (BMV) should be initiated in the apneic patients and in those with poor respiratory drive to ensure adequate pre-oxygenation. To further increase the safe apnea time and the success rate of the first intubation attempt, apneic oxygenation is used during rapid sequence intubation (RSI) in adults (Singh and Frenkel 2013; Weingart and Levitan 2012; Mittiga et al. 2015). This entails the application of oxygen via nasal prongs in addition to pre-oxygenation, and acts as an adjunct to pre-oxygenation by providing an oxygen filled pharynx used as a reservoir for alveolar ventilation (Weingart and Levitan 2012). Although the adult evidence shows promise

(Singh and Frenkel 2013; Mittiga et al. 2015), pediatric research on this issue is limited (Steiner 2016).

Although uncuffed tubes were previously recommended in pediatrics due to airway narrowing at the glottis and concerns about mucosal injury, evidence suggests that pediatric cuffed endotracheal tubes are safe to use in the pediatric population. The use of cuffed tubes is associated with fewer tube changes, decreased risk of aspiration and allows for higher airway pressures during ventilation without an increased risk of complications (Kleinman et al. 2010a; Weiss et al. 2009; Shi et al. 2016). It is important that cuffed tubes are inflated to no more than 20 cm of water. The size of tube can be estimated by length-based tools or by using the following age-based formulas: $\text{age}/4 + 3.5$ for cuffed tubes or $\text{age}/4 + 4$ for uncuffed tubes (Kleinman et al. 2010a). An endotracheal tube one size above and below the estimated size should also be available, and consideration should be given to using a stylet. Successful placement should be confirmed through direct visualization, CO₂ detection, and chest x-ray or ultrasound confirmation in addition to auscultation (Mittiga et al. 2015; Kleinman et al. 2010a; Chou et al. 2015). Cricoid pressure is no longer routinely recommended during rapid sequence intubation as it has been shown to decrease the success of intubation with little effect on the risk of aspiration (Kleinman et al. 2010a; Ellis et al. 2007). If BMV is unsuccessful and intubation is not possible a Laryngeal-Mask Airway (LMA) may be used to provide a patent airway and ventilation support (de Caen et al. 2015a).

Medications

Medications should be used to help facilitate the success of intubation and decrease complications. Contrary to previous recommendation to use atropine to mitigate the risk of pediatric bradycardia, evidence to demonstrate this benefit

has been lacking (Singh and Frenkel 2013; de Caen et al. 2015a). The most recent PALS guidelines do not support the routine use of atropine during pre-intubation in children (de Caen et al. 2015a). The use of atropine may be considered in children at increased risk of bradycardia (such as in infants under one year of age, when using succinylcholine in children under 5 years of age or in patients receiving multiple doses of succinylcholine) or in those who are bradycardic prior to intubation (Singh and Frenkel 2013). The recommended dose of atropine when used as a premedication agent for RSI is 0.02 mg/kg, with no minimum dose (de Caen et al. 2015a).

Common sedatives used for RSI in pediatrics include etomidate and ketamine. Etomidate, at a dose of 0.3 mg/kg is an excellent sedative medication for this purpose due to its minimal associated cardiovascular side effects. Given the risk of possible adrenal suppression, etomidate is not currently recommended in the septic patient (Kleinman et al. 2010a; den Brinker et al. 2008; Chan et al. 2012; Bruder et al. 2015). Ketamine is a dissociative sedative agent used at doses of 1–3 mg/kg. Ketamine is particularly useful in hypotensive patients or those with severe asthma. Since ketamine does not inhibit spontaneous respirations, it is a useful sedative for difficult intubations. Contrary to previous belief, recent evidence suggests that ketamine is safe to use in children with increased intracranial pressure. (Filanovsky et al. 2010; Hughes 2011). Although commonly used for intubation, the use of propofol in the emergency department should be limited to experienced personnel due to a significant risk of hypotension (Shaw and Bachur 2016; Singh and Frenkel 2013). Other medications such as benzodiazepines and opiates can also be used for sedation in RSI but these may not be as reliable or effective (Singh and Frenkel 2013; Stollings et al. 2014).

Rocuronium and succinylcholine are the most commonly used neuromuscular blocking agents. Succinylcholine at dose of 1–2 mg/kg provides a rapid onset of action with a short duration. It is contraindicated in patients with hyperkalemia,

myopathies or a history of malignant hyperthermia and it can cause bradycardia with repeated doses (Singh and Frenkel 2013). Rocuronium is a longer-acting paralytic agent at doses of 0.6–1.2 mg/kg. Lower doses of rocuronium result in a shorter duration of action but require a longer time to take effect. Unlike succinylcholine, rocuronium does not have any contraindications but care should be taken in using rocuronium patients with difficult airways (Singh and Frenkel 2013; Stollings et al. 2014).

Cardiopulmonary Resuscitation

There is ongoing evidence that cardiopulmonary resuscitation (CPR) should be performed hard and fast. In infants and children; the chest should be compressed to one-third of the anterior-posterior diameter of the chest, at a rate of 100–120 compressions per minute (Atkins et al. 2015). Full recoil should occur between compressions and all efforts should be made to minimize interruptions in CPR. Compressions to ventilation should occur at a ratio of 15:2 until a definitive airway or LMA is present (Atkins et al. 2015). Respirations can be provided by BMV using adjuncts such as naso-pharyngeal or oropharyngeal airways to improve oxygenation. If skilled personnel are present, tracheal intubation may be attempted while minimizing interruptions to chest compressions. If BMV is unsuccessful and intubation is not possible, ventilation via LMA should be considered (de Caen et al. 2015a). Early vascular access is important to allow for the administration of fluids and medications. Early insertion of an intraosseous needle provides timely and effective access during resuscitation; intraosseous medications can be given at the IV-recommended doses.

Defibrillation is the asynchronous delivery of an electrical current to the myocardium in an effort to establish sinus rhythm. Defibrillation should be administered as soon as possible in patients with ventricular fibrillation or pulseless ventricular tachycardia at an initial dose of 2 J/kg (de Caen et al. 2015a). Adult size paddles should

be used for patients older than a year of age or weighing more than 10 kg and can be placed on the right upper chest and apex. If unsuccessful, repeated doses can be given at 4 J/kg (de Caen et al. 2015a).

Cardioversion is the synchronous delivery of an electrical current to the myocardium in an effort to prevent ventricular fibrillation. It is indicated for the treatment of perfusing rhythms when a pulse is present, such as stable ventricular tachycardia or supraventricular tachycardia. The initial recommended cardioversion dose is 0.5–1 J/kg, which can be increased to 2 J/kg with subsequent attempts (Kleinman et al. 2010a).

In depth review of all the PALS algorithms are beyond the scope of this book. Please refer to PALS algorithms for further details.

Post-cardiac Arrest Hypothermia

After return to spontaneous circulation, every effort should be made to maintain normothermia and to treat any hyperthermia. Although there have been several studies evaluating the neuro-protective effects of hypothermia in pediatrics, a recent randomized controlled trial and meta-analysis both demonstrated lack of improved survival after permissive hypothermia (Moler et al. 2015; Bistriz et al. 2015).

Introduction

Sepsis is a systemic and often deleterious host response to infection. It is widely accepted that the onset and progression of sepsis results from a dys-regulated inflammatory response that leads to widespread tissue injury and end organ dysfunction (Hotchkiss and Karl 2003). Practically speaking, sepsis represents a spectrum of disease ranging from the systemic inflammatory response (SIRS) to septic shock and multi-organ system dysfunction. The tendency to proceed along this spectrum is more likely determined by the host

response to infection that the offending pathogen itself.

Definitions

Definitions for sepsis and organ dysfunction in children have been developed by the International Consensus Conference on Pediatric Sepsis (Goldstein et al. 2005). SIRS is a non-specific inflammatory reaction in response to insults such as infection, trauma, burns, pancreatitis and other diseases. *SIRS* in children is characterized by a temperature abnormality (fever or hypothermia) **or** an age-specific abnormality in the white blood cell count, **and** one of the following: tachycardia (or bradycardia in infants under 1 year of age), tachypnea or an acute respiratory condition requiring mechanical ventilation. SIRS in the presence of confirmed or suspected infection constitutes *sepsis*. *Severe sepsis* is defined as sepsis associated with cardiovascular dysfunction, acute respiratory distress syndrome (ARDS), or dysfunction in two or more other organ systems (specific definitions of respiratory, cardiovascular, neurologic, hematologic, hepatic and renal dysfunction are based on expert opinion). *Septic shock* is defined as sepsis in the presence of cardiovascular dysfunction. *Compensated shock* refers to a shock state in which the blood pressure remains in age-appropriate range. Hypotension represents a late and often ominous sign in pediatric patients. The presence of hypotension is the hallmark of *decompensated shock*.

Epidemiology and Risk Factors

The global burden of illness from pediatric sepsis is very high. Infectious diseases such as malaria, gastroenteritis and pneumonia, often culminating in severe sepsis and septic shock, are the most common cause of death in infants and children worldwide. In the United States the prevalence of severe sepsis has been rising over

the past decade (Ruth et al. 2014; Balamuth et al. 2014), with estimated pediatric hospitalizations due to severe sepsis exceeding 75,000 cases annually (Hartman et al. 2013). Young infants, especially low birth weight neonates, are at the highest risk, and children with co-morbid medical conditions account for more than half the cases. This includes children with chronic lung disease, congenital heart disease, malignancy, and those with conditions impacting the immune system (Hartman et al. 2013). Children with indwelling devices and anatomic abnormalities are also at high risk for bacterial seeding and infection. In North America, the mortality rate from pediatric severe sepsis and septic shock is estimated to be 5–15% but approaches 30% in those with comorbid disorders and significant organ dysfunction (Ruth et al. 2014; Hartman et al. 2013; Watson et al. 2003; Kutko et al. 2003; Weiss et al. 2015a).

Etiology and Microbiology

The most common primary sites of infection in children are respiratory (40–50%) and bloodstream (10–20%) (Weiss et al. 2015a), with abdominal, genitourinary, central nervous system and skin infections accounting for the majority of remaining cases. Although bacterial and viral pathogens are most common, fungal, parasitic, or rickettsial infections can also lead to sepsis. The most commonly implicated bacterial organisms are staphylococcal species (including *Staphylococcus aureus* in previously healthy patients and coagulase-negative staphylococci in those with indwelling catheters) and streptococcal species. Gram-negative organisms are frequently responsible for urinary tract infection (UTI)-related sepsis and sepsis in immunocompromised hosts. The most common viral pathogens include the respiratory viruses (influenza, parainfluenza, respiratory syncytial virus (RSV), adenovirus) (Gaines et al. 2012). It should be noted however, that in up to two thirds of septic shock cases, no infectious pathogen is

identified. This is commonly referred to as “culture-negative” sepsis.

Pathophysiology

The longstanding pediatric mantra that “children are not little adults” certainly applies to sepsis. The differences between the pediatric and adult response to infection have important implications on the presentation and treatment of sepsis in children compared to older patients (Brierley et al. 2009). First, severe hypovolemia, likely due to a combination of dehydration and increased microvascular permeability, is a hallmark of pediatric septic shock. Therefore, children frequently respond well to aggressive fluid resuscitation. Second, the hemodynamic response to sepsis is significantly different in the two populations (Fig. 8.1). Up to 90% of adult patients present with a “hyperdynamic shock”, otherwise known as “warm shock”. Despite myocardial dysfunction, cardiac output (CO) is typically maintained by an increase in heart rate and decrease in systemic vascular resistance (SVR). Thus, the adult response to sepsis is characterized by tachycardia, hypotension and a normal, or increased, cardiac output. The predominant cause of mortality in adult septic shock is vasomotor paralysis (when SVR cannot be further increased with vasopressor agents). In contrast, at least 50% of infants and children present with “cold shock”. Although an increase in heart rate is a child’s principal means of maintaining CO, a predominant response to a decreased CO in children is vasoconstriction. Blood flow is redistributed from non-essential vascular beds such as the skin, to essential organs such as the heart, brain and lungs. This increase in SVR maintains a normal blood pressure, even with significant decreases in CO. Hypotension is therefore a late sign in pediatric septic shock, and often signifies impending cardiovascular collapse. Thus, the pediatric response to sepsis is often characterized by tachycardia, normal blood pressure and decreased cardiac output. In children, low CO is most often

Fig. 8.1 Comparison of cold and warm septic shock. *HR* heart rate, *SVR* systemic vascular resistance, *CO* cardiac output, *BP* blood pressure

| | COLD SHOCK | WARM SHOCK |
|--|---|--|
| Hemodynamics | ↑HR, ↑SVR, ↓CO, BP maintained until late | ↑HR, ↓SVR, ↑CO, ↓BP |
| Clinical Features | Capillary refill >2sec, Cool, mottled skin, Weak pulses, Narrowed pulse pressure, Altered mental status, Decreased urine output | Flash capillary refill <1sec, Warm, flushed skin, Bounding pulses, Widened pulse pressure, Altered mental status, Decreased urine output |
| First Line Vasoactive Support for fluid-refractory shock | Epinephrine (0.05-0.3mcg/kg/min); Can use Dopamine (5-10 mcg/kg/min) if epinephrine unavailable | Norepinephrine (0.03-0.05mcg/kg/min) Can use Dopamine (>10mcg/kg/min) if norepinephrine unavailable |

associated with mortality, in contrast to adults who often succumb to low SVR. It should be noted however, that the clinical presentation of septic shock in children can be highly variable and can include a combination of hemodynamic abnormalities.

Diagnosis

Although the specific definitions of cardiovascular dysfunction set forth by the international consensus criteria help standardize patient populations for research purposes, they may be less pertinent in the everyday clinical setting (Weiss et al. 2012, 2015b). Clinical suspicion for septic shock should always supersede reliance on the presence of specific consensus criteria. The diagnosis of septic shock should be made in children with sepsis (SIRS with infection) and *signs of inadequate tissue perfusion* including any of the following: decreased or altered mental status, decreased urine output (<1 ml/kg/h), capillary refill >2 s (cold shock), cool or mottled extremities (cold shock), diminished pulses (cold shock), flash capillary refill (warm shock), bounding peripheral pulses (warm shock), and wide pulse pressure (warm shock) (Brierley et al. 2009). The presence of hypotension, although not necessary for diag-

nosis, is confirmatory in a child with suspected infection. Although no laboratory test is sensitive or specific enough to be used alone, some experts recommend using lactic acid (a by product of anaerobic metabolism and marker of tissue hypoperfusion) as a diagnostic adjunct. Elevated initial lactic acid levels (≥4.0 mmol/L), and failure of lactate levels to normalize (<2 mmol/L) or progressively clear with resuscitative efforts may be poor prognostic indicators in pediatric sepsis (Scott et al. 2012, 2016).

Management

Early recognition and aggressive treatment of septic shock are essential to reducing morbidity and mortality. The American College of Critical Care Medicine (ACCM) and the Pediatric Advanced Life Support (PALS) course have published internationally recognized guidelines for the management and hemodynamic support of pediatric septic shock (Brierley et al. 2009; Kleinman et al. 2010a, b). The two guidelines outline a similar step-wise approach to resuscitation directed at restoring physiologic indicators of perfusion: normal mental status, threshold heart rates, normal peripheral perfusion (cap refill <3 s), palpable distal pulses and

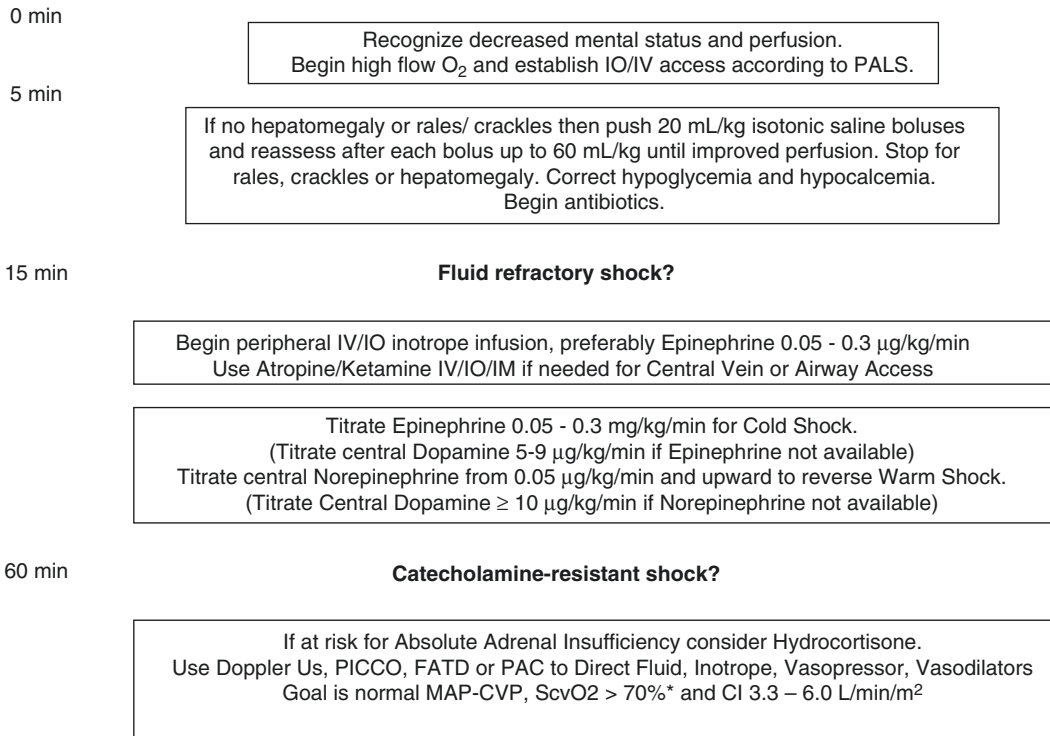


Fig. 8.2 First hour goals for the management of hemodynamic support in infants and children with septic shock (intensive care unit goals not shown). Reproduced with permission from Brierley J, Carcillo JA, Choong K, Cornell T, DeCaen A, Deymann A et al. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American

College of Critical Care Medicine. *Crit Care Med* 2009;37:666. **Of note, this guideline and algorithm is undergoing review by the American College of Critical Care Medicine. The updated version of these guidelines is expected to support epinephrine as the first line vasoactive agent for cold shock

normal blood pressure. The ‘first-hour’ therapeutic actions outlined in the ACCM guidelines should be regarded as best practices for emergency department resuscitation (Fig. 8.2). It has been shown that adherence to PALS-ACCM guidelines significantly reduces mortality and hospital length of stay (Han et al. 2003; Paul et al. 2012; Carcillo et al. 2009; Oliveira et al. 2008).

Within the first 5 min of septic shock recognition, 100% oxygen via a non-rebreathing mask should be applied to maximize oxygen delivery to tissues. A significant amount of cardiac output supports work of breathing so ventilation should be supported as required. If rapid sequence intu-

bation is necessary, hemodynamic stability should first be optimized with fluids. Ketamine is the sedative of choice. Etomidate should be avoided due to the potential for adrenocortical axis suppression (Brierley et al. 2009; den Brinker et al. 2008).

Intravenous access should be established within 5 min. If a peripheral IV cannot be established within this timeframe, an intraosseous catheter should be inserted. Laboratory tests, including blood cultures, should ideally be obtained at the time of intravenous access. Patients in septic shock are at risk for hypoglycaemia and hypocalcemia, so clinicians should be prepared to administer dextrose and calcium

as needed. Children with hypoglycaemia should be administered and IV bolus of 0.25 g/kg of dextrose (2.5 mL/kg of D10W OR 1 mL/kg of D25W). Hypocalcemia can be corrected via infusion of calcium gluconate 10% solution in a dose of 50–100 mg/kg (0.5–1 mL/kg).

Volume resuscitation is the cornerstone of the ACCM management. Initial therapy should begin with a bolus of 20 mL/kg of isotonic crystalloid solution infused over 5 min or as rapidly as possible, preferably with a manual “push-pull” technique or rapid infuser. Repeated 20 mL/kg fluid boluses should be given until markers of tissue perfusion (discussed above) normalize, or signs of fluid overload (lung rales, gallop rhythm, hepatomegaly) develop. Many children require up to 60 mL/kg within the first hour. Recently, a large trial in sub-Saharan Africa demonstrated increased mortality from fluid boluses in children with compensated septic shock (Maitland et al. 2011). Although it is the only study of its kind to date, it highlights the potential for harm if fluid resuscitation is used indiscriminately in children in resource-poor settings with limited availability of mechanical ventilation and vasoactive support. The most recent PALS update maintains, that in resource rich settings, fluid resuscitation remains a key component of goal directed therapy but emphasizes the need for individualized clinical evaluation and frequent reassessments to determine the appropriate volume of fluid resuscitation in every patient (de Caen et al. 2015b, c). Studies are currently underway to determine whether children in developed countries might benefit from fluid-sparing strategies.

Intravenous antimicrobial therapy should be administered within 60 min of recognition. Appropriate antibiotic regimens depend on age, likely responsible pathogens and known local patterns of infection and resistance. Generally speaking, a third or fourth generation cephalosporin **plus** vancomycin for methicillin-resistant *Staphylococcus aureus* coverage represent an appropriate regimen for most children. In addition to the above, neonates should be treated with

ampicillin to cover for *Listeria*. Immunocompromised children at risk for *Pseudomonas* infections should also be treated with broader spectrum agents including carbapenems. Piperacillin with tazobactam, aminoglycosides and/or metronidazole should be used when enteric organisms are suspected, and clindamycin is recommended in cases of suspected toxic shock or necrotizing fasciitis.

Based on expert opinion, the ACCM recommends starting a vasoactive agent when a patient remains in shock despite 40–60 mL/kg of fluid resuscitation (‘fluid-refractory shock’). Although central access is preferred, peripheral intravenous access can, and should be, used for initial vasoactive infusions (Brierley et al. 2009). Due to widespread availability and clinician familiarity, dopamine has traditionally been the first line vasoactive agent. However, recent evidence suggests that epinephrine is likely a safer and more effective first choice, especially for those with cold shock (Ventura et al. 2015). According to the most recent ACCM guidelines, peripheral epinephrine is the preferred first line agent for fluid-refractory shock. Thereafter, cold shock should be reversed by titrating epinephrine (or low dose central dopamine), and warm shock reversed by titrating central norepinephrine (or high dose central dopamine). Please see Fig 8.2. Patients with catecholamine-resistant shock often need a variety of vasodilators, afterload reducing agents and/or other vasopressors that should be titrated in an intensive care setting.

The use of corticosteroid therapy in those with catecholamine-resistant shock remains controversial as consistent, high quality evidence is lacking (Pizarro et al. 2005; Atkinson et al. 2014; Menon et al. 2013; Zimmerman and Williams 2011). Adjunctive steroid therapy is likely most important for patients at risk of adrenal insufficiency, children with purpura fulminans, those with a history of chronic steroid therapy or known hypothalamic, pituitary or adrenal abnormalities.

Summary

Signs and symptoms of shock may be subtle in children, leading to delays in recognition and underestimation of the severity of illness. The best approach to diagnosis involves a high level of clinical suspicion combined with the clinical history, vital signs and physical examination. Altered mental status and persistent tachycardia (often a sign of circulatory dysfunction) should not be overlooked. Standardized emergency department sepsis screening tools and protocols, which rely on abnormal vital signs and physical examination findings to help identify patients at risk, have been shown to reduce time to both fluid and antibiotic administration (Cruz et al. 2011; Larsen et al. 2011; Paul et al. 2014; Tuuri et al. 2016).

Emergency department nurses and physicians are in a unique position to affect sepsis outcomes since the therapies that a child receives during the initial treatment largely determine their prognosis. It is therefore crucial that every clinician who cares for children has a reliable approach to the recognition and resuscitation of pediatric septic shock.

Ill and injured children often seek medical care at physician offices and community hospitals (McPherson et al. 2008). Healthcare providers working in these settings must know how to safely transport a child who requires additional resources or an escalation in level of care. The regionalization of pediatric intensive care units and trauma services has made it imperative for providers to understand general principles of transport medicine (Lorch et al. 2010).

Despite existing recommendations by expert working groups, there are major variations in transport practice across North America and the world (Lorch et al. 2010; Whyte and Jefferies 2015). This chapter provides an overview of pediatric inter-facility transport and is divided into four sections, each exploring a different clinical question:

1. Which transport team should provide care for this child?
2. What is the best mode of transport?
3. How can medical care be optimized prior to transport?
4. What supplies and equipment should be prepared for transport?

References at the end provide additional information on the transport of neonates (Whyte and Jefferies, 2015) and pediatric trauma patients (Michailidou et al. 2014; Meyer et al. 2016).

Team Composition

Healthcare providers and parents often feel pressured to quickly move children to the centre where they will receive definitive care. However, most experts agree that the majority of children are best served by stabilization at the referral centre prior to departure (Ramnarayan et al. 2010; Barry and Leslie 2003). The child's expected clinical course is the most important factor in determining transport team composition and urgency of dispatch (Barry and Leslie 2003). For a critically ill child who is expected to deteriorate or require significant support, it is usually better to wait for dispatch of a specialized team than for an ad-hoc team to be hastily assembled.

Most evidence examining significant outcomes for children who require transport to a PICU comes from small retrospective and a few prospective studies. A Cochrane review found there is no high quality evidence from randomized controlled trials to support or refute that specialist teams for neonatal transport reduce mortality or morbidity among newborns requiring retrieval to a newborn intensive care unit (NICU) (Chang et al. 2008). Nevertheless, specialized transport teams are recommended as being the best option for most critically ill infants and children who require inter-facility transport (Whyte and Jefferies 2015). Ramnarayan et al. (2010) found that use of a specialized retrieval

team was associated with decreased mortality risk in children transported to a pediatric intensive care unit (PICU). Orr et al. also found that children transported by specialized teams had a lower death rate of 9%, versus 23% for those transported by nonspecialized teams (Orr et al. 2009). They also found that nonspecialized teams who transport children have more significant adverse events including airway issues, cardiopulmonary arrest, sustained hypotension, loss of a crucial intravenous access and equipment failure with deterioration of patient status (Orr et al. 2009). Although the majority of critically ill children benefit from transport by a specialized team once they are stabilized at the referring centre, exceptions to this rule include children with epidural hematomas or bowel ischemia requiring emergent surgery. The relative benefits of immediate transport versus stabilization prior to departure should be carefully weighed in these children.

It is important to assess the transport team’s comfort and experience with stabilizing children before transferring patient care. A clear team handover should take place with each team member’s responsibilities being clearly outlined

(Whyte and Jefferies 2015; Barry and Leslie 2003). The referring physician is generally responsible for patient care until arrival at the receiving, facility unless alternate arrangements have been made. Additional medication orders, supplies or resources should be anticipated and provided before departure.

Emergency medical services (EMS) teams are often appropriate for infants and children who require ongoing care, medications or fluids during transport e.g. an adolescent with suspected appendicitis who requires surgical consultation. EMS personnel and clinicians such as a nurse, respiratory therapist or physician may work together as a temporary team.

Parents and caregivers can transport stable children with no active airway or hemodynamic issues e.g. a child who requires foreign body removal from an ear, by a specialist physician.

Transport Mode

The relative merits of different transport modes are outlined in Table 8.2. Transport specialists in the PICU or NICU, emergency departments or

Table 8.2 Modes of transport

| Transport mode | Advantage | Disadvantage |
|-----------------------|---|--|
| Private vehicle | No dispatch time Already has car seat or booster | No medical providers |
| Land ambulance | Easily available Fast dispatch time Can stop for procedures Accommodates extra team or family members Can be safer than helicopter for crew and patient (Meyer et al. 2016) | Slower than long distance flight Traffic can be slow Potholes and poor road conditions can worsen pain |
| Helicopter/rotor-wing | Faster than long distance drive Can do scene calls in remote and austere settings Can land on helipad at hospital | Affected by weather or night visibility Pressure at altitude can worsen some injuries and diseases May not be able to accommodate family members |
| Fixed wing | Can be faster than driving long distances | Requires additional transport leg to/from airport Affected by weather or night visibility Small work area, loud and turbulent Pressure at altitude can worsen some injuries and diseases May not be able to accommodate family members |

regional air ambulance service should always be available to guide decisions about the safest and most effective way to transport children. This decision depends on many factors, including:

- The child's current condition and expected clinical course.
- Out-of-hospital time.
- Distance.
- Traffic conditions.
- Weather.
- Availability of specialized teams for air/land transport.

Pediatric trauma patients are frequently thought to require inter-facility transport by helicopter; although transport by helicopter is typically faster, the decreased transport time comes at the expense of increased risk to the patient and may not necessarily result in time-sensitive interventions at the receiving facility (Michailidou et al. 2014; Meyer et al. 2016).

Preparation for Transport

Critically ill children should be stabilized and trauma patients should have a full primary and secondary survey prior to departure, unless extenuating circumstances are present. Many transport teams now use pre-departure checklists or EMS protocols. These resources can be invaluable for ad-hoc teams tasked with infrequent pediatric transport.

Airway and Breathing Considerations

The airway should be patent or adequately protected, and the cervical spine should be immobilized in injured patients. Children may require intubation for oxygenation failure, ventilation failure, pulmonary toilet or expected clinical course. If the child is intubated, their endotracheal tube should be well secured after placement is confirmed according to local practice guidelines. A gastric tube should be left open to drainage in these children. A blood gas is strongly

recommended to optimize oxygenation and ventilation parameters immediately before departure.

Oxygen saturation and end-tidal CO₂ should be continuously monitored in all ill infants and children. Before departure, oxygen tanks and suction should be checked to ensure adequate supply for the full duration of transport.

Tube thoracostomy should be considered for children with pulmonary injury or pleural effusion.

There are two special considerations in children who will be transported by air. First, *hypoxia* will worsen during flight as the fraction of inspired air (FiO₂) decreases with altitude. Children with pulmonary injury or disease should receive supplemental oxygen during flight, and flight plans may need to be reconsidered for children with an FiO₂ requirement >0.8 on the ground. Second, the possibility of *air entrapment* in a closed body cavity should be considered. Air expands at higher altitudes and this can cause pain and organ damage in children with pneumocephaly, pneumothorax and ocular, dental or bowel injury. The operations planner or flight team should be asked to limit altitude, or pressurize the cabin, when caring for children with either of these real or potential problems.

Circulatory Considerations

Adequate and/or ongoing volume resuscitation should be provided for children with tachycardia or signs of poor perfusion. At least one, and preferably two, reliable intravenous or intraosseous lines should be available for transport. The cannula sites must be visible with ports readily accessible and sufficient fluids, blood products and/or inotropic supports should be available for the duration of transport.

Pediatric trauma patients need to be inspected for signs of external bleeding, which should be managed with direct pressure, sutures, staples or other hemostatic controls. Sources of internal hemorrhage such as thoracic or abdominal injury, as well as significant external hemorrhages

should be clearly delineated to the receiving facility. Urinary catheterization to monitor urine output in critically ill children should be considered.

Disability and Exposure Considerations

Blood glucose should be measured prior to departure and normoglycemia assured. A focused neurologic examination, including Glasgow Coma Scale, assessment of pupillary response, motor activity and tone in all limbs, should be performed prior to administration of sedatives or paralytic agents. Targeted treatments should be considered if increased intracranial pressure is suspected.

Temperature should be recorded for all children and measured continuously for infants, small children and unconscious patients. Thermoregulation can be maintained with a head covering, warm blankets or increasing the ambient temperature as needed. Fever and hyperthermia should be treated with antipyretics. A head-to-toe physical examination to document rashes, bruises or skin marks should be performed and recorded prior to departure.

Supplies and Equipment

Many transport teams use pre-departure packing lists to organize supplies and equipment prior to transport. One example of a simplified checklist is provided in Table 8.3. A variety of neonatal, pediatric and adult sizes should be available for all equipment listed.

Essential medications depend on the child’s condition and expected course. Most regions have local EMS protocols for paramedics to deliver necessary and life-saving medications in the prehospital setting. As a general rule, most specialized teams carry cardiac drugs, antibiotics, anticonvulsants, analgesics, sedatives, paralytics and intravenous fluids on each transport. Blood products may also be prepared for transport of a trauma patient.

Table 8.3 Essential equipment and supplies

| Type of intervention | Equipment and supplies |
|-------------------------------|---|
| Airway and breathing | Bag-valve device, endotracheal tubes, laryngoscope Oxygen and nonbreather masks Portable ventilator and circuit Portable oxygen and air cylinders Suction unit and catheters Chest tubes Difficult airway adjuncts – e.g. LMA, oropharyngeal airway Cervical immobilizers |
| Circulation | Intravenous cannulas Intraosseous needles Infusion pumps Extra tubing, stopcock, T-connectors Defibrillator Backboard |
| Monitoring and investigations | Pulse oximetry EtCO ₂ monitors Cardiorespiratory monitors Blood pressure cuffs Thermometer Glucometer Point-of-care laboratory testing device and analyzer |
| Medications ^a | Useful medications to consider include: Analgesics and sedatives – e.g. ketamine, fentanyl, morphine, nitrous oxide Anaphylaxis – e.g. epinephrine 1:1000, epinephrine auto-injector Anti-arrhythmics and cardiac medications – e.g. epinephrine 1:10,000, adenosine, amiodarone, atropine, lidocaine, prostaglandin, inotropes and pressors Antimicrobials –e.g. ceftriaxone, ampicillin, cefotaxime and/or gentamycin Anti-epileptics – e.g. lorazepam, midazolam, diazepam, fosphenytoin, phenytoin, phenobarbital Blood products and fluids – e.g. normal saline, dextrose 10%, dextrose 50%, 3% hypertonic saline, sterile water, albumin Other – e.g. steroids (dexamethasone, hydrocortisone, methylprednisolone), paralytics (succinylcholine, rocuronium), activated charcoal, salbutamol, diphenhydramine, glucagon, insulin, magnesium sulphate, sodium bicarbonate |

Table 8.3 (continued)

| | |
|----------------------------------|--|
| Type of intervention | Equipment and supplies |
| Moving the child safely | Stretcher or incubator Safety belts Metal pole or shelf to secure monitors, pumps and equipment |
| Record-keeping and communication | Patient transport record Resuscitation drug chart Mobile telephone Information package for parents with contact numbers Pen and medication/infusion labels |
| Additional supplies | Personal protective equipment—gowns, gloves, and masks Extra batteries for all electronics |
| Personal | Warm clothing and appropriate footwear Personal items Food and beverage |

^aLocal EMS and specialized teams may carry a wide range of medications depending on their protocols and scope of practices. Never assume a given medication will be available. The child's expected clinical course should dictate which medications are prepared and drawn up prior to departure from the referring hospital

It is challenging and rewarding to care for an infant or child who requires inter-facility transport. An organized approach can be helpful to ensure the child, family and team are prepared for transport. The transport team should have the appropriate skills and expertise to care for the patient, based on the child's anticipated clinical trajectory. Choice of transport mode should be established collaboratively based on several extraneous factors, but including the child's clinical condition. Checklists are useful, if not essential, to ensure that all necessary supplies, equipment and medications are available for the entire transport. The references below provide additional checklists and further reading for those interested in neonatal, trauma and other specialized pediatric populations.

Acute pain in children is a common presenting symptom in the emergency setting, accounting for up to 78% of visits. (Dong et al. 2012;

Grant 2006; Alexandre and Manno 2003; Krauss et al. 2016). An addition, fear of procedures is reported by children to be a significant anxiety-provoking aspect of their emergency room visit and the pain experience itself can have long term consequences (Kennedy et al. 2008). Pain and anxiety in infants and children can be successfully treated in the emergency room with use of age-appropriate pain assessment tools and implementation of non-pharmacologic and pharmacologic pain management strategies.

Pain Assessment

Pain assessment can be difficult particularly in younger children and infants as they are unable to verbalize their pain and often have associated anxiety related to fear of procedures or the emergency setting itself. Pain assessment tools are widely available and ideally should be used in triage as the first step in pain management (Srouji et al. 2010; Drendel et al. 2011). Early use of pain assessment scores has been shown to increase provision of analgesia and decrease time to provision of analgesia (Boyd and Stuart 2005; Nelson et al. 2004). Measures of pain include physiologic measures (e.g. heart rate and blood pressure), observational and behavioral measures and self-report. Self-report is the gold standard as behavioral measures may also reflect anxiety and fear. Physiologic measures may reflect stress reactions and hence are often used as adjuncts to other pain assessment tools. The Children's Hospital of Eastern Ontario pain scale is a widely used behavioral scale for younger infants and non-verbal children. Children as young as 3–4 years can self-report pain using visual scales such as the Faces Pain Scale (FPS-R), Wong-Baker FACES scale or the OUCHER pain scale. Numerical and 10-cm visual analogue scales are generally reserved for children older than 8 years with cognitive abilities to understand these abstract concepts (Srouji et al. 2010; Drendel et al. 2011).

Non-pharmacologic Management of Acute Pain

A child-centred approach is a key factor for successful management of pain in the emergency department. Parents and caregivers play a role in responding to their child's pain and should be encouraged to act as positive assistants for procedures rather than negatively restraining their child (Srouji et al. 2010). Open communication and preparation of the child and family for procedures with explanation of the procedure using non-medical jargon helps to reduce anxiety and fear. Cognitive or psychological measures such as age appropriate distraction techniques (e.g. bubbles, stories, videos and music) are useful adjuncts to reducing anxiety associated with procedures. Other behavioral strategies such as breastfeeding or non-nutritive sucking, kangaroo care (skin-to-skin contact), swaddling/tucking and rocking/holding have also been shown to be beneficial in neonates and young infants (Ali et al. 2016).

Pharmacologic Management of Acute Pain

Mild Pain

Oral analgesics such as acetaminophen or ibuprofen are safe and effective for the treatment of mild to moderate pain and are also used in conjunction with opioids for management of moderate to severe pain (Perrott et al. 2004). A higher initial loading dose of acetaminophen can be given, however, it is important to not exceed the recommended daily maximum doses. Ibuprofen is generally well tolerated in children with minimal adverse renal or gastrointestinal effects. More recently, alternating or simultaneous use of acetaminophen and ibuprofen strategies have been used if monotherapy is ineffective (Ong et al. 2010).

Moderate Pain

Oral opioid agents such as morphine in conjunction with NSAIDs (non-steroidal anti-inflammatory agents) and/or acetaminophen are generally used to

treat moderate pain. Codeine, however often lacks analgesic potency as the enzyme necessary to metabolize the inactive pro-drug codeine (CYP 450 2D6) to morphine is missing in 10–12% of the Caucasian population (Le May et al. 2013). CYP2D6 polymorphisms can also result in ultra-rapid metabolism of codeine with potential for significant adverse effects including death (Kelly et al. 2012). NSAIDs can also be used for moderate pain and have been reported to be equally effective to low dose opioids with less side effects in some studies (Poonai et al. 2014).

Severe Pain

Intravenous morphine is the gold standard for management of severe pain. Fentanyl is a synthetic opioid, 100 times more potent than morphine. With a rapid onset of action (30 s), short duration of action (20–40 min) and lack of sedative properties at low dosing, fentanyl is an ideal agent for short painful procedures (Sahyoun and Krauss 2012). Intranasal fentanyl is well tolerated and has been shown to be equally effective for pain reduction to intravenous morphine (Borland et al. 2007). Hydromorphone is a potent opioid with a longer duration of action and generally used for patients with poor response or habituated response to morphine (e.g. sickle cell patients) (Sahyoun and Krauss 2012). Equipotent doses of all commonly used opioid agents produce similar degrees of nausea, vomiting, biliary tract spasm, pruritus, constipation and respiratory depression, however, individual responses may be variable and careful monitoring and titration of these agents is essential. Rigid chest syndrome with inability to ventilate a patient has been reported with large boluses of rapidly administered fentanyl, hence careful titration is necessary (Sahyoun and Krauss 2012). Dosage guidelines for use of opioid for acute pain management are listed in Table 8.4.

Procedural Pain

Fear of procedures is reported by children to be a significant anxiety-provoking aspect of their

Table 8.4 Dosage guidelines for use of opioid agents for acute pain in infants and older children

| Opioid agent | Route of administration | Dosage |
|----------------|-------------------------|--|
| Morphine | PO | <i>Analgesia:</i> 0.2–0.5 mg/kg/dose Usual dose limit: 15 mg/dose <i>Sedation:</i> 0.3 mg/kg, given 30–60 minutes prior to procedures |
| | IV | <i>Analgesia:</i> 0.05–0.1 mg/kg q2–4 h Usual dose limit: 5 mg/dose <i>Continuous infusion:</i> 10–40 µg/kg/h <i>Moderate Sedation:</i> 0.05–0.1 mg/kg IV, may repeat X 1 in 15 min prn |
| Fentanyl | IN | 1.5 µg/kg, repeat q5 min prn for total of three doses Maximum volume: 0.5 mL per nostril in infants or 1 mL/nosrtil in children. Larger volumes should be divided between both nostrils |
| | IV | 1–2 µg/kg/dose IV q30–60 min <i>Continuous infusion:</i> 0.5–2 µg/kg/h |
| Hydro-morphone | PO | Children ≤50 kg 0.04–0.08 mg/kg/dose q3–4 h prn Children >50 kg 2–4 mg/dose q3–4 h prn Dose limit: 4 mg/dose |
| | IV | 0.015–0.2 mg/kg/dose q2–4 h <i>Continuous infusion:</i> 4–8 µg/kg/h Dose limit: 1 mg/dose |

emergency room visit and the pain experience itself can have long term consequences (Kennedy et al. 2008). Although some procedures such as venipuncture and intravenous cannulation are viewed as minor, they often result in significant distress and anxiety for children and their caregivers (Kennedy et al. 2008). Even non-painful procedures for diagnostic imaging such as a CT scan which requires a child to lie motionless may provoke a high degree of anxiety. Other procedures such as fracture reduction and burn debride-

ment are highly painful requiring a higher degree of analgesia and sedation.

Procedural sedation is a technique whereby sedative or dissociative agents with or without analgesic agents are used to induce a state that allows a patient to tolerate unpleasant procedures while maintaining cardiorespiratory function (American College of Emergency Physicians 2014). It has increasingly been adopted by emergency physicians skilled in advanced airway management and cardiopulmonary resuscitation. Safe sedation does require implementation of appropriate sedation guidelines and policies to minimize potential adverse effects (American College of Emergency Physicians 2014). Commonly used agents for minor procedures for anxiolysis with minimal sedative effects include midazolam (PO, IN) and inhaled nitrous oxide. Midazolam has no analgesic effects and hence requires additional analgesics for pain control. Intravenous midazolam is often combined with intravenous fentanyl and, with careful titration, produces more moderate sedation. Inhaled nitrous oxide is blended with oxygen and induces mild to moderate sedation and analgesia and has the advantage of onset and offset within 2–5 min. It is often used as an adjunctive agent for more painful procedures. Ketamine (IV, IM) is a dissociative agent characterized by potent analgesic and amnestic effects with relative lack of cardiopulmonary depression. It is a commonly used agent for procedural sedation in children and ideal for intensely painful procedures. Propofol is a deep anesthetic agent with rapid onset and pleasant recovery and is increasing being used in the emergency setting. It has a narrow therapeutic window and may result in significant respiratory depression and hypotension. It can be used alone for painless procedures requiring motion control such as CT scan and MRI, but additional analgesic agents are necessary for painful procedures (American College of Emergency Physicians 2014).

Sucrose Solution

Sucrose is a safe and effective method for reducing pain in infants for minor procedures such as

venipuncture and heel lance (Stevens et al. 2013). This sweet solution can be prepared by pharmacy or available commercially and is generally instilled with a syringe in the infant's mouth 2 min prior to a procedure with or without a pacifier. Although the mechanism of action is unknown, pain reduction is thought to be mediated by both endogenous and non-opioid systems. While it appears most effective in neonates, it is often used in infants up to 12 months of age (Ali et al. 2016).

Topical Agents for Pain

Application of topical agents prior to needle insertion for venipuncture and intravenous cannulation are effective for reducing pain associated with these procedures. Comparison between commonly used topical agents including amethocaine (4% tetracaine, Ametop™), eutectic mixture of local anesthetics (lidocaine 2.5% and prilocaine 2.5%, EMLA™) and liposomal lidocaine (Maxilene™) are comparable in effectiveness with minimal side effects. Lidocaine-prilocaine requires an application time of 60 min and is associated with some blanching of the site, whereas amethocaine requires an application time of 30–45 min and can be associated with some erythema at the site (Ali et al. 2016). Concerns have been raised with use of lidocaine-prilocaine in young infants for methemoglobinemia due to a reduced level of methemoglobin reductase. Hence, alternative topical agents or a single dose of 1–2 g lidocaine-prilocaine cream with limited application time of 60 min should be considered (Taddio et al. 1998). Liposomal lidocaine is a newer topical anesthetic with a shorter application time of 30 min and has been associated with higher cannulation success rates (Taddio et al. 2005). Vapocoolant sprays are rapid acting evaporation-induced skin cooling agents that are also effective for reducing pain associated with IV cannulation (Farion et al. 2008).

LET (4% lidocaine, 0.1% epinephrine and 0.5% tetracaine) solution is a topical local anesthetic agent for laceration repair. It can be pre-

pared by pharmacy or available commercially as a gel and is applied directly to wounds for 20–30 min. It is most effective on the scalp and face in producing wound anesthesia but also significantly reduces pain of subsequent injection of lidocaine if needed (Eidelman et al. 2011). Generally, use of LET on mucous membranes or end organs such as fingers is avoided, but small amounts applied with a cotton tip have been shown to be safe and effective (Bonadio 1996; White 2004). Pain associated with injection of lidocaine can also be reduced by slow injection, use of a fine needle and buffering with a solution of sodium bicarbonate (1 mL of 8.4% sodium bicarbonate to 9 mL of 1% or 2% lidocaine) (Fein et al. 2012).

Introduction

Trauma and injury are the biggest killers of children in the developed world. Although primary prevention is the best way to reduce casualties, robust and systematic management of traumatic injuries have been critical to reducing morbidity. This chapter reviews the basics of trauma management including the ABCDE approach (“primary survey”), with specific focus on pediatric physiology, interventions and management. We also provide an overview of the adjuncts to the primary survey, including, but not limited to radiography, ultrasound and CT scans. You will also find the basics of the “secondary survey”, and a review of specific high yield injury topics, including C-spine injury, thoracic trauma, and abdominal trauma.

Scope of Pediatric Trauma

Traumatic injuries are the biggest killer of children in the developed world. Often referred to as ‘accidents’, most traumatic injuries represent discrete, potentially preventable events. Therefore, trauma has patterns, risk factors, and identifiable high-risk populations with preventative interventions. Traumatic injuries cost Canadian society millions of dollars annually (Public Health

Agency of Canada 2015); leading causes include include motor vehicle collisions (MVC), pedestrians and cyclists struck by vehicles, suffocation, falls from height, fires, and drowning. Blunt trauma accounts for >90% of injuries in children. Children are at greater risk of serious injury than adults when operating all-terrain vehicles and snowmobiles (Yanchar et al. 2012).

Pre-hospital Care

Trauma systems and regionalized trauma care have been shown to improve outcomes in severely injured trauma patients. Although critically ill injured children may have better outcomes when treated in designated pediatric trauma centers and tertiary intensive care units, specific criteria and age cut-offs for transfer to the pediatric trauma centers vary across the country. Pre-hospital triage scores used by pre-hospital care providers consider factors such as age, weight, airway compromise, hemodynamic instability, level of consciousness or Glasgow Coma Scale (GCS), and the presence of open or multiple fractures (Tepas et al. 1987).

The majority of traumatic injuries occur in adults, and thus the standard Advanced Trauma Life support (ATLS) course focuses primarily on adult trauma. While there are numerous differences in pediatric trauma management, the general approach to assessing the child with multiple injuries is the same.

ABCDE Approach

The traditional “ABCDE” (airway with cervical-spine [c-spine] control, breathing, circulation with hemorrhage control, disability, exposure) approach to trauma should be employed in all injured children.

Airway

A is for airway, which needs to be managed first. The oropharynx should be examined for foreign

bodies such as loose teeth, and any debris removed. If the child is alert and crying, airway patency is usually not of concern, with the notable exception of neck trauma, where a rapidly expanding hematoma may occlude the airway if not identified early. Specific details related to the pediatric airway are beyond the scope of this chapter.

In trauma, ‘A’ includes c-spine control, as it is prudent to assume any blunt trauma victim has a c-spine injury until proven otherwise. This can be established through placement of a cervical collar until injury to the spine can be excluded (to be discussed below). Endotracheal intubation may be difficult due to distorted anatomy or due to blood, foreign bodies or teeth occluding the airway. Since in-line stabilization is initially required for all airway manipulation, airway support in trauma is considered ‘difficult’, with adjuncts such as laryngeal mask airways (LMAs), bougie, video laryngoscopy and surgical airways sometimes being required.

Breathing

Once a definitive airway is established, breathing adequacy must be assessed. A significant proportion of traumatic deaths occur due to hypoxia, and adequate oxygenation and ventilation of the trauma patient is of paramount importance. Immediate placement of all trauma patients on a non-rebreather face mask with 100% oxygen should be considered. The patient should be assessed for bilateral breath sounds and signs of hemo-pneumothorax, such as uneven or decreased breath sounds and subcutaneous emphysema. Progressive buildup of air in the pleural space, often from a lung laceration, can lead to a tension pneumothorax. The ‘one-way valve’ effect can be exacerbated by positive pressure ventilation. Classic signs of a tension pneumothorax are tracheal deviation away from the side of tension, hyper-expanded chest with poor chest wall movements, decreased breath sounds and increased percussion note on the affected side, although these signs can be difficult to appreciate in a busy trauma bay. Increasing

tachypnea, tachycardia and hypoxia should raise the suspicion of a tension pneumothorax. Left untreated, ensuing circulatory collapse with hypotension may lead to traumatic arrest due to impaired venous return to the heart (obstructive shock).

Procedural interventions required include needle decompression of a tension pneumothorax and tube thoracostomy (chest tube) to drain air or blood from the chest. Needle decompression can be achieved using a large gauge (14–16 G) over the needle catheter inserted in the second intercostal space at a mid-clavicular line. The chest tube should be inserted between the anterior and mid-axillary lines of the fourth or fifth intercostal space. In trauma, the open procedure with a large size chest tube is preferable as blood may block smaller tubes.

Circulation and Hemorrhage Control

Hemodynamic status can be monitored clinically through frequent assessment of vital signs, mental status, skin color, pulses, capillary refill and urinary output. Tachycardia is the most sensitive sign of blood loss, with pain and fear also being major contributors. A fall in blood pressure is a late sign of blood loss in children who frequently maintain a perfusing pressure with up to 35–40% blood volume loss prior to becoming hypotensive. Since a drop in hemoglobin takes time, initial blood results are not reliable in identifying ongoing blood loss.

Two large bore intravenous lines (IV) are often needed for resuscitation, especially if there is hemodynamic compromise. As obtaining IV access can be difficult in young children, an intraosseus needle should be inserted if no IV access has been obtained within 90 seconds. Central venous access in young traumatized children is discouraged, as it can be procedurally difficult and time consuming and the length of catheter often precludes delivery of the high volumes of fluid/blood required.

Any obvious hemorrhage should be controlled with direct pressure. Although tourni-

quets have limited indications in trauma management, they can be considered if direct pressure does not stop the bleeding. Full exposure of the patient should be performed early to identify additional sources of blood loss. If there are signs of shock but no obvious external hemorrhage, internal bleeding sources must be identified. Massive hemorrhage can occur in the chest (hemothorax), in the abdomen and pelvis, in fractured long bones in adolescents and the scalp in infants. Obstructive shock from cardiac tamponade or tension pneumothorax (see ‘B’ above) must also be considered in the differential diagnosis of the hypotensive trauma patient.

Fluid Resuscitation and Hemorrhage

In patients with abnormal hemodynamics and signs of hemorrhagic shock, an initial bolus of normal saline or lactated Ringers’ (20–40 ml/kg) is indicated. If the patient is unresponsive to the initial fluid bolus, blood products should be given, as excessive fluid resuscitation with crystalloids can be harmful.

Close monitoring of coagulation parameters is necessary, as disseminated intravascular coagulation (DIC) is a frequent result from trauma, with or without major hemorrhage. Massive transfusion protocols are becoming widely adopted by trauma centers to minimize the coagulopathy associated with trauma (Chidester et al. 2012; Hendrickson et al. 2011). Balanced blood resuscitation using packed red blood cells, fresh frozen plasma (FFP) and platelets has been advocated, although ideal ratios of these products remain unknown and the use of massive transfusion protocols varies considerably across the country (Horst et al. 2016). A foundation 2:1 ratio of red blood cells to platelets may be considered, along with goal directed therapy for replacement of platelets, cryoprecipitate and calcium (Dzik et al. 2011).

Tranexamic acid (TXA) has been shown to be safe and effective in high doses in pediatric surgery (Hasegawa et al. 2014). Although there is

minimal evidence supporting its use in pediatric trauma, many experts feel that it should be considered within three hours of injury if there is obvious blood loss (Beno et al. 2014; Eckert et al. 2014), or if any blood transfusion is required.

Disability and GCS

A pediatric GCS (described elsewhere) and AVPU (alert, verbal, pain, unresponsive) scale should be used serially to describe all trauma patients. After establishing GCS or AVPU, a rapid assessment of neurologic status in all trauma patients is required. Pupils should be examined, and a brief neurologic exam should be performed if possible prior to intubation or use of drugs that may alter the neurologic exam. Significant bradycardia and hypotension refractory to fluid resuscitation should alert the trauma team to the possibility of an upper C-spine injury leading to neurogenic shock. Presence of hypertension and bradycardia may signal increased intracranial pressure.

Exposure and Temperature Control

The final step in the primary survey of all trauma patients is exposure, whereby the child should be fully exposed and log-rolled to assess for injuries to the back of the head and deformities or tenderness of the spine. Although an external genitourinary exam is an important, a digital rectal exam (DRE) should only be considered in select patients where there is concern about spinal injury. It has poor sensitivity in detecting spinal cord injuries, bowel and rectal injuries, pelvic fractures or urethral disruptions. It adds little to the assessment, can be falsely reassuring and may be upsetting for the pediatric patient (Shlamovitz et al. 2007). Since iatrogenic injury from prolonged stay on a backboard has been described, the patient should be removed from the backboard at this point (Totten and Sugarman 2009; Langevin 2016).

Keeping the patient warm is imperative as temperature instability and hypothermia are part of the ‘trauma triad of death’ (along with coagulopathy and acidosis) (Mikhail 1999). The trauma room should be appropriately warm, and warm blankets should be covering the patient. This is particularly true in children, who lose much more heat than adults due to increased body surface area to weight ratio. If the patient remains hypothermic or need for ongoing fluid resuscitation is anticipated, warmed crystalloids and blood products should be considered (this can be achieved through a level 1 infusion pump/rapid infuser if available).

Adjuncts to Primary Survey

Imaging, such as radiography and a focused assessment of sonography in trauma (FAST) are important adjuncts that may need to be considered. While there is no standard set of images to be done on every trauma patient, plain films of the c-spine, chest and pelvis are frequently performed. Recent evidence suggests that hemodynamically stable children with multiple trauma and GCS ≥ 13 who have normal examination of the pelvis and hip, no hematuria and do not have a femur fracture can safely forego pelvic imaging (Haasz et al. 2015). Radiographs for suspected skeletal injuries may be performed but should not delay definitive care for life threatening injuries. Other imaging modalities can be employed, depending on clinical and radiographical findings. Although adult trauma patients often get ‘pan CTs’, this approach is strongly discouraged in children due to the long term effects of ionizing radiation (Nellensteijn et al. 2016; Pandit et al. 2016). Additionally, if the patient is being transferred to a trauma center, CT scan can usually be safely deferred (Fahy et al. 2016).

The FAST exam, traditionally incorporated into adult trauma activations, is a recent addition to pediatric trauma care. Since the utility of this exam is currently being investigated in children, a negative FAST in children does not rule out

intra-abdominal injury (Scaife et al. 2013) and a positive FAST does not necessarily indicate the need for operative intervention (Berona et al. 2016), and it is insufficiently sensitive to replace CT (Menaker et al. 2014). Extending the FAST exam may be useful, as it can detect small pneumothoraces, heart function and more (Marin et al. 2015). These examinations should only be performed in conjunction with traditional imaging, and interpreted within appropriate clinical context.

Blood work, often referred to as a ‘trauma panel’ can be drawn upon insertion of the two large bore IVs (see Circulation). Suggested bloodwork includes complete blood count, blood gas, group and screen/crossmatch, amylase and/or lipase, liver function tests (AST, ALT), coagulation profile including fibrinogen, renal function, electrolytes, glucose as well as β HCG and toxicology screen. Urinalysis should be assessed for macroscopic hematuria (>50 red blood cells/hpf) to screen for renal or genitourinary injury (Santucci et al. 2004; Perez-Brayfield et al. 2002).

Secondary Survey

After the primary survey is completed and the child stabilized, a secondary survey should be performed. The secondary survey is a comprehensive examination of the patient’s history, a detailed physical examination and the completion of any adjunctive laboratory or imaging tests not yet performed. An AMPLE history should be performed: **A**llergies, any relevant **M**edications, **P**ast medical history, time of **L**ast meal and **E**vents leading up to the trauma.

Specifically, the head and face should be examined for hematomas (boggy or firm), depressed skull fractures, and scalp lacerations. Signs of a basilar skull fracture such as hemotympanum, periorbital ecchymosis (‘racoon eyes’), bruising over the mastoid (‘Battles’ sign’) and cerebrospinal fluid rhinorrhea/otorrhea should be noted. Pupillary diameter and reactivity should be documented, the facial

bones palpated, and the oral cavity examined for missing teeth or signs of malocclusion. The chest should be re-examined for respiratory effort, heart/breath sounds, flail chest or other injuries. Any bruising on the abdomen (especially in seatbelt distribution, abdominal tenderness or peritoneal irritation) should be noted. The genitourinary system should be examined for vaginal bleeding, blood at the urethral meatus or perineal or scrotal bruising, which may suggest injury to the genitourinary system. Extremities should be examined for deformity, open fracture or neurovascular compromise. Finally, a mental status assessment and peripheral neurologic exam should be performed, including sensation, motor function (power, tone), deep tendon reflexes, and paresthesias, with special attention to focal neurologic deficits. This examination aspect may be challenging in young children.

Children and infants are at a much higher risk for spinal ligamentous injury, due to ligamentous laxity and skeletal immaturity. Additionally, spinal cord injury without radiographic abnormality (SCIWORA) is much more common in children compared to adults.

Radiography of c-spine rules out the majority of related injuries (Connelly et al. 2016). However, given the higher incidence of SCIWORA in children compared to adults, MRI may be required in select cases. Important anatomic differences that predispose children to C-spine injury include: ligamentous laxity, shallow angle of facet joints, relatively larger head leading to a higher rate of axial injuries in young children, and multiple vertebral ossification centers, all of which make radiological interpretation challenging. Risk factors for c-spine injury include: altered mental status, focal neurological deficit, neck pain, torticollis, substantial torso injury, predisposing condition (e.g. arthritis, Trisomy 21), diving, high risk MVC (Leonard et al. 2011). Although a detailed discussion about clearing the pediatric cervical spine is beyond the scope of this text, clinical decision rules such as the NEXUS criteria may be helpful to aid in clinical clearance in a coop-

erative child (Vinson 2001; Michaleff et al. 2012). Plain films in children are about 90% sensitive for C-spine injury, and therefore should be the first imaging modality in alert, non-intubated children who cannot be cleared clinically. (Nigrovic et al. 2012). If the cervical spine cannot be evaluated as normal, it is advisable to keep the patient in a soft collar (or bags besides his/her head if the child is too small for a traditional collar) until detailed imaging (usually MRI) can be performed.

Traumatic Brain Injury

Compared to adults, children are more susceptible to intracranial injuries due to their larger head-to-body size ratio, open sutures and thinner cranial bones. Additionally, a high brain water content and relative paucity of myelinated tissue predispose children to cerebral edema and diffuse axonal injury.

Mild head injury is defined as a GCS score >13. Although this may result in concussion, detailed discussion about concussion is beyond the scope of this chapter. A number of clinical decision rules exist to help risk stratify children with respect to the need for neurological intervention and likelihood of brain injury on CT scan (CATCH rules) (Osmond et al. 2010) as well as to identify children at low risk of clinically important traumatic brain injury (PECARN and CHALICE rules) (Kuppermann et al. 2007; Harty and Bellis 2010). Based on previous studies, factors that warrant consideration for a CT scan to rule out a clinically important traumatic brain injury in children >2 years old include GCS <15, altered mental status and signs of a basal skull fracture. Vomiting more than once, loss of consciousness for more than five seconds, severe headache or severe mechanism of injury (fall >5 ft, MVC with rollover, ejection or fatality, pedestrian/bicycle without helmet versus vehicle or struck by high velocity object) should also raise suspicion of a possible intracranial bleed (Kuppermann et al. 2007). In children <2 years

old, palpable skull fractures, the presence of a scalp hematoma (other than frontal), and abnormal behavior as per parents may also suggest significant head trauma.

After a traumatic head injury has occurred, the primary management goal is to minimize secondary injury to the brain, the most common of which are hypoxia, hypotension and hypothermia. Coagulopathy, acidosis and GCS have also been associated with increased mortality, and may help identify high risk patients (Davis et al. 2017).

Hypoxia is minimized by timely provision of 100% supplemental oxygen via a non-rebreather mask and by early consideration of intubation with significant neurologic deterioration. Children should be intubated by the most experienced individual, as multiple intubation attempts can create spikes in intracranial pressure. Ketamine can be used as a sedative agent for intubation in trauma, as the previously held belief regarding its contraindication has been disproven (Wang et al. 2014; Bar-Joseph et al. 2009; Chang et al. 2013).

Physicians need to be aware of the possibility of brainstem herniation, classically presenting with Cushing's triad of hypertension, irregular respirations and bradycardia. Asymmetric pupils and progressive obtundation are the hallmark of herniation and warrant urgent intervention and an immediate neurosurgical consultation. Management consists of elevating the head of the bed to 30°, assuring that venous drainage is not blocked by a tight cervical collar, administration of IV mannitol (1 g/kg) and/or IV 3% hypertonic saline (3–5 ml/kg), sedation and appropriate airway management with ventilation parameters targeting a low normal end tidal CO₂ (approximately 35 mmHg). Hyperventilating the patient below the lower limit of normocapnia may reduce cerebral blood flow to the point of impaired oxygen delivery, leading to brain ischemia (Skippen et al. 1997), and, is therefore reserved for refractory patients with a 'blown' pupil while awaiting definitive operative management.

Temperature must be strictly monitored, and the patient should be warmed to normothermia.

There is currently no role for therapeutic hypothermia in children with traumatic brain injuries (Hutchison et al. 2008, 2010).

Thoracic Trauma

After head injury, thoracic trauma is the second most common cause of injured related mortality in children. Children are less likely to have rib fractures than adults due to increased chest wall compliance, with forces preferentially transmitted to internal organs. This results in more pulmonary contusions and hemo/pneumothorax. Tension pneumothorax can also develop more rapidly. Children are more prone to hypoxia due to higher metabolic rate, increased oxygen consumption per kg body weight and reduced functional residual capacity.

High energy mechanisms can still lead to rib fractures. A flail chest occurs when two or more ribs are fractured in two or more places, leaving a 'floating' segment which in turn results in paradoxical chest movement with respiratory pressure changes. If associated with an underlying pulmonary contusion, this scenario can lead to respiratory insufficiency or failure requiring respiratory support.

Abdominal Trauma

Eight to twelve percent of seriously injured children sustain an intra-abdominal injury and the most common causes are MVCs, pedestrian collisions and falls (Cooper et al. 1994). Abdominal trauma needs to be strongly considered in children with seatbelt and handlebar injuries, and those with non-accidental injuries. Management of children with solid organ injuries has evolved markedly over the last two decades and most solid organ abdominal injuries are now treated non-operatively. (Dodgion et al. 2014; Wisner et al. 2015). The most commonly injured abdominal organs are the spleen and the liver. Compared to adults: children are smaller and their ribs are more pliable which results in transfer of greater

kinetic energy to thoracic and upper abdominal organs, and their weaker abdominal musculature and thinner abdominal wall provides less organ protection. Furthermore, intra-abdominal organs in children are in closer proximity to each other increasing the risk of multiple organ injury.

Clinical predictors of blunt abdominal injury include: (in order of importance): (1) Evidence of abdominal wall trauma or seat belt sign, (2) GCS score <14, (3) Abdominal tenderness, (4) Evidence of thoracic wall trauma, (5) Abdominal pain, (6) Decreased breath sounds, (7) Vomiting.

Penetrating abdominal injuries involve the gastrointestinal tract more often than the solid organs—most children with these injuries require operative management. A seatbelt sign (transverse abdominal ecchymosis caused by acute flexion over a lapbelt) should raise suspicion of injury of the small bowel and duodenum, mesenteric avulsions, and associated lumbar distraction injuries (Chance fracture). As these may be missed on initial imaging, they warrant close monitoring as well as serial exams.

References

- Alexandre J, Manno M. Under use of analgesia in very young pediatric patients with isolated painful injuries. *Annu Emerg Med.* 2003;41(5):617–22.
- Ali S, McGrath T, Drendel AL. An evidence-based approach to minimizing acute procedural pain in the emergency department. *Pediatr Emerg Care.* 2016;32(1):36–42.
- American College of Emergency Physicians. Clinical policy: procedural sedation and analgesia in the emergency department. *Ann Emerg Med.* 2014;63(2):247–57.
- Atkins DL, et al. Part 11: Pediatric basic life support and cardiopulmonary resuscitation quality: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation.* 2015;132(18 Suppl 2):S519–25.
- Atkinson SJ, Cvijanovich NZ, Thomas NJ, et al. Corticosteroids and pediatric septic shock outcomes: a risk stratified analysis. *PLoS One.* 2014;9(11):e112702.
- Balamuth F, Weiss SL, Neuman MI, et al. Pediatric severe sepsis in U.S. children's hospitals. *Pediatr Crit Care Med.* 2014;15:798.
- Bar-Joseph G, Guilburd Y, Tamir A, Guilburd JN. Effectiveness of ketamine in decreasing intracra-

- nial pressure in children with intracranial hypertension. *J Neurosurg Pediatr.* 2009;4(1):40–6.
- Barry P, Leslie A. Paediatric and neonatal critical care transport. London: BMJ Publishing Group; 2003.
- Batton DG, Barrington KJ, Wallman C, American Academy of Pediatrics, Committee on Fetus and Newborn, Section of Anesthesiology and Pain Medicine; Canadian Paediatric Society Fetus and Newborn Committee. Prevention and management of pain the neonate: an update. *Pediatrics.* 2006;118(5):2231–41.
- Beno S, Ackery AD, Callum J, Rizoli S. Tranexamic acid in pediatric trauma: why not? *Crit Care.* 2014;18(4):313.
- Berona K, Kang T, Rose E. Pelvic free fluid in asymptomatic pediatric blunt abdominal trauma patients: a case series and review of the literature. *J Emerg Med.* 2016;50(5):753–8.
- Bistriz JF, Horton LM, Smaldone A. Therapeutic hypothermia in children after cardiac arrest: a systematic review and meta-analysis. *Pediatr Emerg Care.* 2015;31(4):296–303.
- Bonadio WA. Safe and effective method for application of tetracaine, adrenaline and cocaine to oral lacerations. *Ann Emerg Med.* 1996;28(4):396–8.
- Borland M, Jacobs I, King B, et al. A randomized controlled trial comparing intranasal fentanyl to intravenous morphine for managing acute pain in children in the emergency department. *Ann Emerg Med.* 2007;49(3):335–40.
- Boyd JR, Stuart P. The efficacy of structured assessment and analgesia provision in the paediatric emergency department. *Emerg Med J.* 2005;22:30–2.
- Brierley J, Carcillo JA, Choong K, et al. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. *Crit Care Med.* 2009;37:666.
- Bruder EA, et al. Single induction dose of etomidate versus other induction agents for endotracheal intubation in critically ill patients. *Cochrane Database Syst Rev.* 2015;1:CD010225.
- Carcillo JA, Kuch BA, Han YY, et al. Mortality and functional morbidity after use of PALS/APLS by community physicians. *Pediatrics.* 2009;124(2):500.
- Chan CM, Mitchell AL, Shorr AF. Etomidate is associated with mortality and adrenal insufficiency in sepsis: a meta-analysis. *Crit Care Med.* 2012;40(11):2945–53.
- Chang A, Berry A, Jones LJ, Sivasangari S. Specialist teams for neonatal transport to neonatal intensive care units for prevention of morbidity and mortality. *Cochrane Database Syst Rev.* 2008;4:CD007485.
- Chang LC, Raty SR, Ortiz J, Bailard NS, Mathew SJ. The emerging use of ketamine for anesthesia and sedation in traumatic brain injuries. *CNS Neurosci Ther.* 2013;19(6):390–5.
- Chidester SJ, Williams N, Wang W, Groner JI. A pediatric massive transfusion protocol. *J Trauma Acute Care Surg.* 2012;73(5):1273–7.
- Chou EH, et al. Ultrasonography for confirmation of endotracheal tube placement: a systematic review and meta-analysis. *Resuscitation.* 2015;90:97–103.
- Connelly CR, Yonge JD, Eastes LE, Bilyeu PE, Kemp Bohan PM, Schreiber MA, et al. Performance improvement and patient safety program (PIPS) guided quality improvement initiatives can significantly reduce CT imaging in pediatric trauma patients. *J Trauma Acute Care Surg.* 2016;81(2):278–84.
- Cooper A, Barlow B, DiScala C, String D. Mortality and truncal injury: the pediatric perspective. *J Pediatr Surg.* 1994;29(1):33–8.
- Cruz AT, Perry AM, Williams EA, et al. Implementation of goal-directed therapy for children with suspected sepsis in the emergency department. *Pediatrics.* 2011;127:e758.
- Davis AL, Wales PW, Malik T, Stephens D, Razik F, Schuh S. The BIG score and prediction of mortality in pediatric blunt trauma. *Crit Care Med.* 2017;45:1061–93.
- de Caen AR, et al. Part 12: Pediatric advanced life support: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Pediatrics.* 2015a;136(Suppl 2):S176–95.
- de Caen AR, Berg MD, Chameides L, et al. Part 12: pediatric advanced life support 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation.* 2015b;132(Suppl 2):S526–42.
- de Caen AR, Maconochie IK, Aickin R, et al. Part 6: Pediatric basic life support and pediatric advanced life support 2015 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Circulation.* 2015c;132(suppl 1):S177–203.
- den Brinker M, et al. One single dose of etomidate negatively influences adrenocortical performance for at least 24 h in children with meningococcal sepsis. *Intensive Care Med.* 2008;34(1):163–8.
- Dodgion CM, Gosain A, Rogers A, St Peter SD, Nichol PF, Ostlie DJ. National trends in pediatric blunt spleen and liver injury management and potential benefits of an abbreviated bed rest protocol. *J Pediatr Surg.* 2014;49(6):1004–8. discussion 1008
- Dong L, Donaldson A, Metzger R, Keenan H. Analgesic administration in the emergency department for children requiring hospitalization for long bone fractures. *Pediatr Emerg Care.* 2012;28:109–14.
- Drendel AL, Kelly BT, Ali S. Pain assessment for children: overcoming challenges and optimizing care. *Pediatr Emerg Care.* 2011;27(8):773–80.
- Dzik WH, Blajchman MA, Fergusson D, Hameed M, Henry B, Kirkpatrick AW, et al. Clinical review: Canadian National Advisory Committee on Blood and Blood Products – massive transfusion consensus conference 2011: report of the panel. *Crit Care.* 2011;15(6):242.
- Eckert MJ, Wertin TM, Tyner SD, Nelson DW, Izenberg S, Martin MJ. Tranexamic acid administration to pedi-

- atric trauma patients in a combat setting: the pediatric trauma and tranexamic acid study (PED-TRAX). *J Trauma Acute Care Surg.* 2014;77(6):852–8. discussion 858
- Eidelman A, Weiss JM, Baldwin CL, et al. Topical anaesthetics for repair of dermal laceration. *Cochrane Database Syst Rev.* 2011;6:CD005364.
- Ellis DY, Harris T, Zideman D. Cricoid pressure in emergency department rapid sequence tracheal intubations: a risk-benefit analysis. *Ann Emerg Med.* 2007;50(6):653–65.
- Fahy AS, Antiel RM, Polites SF, Ishitani MB, Moir CR, Zielinski MD. Pretransfer computed tomography delays arrival to definitive care without affecting pediatric trauma outcomes. *J Pediatr Surg.* 2016;51(2):323–5.
- Farion KJ, Splinter KL, Newhook K, et al. The effect of vapocoolant spray on pain due to intravenous cannulation in children: a randomized controlled trial. *CMAJ.* 2008;179(1):31–6.
- Fein JA, Zempsky WT, Cravero JP, The Committee on Pediatric Emergency Medicine and Section on Anesthesiology and Pain Medicine. Relief of pain and anxiety in pediatric patients in emergency medical systems. *Pediatrics.* 2012;130(5):e1391–405.
- Filanovsky Y, Miller P, Kao J. Myth: ketamine should not be used as an induction agent for intubation in patients with head injury. *CJEM.* 2010;12(02):154–7.
- Gaines NN, Patel B, Williams EA, Cruz AT. Etiologies of septic shock in a pediatric emergency department population. *Pediatr Infect Dis J.* 2012;31:1203.
- Girotra S, et al. Survival trends in pediatric in-hospital cardiac arrests: an analysis from get with the guidelines-resuscitation. *Circulation.* 2013;6(1):42–9.
- Goldstein B, Giroir B, Randolph A. International consensus conference on pediatric sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med.* 2005;6:2.
- Grant PS. Analgesia delivery in the emergency department. *Am J Emerg Med.* 2006;24:806–9.
- Haasz M, Simone LA, Wales PW, Stimec J, Stephens D, Beno S, et al. Which pediatric blunt trauma patients do not require pelvic imaging? *J Trauma Acute Care Surg.* 2015;79(5):828–32.
- Han YY, Carcillo JA, Dragotta MA, et al. Early reversal of pediatric-neonatal septic shock by community physicians is associated with improved outcome. *Pediatrics.* 2003;112:793.
- Hartman ME, Linde-Zwirble WT, Angus DC, Watson RS. Trends in the epidemiology of pediatric severe sepsis. *Pediatr Crit Care Med.* 2013;14:686.
- Harty E, Bellis F. CHALICE head injury rule: an implementation study. *Emerg Med J.* 2010;27(10):750–2.
- Hasegawa T, Oshima Y, Maruo A, Matsuhisa H, Tanaka A, Noda R, et al. Intraoperative tranexamic acid in pediatric bloodless cardiac surgery. *Asian Cardiovasc Thorac Ann.* 2014;22(9):1039–45.
- Hendrickson JE, Shaz BH, Pereira G, Parker PM, Jessup P, Atwell F, et al. Implementation of a pediatric trauma massive transfusion protocol: one institution's experience. *Transfusion.* 2011;52(6):1228–36.
- Horst J, Leonard JC, Vogel A, Jacobs R, Spinella PC. A survey of US and Canadian hospitals' paediatric massive transfusion protocol policies. *Transfus Med.* 2016;26(1):49–56.
- Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. *N Engl J Med.* 2003;348:138.
- Hughes S. Towards evidence based emergency medicine: best BETs from the Manchester Royal Infirmary. BET 3: is ketamine a viable induction agent for the trauma patient with potential brain injury. *Emerg Med J.* 2011;28(12):1076–7.
- Hutchison JS, Ward RE, Lacroix J, Hébert PC, Barnes MA, Bohn DJ, et al. Hypothermia therapy after traumatic brain injury in children. *N Engl J Med.* 2008;358(23):2447–56.
- Hutchison JS, Frndova H, Lo T-YM, Guerguerian A-M. Hypothermia Pediatric Head Injury Trial Investigators, Canadian Critical Care Trials Group. Impact of hypotension and low cerebral perfusion pressure on outcomes in children treated with hypothermia therapy following severe traumatic brain injury: a post hoc analysis of the Hypothermia Pediatric Head Injury Trial. *Dev Neurosci.* 2010;32(5–6):406–12.
- Kelly LE, Rieder M, van den Anker J, et al. More codeine fatalities after tonsillectomy in North American Children. *Pediatrics.* 2012;129:e1324–7.
- Kennedy RM. Sedation in the emergency department: a complex and multifactorial challenge. In: Mason KP, editor. *Pediatric sedation outside of the operating room.* New York, NY: Springer; 2015. p. 367–422.
- Kennedy RM, Luhmann J, Zempsky WT. Clinical implications of unmanaged needle-insertion pain and distress in children. *Pediatrics.* 2008;122:S130–3.
- Kleinman ME, et al. Part 14: pediatric advanced life support: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation.* 2010a;122(18 Suppl 3):S876–908.
- Kleinman ME, de Caen AR, Chameides L, et al. Pediatric basic and advanced life support: 2010 International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Pediatrics.* 2010b;126:e1261.
- Krauss BS, Calligari L, Green SM, Barbi E. Current concepts in management of pain in children in the emergency department. *Lancet.* 2016;387:83–92.
- Kuppermann N, Holmes J, Dayan P, Hoyle J, Atabaki S, Dean J, et al. Blunt head trauma in the pediatric emergency care applied research network (PECARN). *Acad Emerg Med.* 2007;14(5 Suppl 1):S94–5.
- Kutko MC, Calarco MP, Flaherty MB, et al. Mortality rates in pediatric septic shock with and without multiple organ system failure. *Pediatr Crit Care Med.* 2003;4:333.

- Langevin M. Ditch the spine board – emergency physicians monthly. *Bel Air, MD: Emergency Physicians Monthly*; 2016. p. 1–6.
- Larsen GY, Mechan N, Greenberg R. An emergency department septic shock protocol and care guideline for children initiated at triage. *Pediatrics*. 2011;127:e1585–92.
- Le May S, Gouin S, Fortin C, et al. Efficacy of an ibuprofen/codeine combination for pain management in children presenting to the emergency department with a limb injury: a pilot study. *J Emerg Med*. 2013;33(2):536–41.
- Leonard JC, Kuppermann N, Olsen C, Babcock-Cimpello L, Brown K, Mahajan P, et al. Factors associated with cervical spine injury in children after blunt trauma. *Ann Emerg Med*. 2011;58(2):145–55.
- Lorch S, Myers S, Carr B. The regionalization of pediatric health care. *Pediatrics*. 2010;126(6):1182–90.
- Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. *N Engl J Med*. 2011;364:2483.
- Marin JR, Lewiss RE, American Academy of Pediatrics, Committee on Pediatric Emergency Medicine, Society for Academic Emergency Medicine, Academy of Emergency Ultrasound, American College of Emergency Physicians, Pediatric Emergency Medicine Committee, World Interactive Network Focused on Critical Ultrasound. Point-of-care ultrasonography by pediatric emergency medicine physicians. *Pediatrics*. 2015;135(4):e1113–22.
- McPherson ML, Jefferson LS, Graf JM. A validated pediatric transport survey: how is your team performing? *Air Med J*. 2008;27(1):40–5.
- Menaker J, Blumberg S, Wisner DH, Dayan PS, Tunik M, Garcia M, et al. Use of the focused assessment with sonography for trauma (FAST) examination and its impact on abdominal computed tomography use in hemodynamically stable children with blunt torso trauma. *J Trauma Acute Care Surg*. 2014;77(3):427–32.
- Menon K, McNally D, Choong K, Sampson M. A systematic review and meta-analysis on the effect of steroids in pediatric shock. *Pediatr Crit Care Med*. 2013;14(5):474.
- Meyer MT, Gourlay DM, Weitze KC, Ship MD, Drayna PC, Wener C, Lerner EB. Helicopter interfacility transport of pediatric trauma patients: are we overusing a costly resource? *J Trauma Acute Care Surg*. 2016;80(2):313–7.
- Michailidou M, Goldstein SD, Salazar J, Aboagye J, Steward D, Efron D, Abdullah F, Haut ER. Helicopter overtriage in pediatric trauma. *J Pediatr Surg*. 2014;49(110):1673–7.
- Michaleff ZA, Maher CG, Verhagen AP, Rebbeck T, Lin C-WC. Accuracy of the Canadian C-spine rule and NEXUS to screen for clinically important cervical spine injury in patients following blunt trauma: a systematic review. *CMAJ Can Med Assoc*. 2012;184(16):E867–76.
- Mikhail J. The trauma triad of death: hypothermia, acidosis, and coagulopathy. *AACN Clin Issues*. 1999;10(1):85–94.
- Mittiga MR, Rinderknecht AS, Kerrey BT. A modern and practical review of rapid-sequence intubation in pediatric emergencies. *Clin Pediatr Emerg Med*. 2015;16(3):172–85.
- Moler FW, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest in children. *N Engl J Med*. 2015;372(20):1898–908.
- Nellensteijn DR, Greuter MJ, Moumni El M, Hulscher JB. The use of CT scan in hemodynamically stable children with blunt abdominal trauma: look before you leap. *Eur J Pediatr Surg*. 2016;26(4):332–5.
- Nelson BP, Cohen D, Lander O, et al. Mandated pain scores improves frequency of ED analgesic administration. *Am J Emerg Med*. 2004;22(7):582–5.
- Nigrovic LE, Rogers AJ, Adelgais KM, Olsen CS, Leonard JR, Jaffe DM, et al. Utility of plain radiographs in detecting traumatic injuries of the cervical spine in children. *Pediatr Emerg Care*. 2012;28(5):426–32.
- Oliveira CF, Nogueira de Sá FR, Oliveira DS, et al. Time- and fluid-sensitive resuscitation for hemodynamic support of children in septic shock: barriers to the implementation of the American College of Critical Care Medicine/pediatric advanced life support guidelines in a pediatric intensive care unit in a developing world. *Pediatr Emerg Care*. 2008;24(12):810.
- Ong CK, Seymour RA, Lirk P, Merry AF. Combining paracetamol (acetaminophen) with nonsteroidal anti-inflammatory drugs: a qualitative systematic review of analgesic efficacy for acute postoperative pain. *Anesth Analg*. 2010;110(4):1170–9.
- Orr RA, Felmet KA, Han Y, McCloskey KA, Dragotta MA, Bills DM, Kuch BA, Watson RS. Pediatric specialized transport teams are associated with improved outcomes. *Pediatrics*. 2009;124(1):40–8.
- Osmond MH, Klassen TP, Wells GA, Correll R, Jarvis A, Joubert G, et al. CATCH: a clinical decision rule for the use of computed tomography in children with minor head injury. *Can Med Assoc J*. 2010;182(4):341–8.
- Pandit V, Michailidou M, Rhee P, Zangbar B, Kulvatunyou N, Khalil M, et al. The use of whole body computed tomography scans in pediatric trauma patients: Are there differences among adults and pediatric centers? *J Pediatr Surg*. 2016;51(4):649–53.
- Paul R, Neuman MI, Monuteaux MC, Melendez E. Adherence to PALS sepsis guides decreases hospital length of stay. *Pediatrics*. 2012;130:e273–80.
- Paul R, Melendez E, Stack A, et al. Improving adherence to PALS septic shock guidelines. *Pediatrics*. 2014;133(5):e1358–66.
- Perez-Brayfield MR, Gatti JM, Smith EA, Broecker B, Massad D, Scherz H, et al. Blunt traumatic hematuria in children. is a simplified algorithm justified? *J Urol*. 2002;167:2543–7.
- Perrott DA, Piira T, Goodenough B, Champion GD. Efficacy and safety of acetaminophen vs. ibu-

- profen for treating children's pain and fever. *JAMA Pediatr.* 2004;15(6):521–6.
- Pizarro CF, Troster EJ, Damiani D, Carcillo JA. Absolute and relative adrenal insufficiency in children with septic shock. *Crit Care Med.* 2005;33(4):855.
- Poonai N, Bhullar G, Kangrui L, et al. Oral administration of morphine versus ibuprofen to manage post-fracture pain in children: a randomized trial. *CMAJ.* 2014;186(18):1358–63.
- Public Health Agency of Canada. The cost of injury in Canada. Ottawa, ON: Public Health Agency of Canada; 2015. p. 1–177.
- Ramnarayan P, Thiru K, Parslow RC, Harrison DA, Draper ES, Rowan KM. Effect of specialist retrieval teams on outcomes in children admitted to paediatric intensive care units in England and Wales: a retrospective cohort study. *Lancet.* 2010;376:698–704.
- Ruth A, McCracken CE, Fortenberry JD, et al. Pediatric severe sepsis: current trends and outcomes from the pediatric health information systems database. *Pediatr Crit Care Med.* 2014;15:828.
- Sahyoun C, Krauss B. Clinical implications of pharmacokinetics and pharmacodynamics of procedural sedation agents in children. *Curr Opin Pediatr.* 2012;24:225–32.
- Santucci RA, Langenburg SE, Zachareas MJ. Traumatic hematuria in children can be evaluated as in adults. *J Urol.* 2004;171(2 Pt 1):822–5.
- Scaife ER, Rollins MD, Barnhart DC, Downey EC, Black RE, Meyers RL, et al. The role of focused abdominal sonography for trauma (FAST) in pediatric trauma evaluation. *J Pediatr Surg.* 2013;48(6):1377–83.
- Scott HF, Donoghue AJ, Gaieski DF, et al. The utility of early lactate testing in undifferentiated pediatric systemic inflammatory response syndrome. *Acad Emerg Med.* 2012;19:1276.
- Scott HF, Brou L, Deakyn SJ, et al. Lactate clearance and normalization and prolonged organ dysfunction in pediatric sepsis. *J Pediatr.* 2016;170:149–55.e1–4. <https://doi.org/10.1016/j.jpeds.2015.11.071>.
- Shaw KN, Bachur RG, editors. *Fleisher and Ludwig's textbook of pediatric emergency medicine.* 17th ed. Philadelphia, PA: Wolters Kluwer; 2016.
- Shi F, et al. Cuffed versus uncuffed endotracheal tubes in children: a meta-analysis. *J Anesth.* 2016;30:3–11.
- Shlamovitz GZ, Mower WR, Bergman J, Crisp J, DeVore HK, Hardy D, et al. Lack of evidence to support routine digital rectal examination in pediatric trauma patients. *Pediatr Emerg Care.* 2007;23(8):537–43.
- Singh A, Frenkel O. Evidence-based emergency management of the pediatric airway. *Pediatr Emerg Med Pract.* 2013;10(1):1–25.
- Skippen P, Seear M, Poskitt K, Kestle J, Cochrane D, Annich G, et al. Effect of hyperventilation on regional cerebral blood flow in head-injured children. *Crit Care Med.* 1997;25(8):1402–9.
- Srouji R, Ratnapalan S, Schneeweiss S. Pain in children: assessment and non-pharmacologic management. *Int J Pediatr.* 2010;2010:Article ID: 474838.
- Steiner, J. The use of apneic oxygenation during prolonged intubation in pediatric patients: a randomized clinical trial. 2016.; <https://clinicaltrials.gov/ct2/show/NCT01886807?term=apneic+oxygenation&rank=3>. Accessed 24 Mar 2016.
- Stevens B, Yamada J, Lee GY, et al. Sucrose for analgesia in newborn infants undergoing painful procedures. *Cochrane Database Syst Rev.* 2013;1:CD001069.
- Stollings JL, et al. Rapid-sequence intubation a review of the process and considerations when choosing medications. *Ann Pharmacother.* 2014;48(1):62–76.
- Taddio A, Ohlsson A, Einarson TR, Stevens B, Koren G. A systematic review of lidocaine-prilocaine cream (EMLA) in the treatment of acute pain in neonates. *Pediatrics.* 1998;101(2):E1.
- Taddio A, Kaur Soin H, Schuh S, et al. Liposomal lidocaine to improve procedural success rates and reduce procedural pain among children: a randomized controlled trial. *CMAJ.* 2005;172(13):1691–5.
- Teepas JJ III, Mollitt DL, Talbert JL, Bryant M. The pediatric trauma score as a predictor of injury severity in the injured child. *J Pediatr Surg.* 1987;22(1):14–8.
- Totten VY, Sugarman DB. Respiratory effects of spinal immobilization. *Prehosp Emerg Care.* 2009;3(4):347–52.
- Tuuri RE, Gehrig MG, Busch CE, et al. "Beat the shock clock": an interprofessional team improves pediatric septic shock care. *Clin Pediatr (Phila).* 2016;55(7):626–38.
- Ventura AM, Shieh HH, Bouso A, et al. Double-blind prospective randomized controlled trial of dopamine versus epinephrine as first-line vasoactive drugs in pediatric septic shock. *Crit Care Med.* 2015;43:2292.
- Vinson DR. NEXUS cervical spine criteria. *Ann Emerg Med.* 2001;37(2):237–8.
- Wang X, Ding X, Tong Y, Zong J, Zhao X, Ren H, et al. Ketamine does not increase intracranial pressure compared with opioids: meta-analysis of randomized controlled trials. *J Anesth.* 2014;28(6):821–7.
- Watson RS, Carcillo JA, Linde-Zwirble WT, et al. The epidemiology of severe sepsis in children in the United States. *Am J Respir Crit Care Med.* 2003;167:695.
- Weingart SD, Levitan RM. Preoxygenation and prevention of desaturation during emergency airway management. *Ann Emerg Med.* 2012;59(3):165–75. e1
- Weiss M, et al. Prospective randomized controlled multicentre trial of cuffed or uncuffed endotracheal tubes in small children. *Br J Anaesth.* 2009;103(6):867–73.
- Weiss SL, Parker B, Bullock ME, et al. Defining pediatric sepsis by different criteria: discrepancies in populations and implications for clinical practice. *Pediatr Crit Care Med.* 2012;13:e219.
- Weiss SL, Fitzgerald JC, Pappachan J, et al. Global epidemiology of pediatric severe sepsis: the sepsis prevalence, outcomes, and therapies study. *Am J Respir Crit Care Med.* 2015a;191:1147.
- Weiss SL, Fitzgerald JC, Maffei FA, et al. SPROUT Study Investigators and Pediatric Acute Lung Injury and

- Sepsis Investigators Network. Discordant identification of pediatric severe sepsis by research and clinical definitions in the SPROUT international point prevalence study. *Crit Care*. 2015b;19:325.
- White NJ, Kim MK, Brousseau DC et al. The anesthetic effectiveness of lidocaine-adrenaline-tetracaine gel on finger lacerations. *Pediatr Emerg Care*. 2004;20(12):812–5.
- Whyte HE, Jefferies AL. The interfacility transport of critically ill newborns. *Paediatr Child Health*. 2015;20(5):265–75.
- Wisner DH, Kuppermann N, Cooper A, Menaker J, Ehrlich P, Kooistra J, et al. Management of children with solid organ injuries after blunt torso trauma. *J Trauma Acute Care Surg*. 2015;79(2):206–14.
- Yanchar NL, Warda LJ, Fuselli P. Child and youth injury prevention: a public health approach. *Paediatr Child Health*. 2012;17(9):511–2.
- Zimmerman JJ, Williams MD. Adjunctive corticosteroid therapy in pediatric severe sepsis: observations from the RESOLVE study. *Pediatr Crit Care Med*. 2011;12(1):2.



Adrenal Insufficiency

Introduction

Adrenal insufficiency refers to a state of decreased glucocorticoid and/or mineralocorticoid production. It can be categorized as primary, or secondary adrenal insufficiency. Primary adrenal insufficiency (AI) results from defects in the adrenal cortex itself. Secondary AI is the result of impaired signaling to the adrenal gland due to diminished adrenocorticotropin (ACTH) release from the pituitary gland or corticotropin-releasing hormone (CRH) from the hypothalamus.

AI is relatively rare in children. AI was first described over 160 years ago and treatment with glucocorticoids has been available for half a decade, yet the diagnosis is often overlooked and our understanding of optimal treatment regimens is still not complete (Shulman et al. 2007; Addison 1980). The initial symptoms of AI are often vague resulting in a missed diagnosis, often until the patient is in life threatening adrenal crisis with associated vascular collapse.

S.D. Marks (✉) • B.A. Wicklow
Assitant Professor, Pediatric Endocrinology and Metabolism, Department of Pediatrics and Child Health, Max Rady College of Medicine, University of Manitoba, Winnipeg, R3E 0Z2 Manitoba, Canada
e-mail: smarks@hsc.mb.ca; bwicklow@exchange.hsc.mb.ca

Etiology

The most common cause of AI in children is acquired secondary AI due to exogenous glucocorticoid treatment of non-endocrine pediatric illnesses. Congenital adrenal hyperplasia (CAH) is the most common cause of primary AI in children. In contrast, in adults, autoimmune adrenal disease is the most common etiology and, perhaps surprising to some, tuberculosis is still the second most common cause of primary AI in adults.

While CAH is the underlying etiology in the large majority of children with primary AI, other causes include autoimmune disease (Addison's disease), adrenoleukodystrophy, adrenal hypoplasia congenita (AHC), infection, infiltrative disease, medication, and syndromes such as Wolman, Triple A and Zellweger (Shulman et al. 2007; Perry et al. 2005). Children with CAH tend to present earlier than the other etiologies even in jurisdictions without newborn screening programs and obviously even more so in those with these screening programs. With the goal of decreasing mortality in infant males and severely virilized females, the Pediatric Endocrine Society (formerly known as the Lawson Wilkins Pediatric Endocrine Society) and the European Society for Pediatric Endocrinology jointly recommended newborn screening for CAH in a 2002 statement (Joint LWPES/ESPE CAH Working Group 2002). With the onset of widespread screening programs, the gender ratio has been found to be

equal in contrast to previous reports indicating a female predominance likely due to early mortality in affected male patients and subsequently underreporting of male infants.

Outside of exogenous glucocorticoid use, secondary AI in children is most commonly caused by congenital hypopituitarism. Secondary, or central, AI may be isolated but is more commonly associated with other pituitary hormone deficiencies. Congenital hypopituitarism is commonly due to transcription factor mutations including HESX1 mutations resulting in septo optic dysplasia and *POU1F1* mutations resulting in multiple anterior pituitary hormone deficiencies. While these transcription factor mutations have been identified as part of clinical research, they are not routinely tested in clinical care. Hypopituitarism may also be acquired from a central tumor, radiation, surgery, trauma, central infection, and infiltrative processes (Shulman et al. 2007; Perry et al. 2005). The most common pediatric tumor resulting in secondary acquired hypopituitarism is craniopharyngioma.

Symptoms of AI can be vague and include fatigue, fever, abdominal pain, weight loss, anorexia, emesis, nausea, back pain, dehydration, hypotension, hyperkalemia, hyponatremia, and hypoglycemia. Salt craving is quite common in primary AI, but may also be present in secondary AI. Primary AI also presents with hyperpigmentation due to elevated levels of POMC a cleavage product of ACTH, which stimulates melanocortin production. Other symptoms are based on the etiology of the AI including virilization as a major presenting symptom in CAH.

Congenital adrenal hyperplasia is most commonly caused by a 21-hydroxylase deficiency. Clinically it presents with ambiguous genitalia in newborn females. These infants are best managed by a specialized interprofessional team including an endocrinologist, geneticist, urologist and psychosocial supports. Newborn males have normal genitalia, and if not picked up in newborn screening, often present around 2 weeks of age in adrenal crisis with failure to thrive, dehydration and emesis.

Secondary AI may present with headaches and visual field disturbances related to the pres-

ence of central lesions. Secondary AI may also be identified due to general pituitary hormone screening in patients presenting with symptoms of other pituitary deficiencies; including decreased growth velocity from growth hormone deficiency, delayed puberty from gonadotropin deficiency, polyuria and polydipsia from diabetes insipidus, or various symptoms of central hypothyroidism.

Investigations

The biochemical profile of primary AI includes decreased cortisol, elevated ACTH, and elevated renin with associated hyponatremia and hyperkalemia. Secondary AI's profile includes decreased cortisol, and a decreased or inappropriately normal ACTH.

Insulin induced hypoglycemia is the gold standard stress test to elicit a cortisol response. However, due to concern and caution around the risk of hypoglycemic seizures and perhaps overall discomfort by health care providers, this test is seldom done in children. However, a critical sample collected during clinical hypoglycemia can be diagnostic. The need for a critical sample with clinical hypoglycemia should be reinforced in all medical teaching given its invaluable diagnostic contribution. A critical sample should include a confirmatory serum glucose along with cortisol, growth hormone, insulin, ketones (beta hydroxybutyrate), carnitine, free fatty acids, ammonia, lactate, and bicarbonate (Shulman et al. 2007; Bornstein et al. 2016).

After hypoglycemia induced stimulation, ACTH stimulation testing remains a gold standard to diagnose primary AI. Recent guidelines advocate that standard dosing with 250 µg corticotropin is recommended for children 2 years old and older. For children under 2 years old, the recommended dosing is 125 µg, and 15 µg/kg for infants. Cortisol levels are measured at 0, 30, and 60 min with a peak level below 500 nmol/L suggestive of AI. This level may be assay dependent and may require some interpretation. A low dose 1 µg corticotropin stimulation test has been purported by some to be more reflective of a natural

stress stimuli and therefore more sensitive in diagnosing secondary AI (Shulman et al. 2007; Bornstein et al. 2016).

First morning cortisol and ACTH levels may also be used for screening but are less accurate and not diagnostic in most scenarios. A cortisol level less than 140 nmol/L and an ACTH 2.5 times above the upper limit may indicate primary AI if paired with a consistent clinical scenario, but is less diagnostic than an ACTH stimulation test. Generally, while an undetectable cortisol level with an elevated ACTH can be diagnostic with the correct clinical picture, other “lowish” cortisol levels are less helpful. In addition, using first morning or random cortisol and ACTH levels in infants is less sensitive.

Early primary AI may be evident with an elevated renin level prior to changes in the cortisol levels.

Treatment

The evidence for appropriate glucocorticoid dosing and regimes is surprisingly limited. In 2016, the Endocrine Society published evidence based clinical practice guidelines on the diagnosis and treatment of primary AI (Bornstein et al. 2016). While the guidelines are adult focused there are pediatric specific recommendations for treatment. Treatment of children with primary AI is recommended with hydrocortisone with a total starting daily dose of 8–12 mg/m² divided three or four times through the day based on the known normal endogenous production of 5–8 mg/m²/day. This starting dose should then be adjusted accordingly to achieve the lowest possible dose to treat the underlying AI while limiting the risk of side effects. CAH will generally require higher dosing to suppress the axis and androgen production but a maximum of 17 mg/m² in older children, and 20 mg/m²/day in infants is a suggested goal (Joint LWPES/ESPE CAH Working Group 2002; Bornstein et al. 2016). Hydrocortisone is the preferred glucocorticoid in children as it is shorter acting than others like prednisolone and dexamethasone. However, the limited availability of low dose hydrocortisone tablets (<10 mg), or a

stable liquid suspension of hydrocortisone often makes the use of prednisolone suspension a necessity in young infants to allow precise dosing. Traditionally described hydrocortisone to prednisolone equivalency ratios of 4:1 or 5:1 are likely too high and may increase the risk of side effects, such as growth suppression. Punthakee et al. suggests a lower starting point of a 15:1 relative potency (Punthakee et al. 2003). It is important to monitor linear growth and weight gain in all children on glucocorticoids in addition to assessing control of AI symptoms, virilization in CAH, and biochemistry.

Children with primary AI and mineralocorticoid deficiency require fludrocortisone treatment at a starting dose of 100 µg/day. Infants often require a higher starting dose of 200 or 300 µg/day. Salt supplementation of 1–2 g sodium chloride divided throughout the day (17–34 mmol/day) is also required in infants under 12 months.

Adrenal crisis requires urgent management with an intravenous or intramuscular hydrocortisone dose of 50 mg/m² followed by 50 mg/m² divided q 6 h for the next 24 h. Hydrocortisone is the preferred glucocorticoid due to its mineralocorticoid effects at high doses in contrast, to Dexamethasone. Glucose levels should be monitored for the risk of hypoglycemia and, if present, treated accordingly with a dextrose infusion.

Intermittent stress such as intercurrent illnesses with fever should be treated with increased glucocorticoid oral or IM “stress” doses equivalent to two to three times the patient’s usual dose to prevent adrenal crisis. Adrenal crisis, precipitated by intercurrent illness is quite common and occurs annually in about 1 in every 12 adults with primary AI (Bornstein et al. 2016). Evidence for optimal stress dosing is limited. Essentially, patients require more corticosteroids when ill with the exact amounts less clear. It is safest to err on the side of caution with a low threshold to stress dose and “rounding up” to higher dosing. Although, too frequent stress dosing can result in growth suppression. Patient education of self-management for intercurrent illness, medical alert identification, and, if capable, home administration of intramuscular hydrocortisone can be lifesaving.

The use of stress dosing for milder stresses such as mild viral illnesses without fever, immunizations, school exam stresses and exercise are controversial with limited evidence (Weise et al. 2004). Recent consensus statements do not recommend stress dosing for these milder scenarios, yet anecdotally many patients practice this milder stress dosing.

Growth

Introduction

Normal growth in childhood and adolescence is a marker of overall health status and can be viewed as a sign of normal internal (genetics, hormones and signaling pathways) and external (nutrition, psychological stimuli) influences. Growth is in part predetermined by the genetic potential for adult height attainment and therefore growth must be evaluated in this context. Growth in humans can be divided into four distinct phases (1) fetal growth (2) Infant growth (3) Childhood growth and (4) adolescent growth. Each phase having its own normal growth trajectory (velocity) and each having its own distinct influences (nutrition in early growth and hormones in later growth) (Touwslager et al. 2011a, b). Fetal growth is the most rapid growth phase in human development with rates up to 20 cm in the second trimester and 12 cm in the third trimester. This rapid growth is supported by maternal fetal circulation and fetal nutrition. Hormonal influences on fetal growth include IGF I and II and insulin. Postnatally growth slows with infants attaining an average of 25 cm in the first year of life, 10–12 cm in the second year of life, 6–8 cm in the third year of life, and then decreasing to 4–8 cm/year in the childhood growth period until the onset of puberty. Infant linear growth rates change over the first 2 years of life with infants crossing percentiles to settle on the percentile more closely correlating with the final adult height. Thus, Infants may cross one to three major percentiles during these first 2 years as they transition from intrauterine and early post-natal nutrition as the main regulators of growth to

“find their growth curve” consistent with their genetic potential (Smith et al. 1976; Rose et al. 2005). Control of growth during this period seems to move away from the major influence of nutrition with an increasing emphasis on hormonal control of growth, specifically the growth hormone-insulin like growth factor I axis and thyroid hormone. There is a normal deceleration in growth velocity before the onset of the pubertal growth spurt. The pubertal growth spurt results from an increase in GH-IGFI axis due to the stimulation of the axis by the subsequent rise in sex steroids (Giustina et al. 1997; Coutant et al. 2004). In early puberty (tanner 2) girls will attain a peak growth velocity of 8 cm/year while boys attain a higher peak velocity of 10 cm/year but at a later pubertal stage (Tanner 3–4). Linear growth is completed upon fusion of the epiphyseal growth plates under the influence of estrogen action on the estrogen receptor (Smith et al. 1994; Morishima et al. 1995).

Clinical Evaluation of Growth

Clinically growth velocity is followed longitudinally to detect growth failure and investigate for potential pathology. It requires accurate sequential growth measurements and charting of growth on appropriate growth charts to prevent unnecessary investigation and evaluation in children with a normal growth velocity. Prior to 2010 the CDC/NCHS growth charts (Kuczmarski et al. 2002) were used almost exclusively to track childhood growth. In 2006 and 2007 growth charts derived from the World Health Organization (WHO) Multicenter Growth Reference Study (MGRS) were published to represent normal growth of a multi-national cohort in optimal growth conditions (WHO Multicentre Growth Reference Study Group 2006; Natale and Rajagopalan 2014).

In 2010 the WHO growth charts were adapted for Canadian use and were endorsed by The Canadian Pediatric Endocrine group (CPEG) and Dieticians of Canada and the Canadian Pediatric Society, the college of family physicians of Canada, Community health nurses of

Canada and the public health agency of Canada. In 2014 due to concerns from Canadian practitioners regarding deficiencies in these new growth charts (particularly the inability to plot weight for age after age 10 years) a CPEG working group designed a new version of the WHO growth charts for use in Canada (Lawrence et al. 2015). These new growth charts use the same individual growth data used to create previous charts but includes the addition of weight for age in older children and a clear shading system to identify children at high risk of growth failure (Rodd et al. 2014; Lawrence et al. 2013). These current growth charts are available for public access at <http://www.whogrowthcharts.ca/>. Separate growth charts are available for children with specific syndromes affecting growth including Trisomy 21, Turner Syndrome, Williams Syndrome and Achondroplasia. For children with trisomy 21 updated growth charts have recently been published (Zemel et al. 2015). New growth charts have also been derived for children with Prader Willi syndrome (not on growth hormone) (Butler et al. 2015) and 22 q.11 deletion syndrome (DiGeorge) (Tarquinio et al. 2012).

Short stature is defined as a height which falls below 2 SDs from the mean for age, sex and population (Cohen et al. 2008). Short stature can be related to familial growth potential, failure of infants born small for gestational age to achieve adequate catch up growth, failure to achieve pubertal growth acceleration at the average age of puberty (constitutional delay), chronic illness, hormone deficiency (thyroid hormone and growth hormone) or excess (cortisol). Evaluation of the rate of growth (using growth chart percentiles) will help to distinguish the short but normally growing child from the child who is failing to grow. In addition, a recent study has reported that children born small for gestational age are more likely to have poor catch up growth (and be stunted in growth at 5 years) if the mother has short stature, there was inadequate maternal gestational weight gain, with a much higher risk of stunting in infants born to mothers who smoked in pregnancy and had poor gestational weight gain (Xie et al. 2016).

Guidelines outlining the child requiring further investigation related to short stature have been outlined in recent reviews (Cohen 2014; Allen and Cuttler 2013; Murray et al. 2016). In brief, children who have severe short stature (height >3 SD below the mean), a height percentile significantly discrepant from mid parental height or less than the 1% for age, or growth failure as determined by a velocity more than 1.5–2SD below the mean (less than the 10% for bone age) with a resultant crossing of percentiles on a growth chart require further investigation. Other indications include other multiple pituitary hormone deficiencies, signs of an intracranial lesion, and neonatal signs and symptoms of growth hormone deficiency (hypoglycemia, characteristic facies).

Investigations in Children with Growth Failure

Children who have been identified as having an abnormal growth pattern require evaluation of the multiple components regulating growth. A thorough history will identify children with intra-uterine growth restriction due to placental insufficiency, maternal malnutrition or illness in particular with the determination of weight, length and head circumference at birth. Developmental history and previous medical history can identify children with short stature related to a syndrome (trisomy 21, Russel Silver syndrome, Noonan's syndrome) or a poorly controlled chronic medical illness (cardiac, renal, pulmonary). Family history including parental heights and age of attainment of puberty guides in the determination of a component of familial short stature or constitutional delay of growth and puberty. Baseline biochemical evaluations include creatinine, urea and electrolytes, liver transaminases, complete blood count, transglutaminases and ESR, and thyroid hormone. Skeletal maturity is determined from a bone age (radiograph of the left hand and wrist) which is delayed in children with constitutional delay of growth and puberty, endocrinopathies, nutritional deficiencies and chronic illness (Martin et al. 2011a, b).

Children on inhaled corticosteroids and stimulant medications have been reported to have a slower growth velocity than expected. The impact of inhaled steroids on adult height seems to be dependent on the age at initiation of treatment and the dose of inhaled steroid. The overall effect on the final adult height however appears minimal with the benefits of treatment outweighing risks of therapy (Kapadia et al. 2016).

A random sampling of growth hormone is not clinically useful as growth hormone is secreted in a pulsatile manner with peak levels being reached overnight and in the early morning hours. Therefore, in children who have growth failure and who do not have evidence of another condition a provocative growth hormone testing is warranted. An insulin like growth factor (IGF)—1 or IGF binding protein 3 level can be a useful screen but IGF deficiency is nonspecific as IGF can be affected by nutrition, intercurrent or chronic illness, and physiological age in addition to growth hormone level and function.

Growth Hormone

Growth hormone deficiency is a rare disease in childhood with a reported prevalence in the UK of 1 in 4000. (National Institute for Health and Care Excellence [NICE] Guidelines on the use of growth hormone 2010). Complete or near complete growth hormone deficiency is clinically evident with significant growth failure. In children who have other multiple pituitary deficiencies it is also a more likely diagnosis for growth failure. However, it is more difficult to distinguish children with more mild or partial forms of growth hormone deficiency with those children who have short stature but normal growth hormone. A recent review examining the controversies in growth hormone deficiency diagnosis and treatment in children (Murray et al. 2016) reports on the suboptimal performance of current growth hormone testing and the clinical variability in treatment. To improve the clinical utility of provocative testing, children are selected for testing with high pretest probability of test failure. These include the children with significant growth fail-

ure (described above) and/or children with other pituitary hormone deficiencies or intracranial pathology. Stimulation of growth hormone secretion can be performed with arginine, glucagon, clonidine, GHRH, levodopa, pyridostigmine, insulin, sleep and exercise. Due to superior performance and lower side effects of testing, glucagon and arginine stimulation are the most common test used. Due to poor reproducibility and false positive rates (between 8.0% and 23.7% dependent on the testing method and cut off values used (Bellone et al. 1996; Carel et al. 1997; Hilczer et al. 2006), failure of two separate provocative tests is needed for the diagnosis. In children with intracranial pathology only one stimulation test may be required. Sex steroid priming for growth hormone testing often is recommended as it increases peak growth hormone concentrations and reduces false positive rates (Marin et al. 1994). In addition, obesity reduces growth hormone peak concentration in some studies resulting in higher rates of false positives in this population (Stanley et al. 2009). In Canada growth hormone is currently licensed for use in children with growth hormone deficiency (as determined by auxological and stimulation test data), Turner syndrome, chronic renal insufficiency, small for gestational age infants who fail to attain catch up growth, and idiopathic short stature (ISS). Due to the lack of strong evidence for significant height gain and the potential for harm the treatment of ISS is controversial (Cohen 2014). A recent small pilot trial examining the utility of treatment of boys with ISS at a later pubertal stage suggest there may be benefit to short term (1 year) GH therapy to increase adult height above predicted adult height (Rothenbuhler et al. 2015).

Recent reports from France have suggested children treated with growth hormone have an increased mortality due to stroke and cancer (Swerdlow et al. 2002; Carel et al. 2012; Poidvin et al. 2014). However, recent reports using national cohort data and matched untreated controls did not find an association of growth hormone treatment with mortality (Berglund et al. 2015). In addition, the pediatric endocrine society has published a recent report summing the

evidence of cancer risk in children on growth hormone therapy. They report no association in low malignancy risk children, for an increased malignancy risk with the use of growth hormone. Data at present is insufficient to report on the risks in children with previous cancer or high cancer risk due to familial risk and the cautious use of growth hormone with surveillance is proposed for these children who are growth hormone deficient (Raman et al. 2015).

Recombinant growth hormone currently is supplied only as an injectable medication which due to a short half-life requires daily or every other day dosing. Due to the pain of injection and the cumbersome daily routine, multiple alternative treatment strategies are being evaluated. A recent review article details the advances in the field that are covered in brief in this chapter (Cai et al. 2014). These include longer acting growth hormone agents which may be dosed weekly or even monthly due to their combination with Zinc complexes, microspheres or hydrogels. In addition to extending the half-life, recent research is focused on alternative delivery systems including intranasal delivery, transdermal delivery. Finally needle free devices which inject the drug subcutaneously through gas pressure have been launched by several drug companies but pain, access and cost have prevented them from reaching most clinical practices.

Other Therapies to Increase Final Adult Height

Other potential treatments for short stature focus on delaying growth plate closure or stimulating an earlier growth spurt (in boys with CDGP). The evidence behind the additive benefit of these therapies is weak with many studies showing conflicting results. A recent review of alternative therapies discusses in more depth the evidence behind their use (Wit and Oostdijk 2015).

The use of low dose testosterone in boys with CDGP appears to increase final adult height without advancing closure of the growth plates (Palmert and Dunkel 2012). Studies using the anabolic steroid oxandrone have suggested an

increase in growth velocity however no studies have reported effects on final adult height in children with ISS (Albanese et al. 1994; Schroor et al. 1995; Dunkel 2011). A moderate increase in final adult height has been reported in girls with Turners syndrome when oxandrone is used in combination with growth hormone therapy with no significant side effects (Sas et al. 2014; Freriks et al. 2013).

Gonadotropin- releasing hormone agonists (GNRH i.e. Lupron) have been tried to prolong the period of growth by delaying skeletal maturation in children with typical pubertal timing with little to no benefit to final adult height (Yanovski et al. 2003; van Gool et al. 2007). The addition of GNRH to GH in children who are growth hormone deficient may be beneficial to children who remain significantly short at the time of puberty despite growth hormone treatment (Mericq et al. 2000; Saggese et al. 2001; Mul et al. 2001).

Aromatase inhibitors have been trialed in boys with short stature to delay the estrogen effects on skeletal maturation. Currently it is considered an experimental treatment as only few trials report outcome data on adult height with little benefit while safety concerns regarding its use remain (Wickman et al. 2001; Mauras et al. 2008; Wit et al. 2012).

Puberty

Introduction

Puberty can be defined as the period over which children attain secondary sexual characteristics and reproductive capacity. Pubertal timing varies between individuals and is influenced by adiposity and nutrition, general health, metabolism, and is also influenced by genetics, and environment. This chapter will review recent literature on the etiology, diagnosis, and treatment of disorders of puberty.

Pubertal Control

The onset of puberty occurs when the hypothalamus increases its pulsatile secretion of GnRH which in turn stimulates the pulsatile secretion of

pituitary hormones LH and FSH which in turn stimulate gonadal maturation and sex hormone secretion. The inciting event for the increase in pulsatile GnRH has been difficult to elucidate however the last decade has resulted in a number of important discoveries (Lomniczi et al. 2013). Human and non-human primate studies have uncovered a complex integration of signaling pathways including the expression of KISS1R (Seminara 2007; Seminara et al. 2003), TAC3, TAC3R and LEPR genes (Lomniczi et al. 2013). Importantly the first report of a monogenetic disorder of puberty was published revealing mutations in the gene MKRN3 resulting in familial central precocious puberty (Abreu et al. 2013). Pubertal delay has been associated with increased levels of FGF21 (a growth factor which increases with fasting) by inhibiting the kisspeptin stimulatory pathway (Owen et al. 2013).

Precocious Puberty

Precocious puberty is traditionally defined as breast development or testicular growth (testicular size >3 cc) prior to 8 years and 9 years for girls and boys respectively. Recently longitudinal cohort data including physical examination in girls has reported up to 23% of African American, 15% of Hispanic and 10% of Caucasian girls will have breast development begin between ages 7–8 years (Biro et al. 2010). There is some evidence to suggest that the average onset of puberty in boys (between ages 8 and 9) is also lowering (Herman-Giddens et al. 2012). Due to conflicting reports suggesting up to 13% of girls with puberty at 7–8 years (Caucasian) or 6–7 years (African American) have pathological etiologies for pubertal onset (Midyett et al. 2003) these newer lower age cut-offs have been slow to be adapted by clinical practice.

Precocious puberty can be divided into two main etiologies. Central precocious puberty (CPP) is physiologically identical to the normally timed pubertal process, only it occurs at an abnormally early age. Peripheral precocious puberty (PPP) occurs due to an abnormal secretion of sex hormones either from the gonads or from a sex hormone secreting tumor. The most common diagnosis for CPP in girls is idiopathic whereas it is more often found to be due to pitu-

itary or hypothalamic pathology in boys (Chen and Eugster 2015). PPP is rare with progressive PPP often due to a genetic gain of function of the stimulation pathways of the gonads, resulting in McCune Albright in girls and male limited familial precocious puberty (testotoxicosis) in males.

Traditionally central precocious puberty (CPP) is diagnosed with a GnRHa stimulation test with post stimulated levels of LH (and occasionally FSH) being within the pubertal range. Originally these stimulation tests measured LH and FSH out to 24 h with more recent testing protocols measuring at 30, 60, 90 (and occasionally 120 min). Newer evidence suggests precocious puberty may be diagnosed with a single post stimulation level of LH at 30 min (captures >95% of positive cases) (Yazdani et al. 2012; Chi et al. 2012). This change in clinical practice would significantly change the resources and time required to perform this testing and presumably, improve the patient experience. Treatment of central precocious puberty has seen recent advances in the methods of treatment available. Currently depot Lupron (GnRHa) is available in monthly and every 3 monthly injections. Recent evidence has shown that every 3 month injections have equal effectiveness in pubertal suppression to monthly treatment (Fuld et al. 2011; Lee et al. 2014). More recently the final report from a phase 3 multicenter trial of once yearly subcutaneous Histrelin (GnRHa) has shown good effectiveness and safety profiles and improves overall adult height in children with central precocious puberty (Silverman et al. 2015). Indeed, a follow up study reported that a single implant was effective in suppressing puberty for up to 2 years in girls with CPP (Lewis et al. 2013). A 6-month depot injection triptorelin is currently in clinical trials and may provide a long term therapeutic option for those not wanting to undergo the subcutaneous implant ([clinicaltrials.gov](https://clinicaltrials.gov/NCT01467882) NCT01467882).

Pubertal Delay

Pubertal Delay is defined as an absence of secondary sexual characteristics (testicular growth to >3 cc or breast bud development) by age

13 in girls and 14 in boys. The single most common etiology for pubertal delay is constitutional delay of growth and development and is a diagnosis of exclusion after investigations fail to determine another etiology, with spontaneous onset of puberty (Palmert and Dunkel 2012). This is considered to be a normal variant of development which does not require treatment. The underlying etiology of the delay in pubertal onset is still unclear however, there appears to be a genetic component. Constitutional delay must be differentiated from permanent hypogonadotropic hypogonadism (central pituitary or hypothalamic deficiency as is seen in Kallmans syndrome), transient hypogonadotropic hypogonadism (often the result of underweight or high physical stress including chronic disease states such as Crohn's disease (DeBoer and Denson 2013)), and primary gonadal failure. It is difficult to distinguish CDGP and hypogonadotropic hypogonadism by any laboratory test. Newer evidence suggests that serum inhibin B levels may be able to distinguish between CDGP and HH (Binder et al. 2015; Harrington and Palmert 2012). Treatment of HH (or severe CDGP) is aimed at developing secondary sexual characteristics and growth. Adolescents with permanent HH will require long term hormone replacement therapy for optimal bone mineral accrual and bone health and for cardiovascular health. Estrogen dosing in girls and testosterone dosing in boys is aimed to mimic the physiologic progression of puberty gradually increasing doses over time. There is some evidence to suggest that the use of the transdermal estrogen patch has less impact on the growth hormone—IGF1 axis and may permit improved linear height attainment (Phelan et al. 2012). New evidence in girls with Turner syndrome suggests the earlier initiation of estrogen at low doses in childhood (as early as age 5), and escalating to pubertal induction doses at age 12 years normalizes the tempo of puberty and improves linear growth outcome (Quigley et al. 2014). The introduction of progesterone late in the course (often after the first spontaneous pelvic bleed) provides safe regular endometrial shedding.

Environmental Exposures and Puberty

A developing area in the investigation of precocious or delayed puberty is the potential influence of environmental exposure. Studies have found some conflicting results on the influence of environmental exposure on pubertal timing in part due to studies being limited to case control investigation many requiring recall of the participant/family for exposure risk. Sample sizes remain small but it is an interesting and novel area of investigation in the field of puberty. Elevated Phalates (a known anti-androgen) have been associated with constitutional delay of growth and puberty (Xie et al. 2015; Ferguson et al. 2014). Phalates belong to a group of plasticizers and have been shown to be ingested, inhaled and absorbed by exposed individuals (Koch et al. 2011; Wittassek et al. 2011).

Thyroid Disease

Introduction

Thyroid disease in children can be congenital or acquired. Acquired thyroid disease can result in hypothyroidism or hyperthyroidism. Acquired hypothyroidism is classified as primary, or secondary. Primary thyroid disease results from defects in the thyroid gland itself while secondary hypothyroidism results from impaired signaling of the thyroid gland due to diminished thyroid stimulating hormone (TSH) release from the pituitary gland or thyrotropin-releasing hormone (TRH) from the hypothalamus. While the diagnosis and initial treatment of congenital hypothyroidism is obviously unique to pediatric age range, the management of acquired thyroid disease is quite similar in children and adults not withstanding some unique pediatric issues.

Congenital Hypothyroidism

Congenital hypothyroidism occurs in 1 in 2000 to 1 in 4000 newborns with some geographical variation. Recent studies show an increasing

incidence possibly due to lower newborn screening cutoffs and identification of milder cases. There is a female predominance. A prompt diagnosis and initiation of treatment with levothyroxine is important as delayed treatment results in a lower intelligence quotient identified by school aged testing. While the aim is to start treatment as quickly as possible, the goal of most programs is to have treatment initiated by 2 weeks of age. Newborn screening programs initiated in the 1970s have successfully prevented severe intellectual disability in this population. Most screening programs measure TSH levels alone, while others measure thyroxine (T4) in combination with TSH. Congenital hypothyroidism is diagnosed by a TSH elevated above a defined threshold such as 20 mU/L measured ideally after 48 h of age. The timing of the screen is important, as there is an initial surge in TSH in the first 24 h of life. Thresholds have been adjusted, and generally lowered, over time. T4 if measured will be low. Most algorithms recommend confirmatory serum testing after an abnormal screen. If the TSH on newborn screen is >40 mU/L then treatment should be initiated once the confirmatory testing is drawn to avoid a delay in treatment awaiting the verifying results to be reported (Rose et al. 2006).

Congenital hypothyroidism results from thyroid dysgenesis such as agenesis, hypoplasia or ectopy of the gland. Thyroid hormone synthesis or secretion defects can also cause congenital hypothyroidism. Congenital hypothyroidism is generally permanent but transient congenital hypothyroidism may result from several etiologies including iodine deficiency, iodine exposure, transfer of maternal antibodies, or maternal antithyroid drug transfer. Central or secondary hypothyroidism may also present in the newborn period as hypopituitarism often with involvement of other pituitary axes deficiencies. Screening programs generally will not detect central hypothyroidism so a clinical suspicion is often required in order to diagnose these infants.

Most children are diagnosed from newborn screening programs and are asymptomatic at birth. If undiagnosed or untreated, symptoms can

include lethargy, a protruding large tongue, large fontanel, hoarse cry, poor feeding, myxedema, hypotonia, prolonged jaundice, hypothermia, and umbilical hernia.

A recent update on Congenital Hypothyroidism was published jointly by The American Academy of Pediatrics, the American Thyroid Association, and the Pediatric Endocrine Society (formerly known as the Lawson Wilkins Pediatric Endocrine Society) in 2006 (Rose et al. 2006). The report includes a useful algorithm for screening and follow up. Infants with abnormal screens require prompt assessment with a history and physical examination. History should include queries of maternal thyroid disease. Treatment should be initiated promptly after confirmatory serum testing is drawn. The recommended initial dosage of levothyroxine is 10–15 µg/kg once daily. Due to the instability of levothyroxine when mixed in suspension, pills and not a suspension should be used. Repeat T4 and TSH should be drawn 2–4 weeks after initiation of treatment. The aim of treatment is normalization of TSH within 1 month. The normal reference range for serum TSH at 2–6 weeks of age drops to 1.7–9.1 mU/L. Many will simply follow TSH to monitor treatment but if FT4 is measured it should be in the upper range of normal. The 2006 update suggests serum monitoring every 1–2 months in the first 6 months, 3–4 months from 6 months to 3 years old, and then every 6–12 months. However, if the monitoring is stable, some practices will monitor less frequently, every 6 months, after 1–2 years of age. The report comments that thyroid uptake scans or ultrasounds are optional diagnostic studies to help further identify etiology but are not mandatory. The use of diagnostic imaging is controversial but is considered important by some practitioners. If done, imaging should not significantly delay treatment (Rose et al. 2006).

In an often-quoted relatively recent study, initial dosing in the higher range of 14.5 µg/kg vs. 10.9 µg/kg resulted in a quicker normalization of FT4 and TSH levels. Further follow up revealed higher full scale IQ scores in the higher dosing group. Verbal and performance IQ scores, however, did not differ (Selva et al. 2005, 2002).

The possibility of transient congenital hypothyroidism can be considered if imaging was performed and there's no evidence of ectopic or absent thyroid, and/or initial screening revealed a TSH <50 mU/L, and/or there has been no further elevation in TSH requiring an increase in the L-thyroxine dose after the initiation of treatment. However, a trial of discontinuing treatment should wait until the child is 3 years of age to limit the risk of developmental effects of stopping therapy if the hypothyroidism is in fact permanent. TSH and FT4 levels should be performed 30 days after stopping therapy. An elevation of TSH and low FT4 would confirm permanent hypothyroidism and therapy should be restarted.

Acquired Hypothyroidism

Acquired hypothyroidism in children is similarly managed as in adults. The most common cause of acquired hypothyroidism in children is autoimmune disease, commonly known as chronic lymphocytic thyroiditis or Hashimoto's thyroiditis. As confirmed by recent ATA guidelines, all children with overt hypothyroidism should be treated with levothyroxine replacement to normalize biochemistry (Jonklaas et al. 2014). Children can be diagnosed at all ages but there is a peak in adolescence with a female predominance. While children develop similar symptoms and signs of hypothyroidism as adults, the additional clinical parameters in children are poor linear growth and delayed pubertal development. Conversely, profound elevations in TSH can lead to precocious puberty, perhaps due to cross reactivity of the alpha subunits of TSH and the gonadotropin receptors, but this is rare.

Dosing requirements of levothyroxine in children are age dependent. Young toddlers require 4–6 µg/kg per day, adolescents require 2–4 µg/kg per day and then transition to adult requirements of 1.6 µg/kg per day (Jonklaas et al. 2014; Lafranchi 1992). Aim of treatment is normal TSH and Free T4 levels.

Much of the recent controversy around hypothyroidism revolves around treatment of subclinical hypothyroidism, defined as mildly elevated

TSH levels but normal FT4 levels. Recent literature indicates that a large majority of these children with TSH levels between 5.5 and 10 mU/L will have resolution of their biochemistry without treatment (Radetti et al. 2012; Lazar et al. 2009). There is also no evidence of negative clinical consequences without treatment in this group. While still controversial, treatment is therefore not generally recommended in this group (Jonklaas et al. 2014).

The recommended treatment of hypothyroidism is levothyroxine. Some patients and practitioners advocate for treatment with liothyronine (T3). There are some controversial studies in adults but in the recent 2014 guidelines, T3 treatment is not routinely recommended in adults with hypothyroidism. There is no good evidence of its use in children.

Acquired Hyperthyroidism

The most common cause of hyperthyroidism in children is Grave's Disease, or autoimmune hyperthyroidism. Other causes include toxic nodules, multinodular goiters, and subacute thyroiditis but these are much less common than Grave's disease in children. Thyrotoxicosis symptoms are similar in children and adults although children tend to tolerate the symptoms better. Symptoms include hyperactivity, tremor, tachycardia, palpitations, heat intolerance, and weight loss. In children, hyperthyroidism can also cause increased linear growth. Ophthalmopathy is less common in children than adults and if present has a greater likelihood of resolution with treatment (Rivkees et al. 1998).

Investigations in hyperthyroidism reveal suppressed TSH and elevated T4 and T3 levels. In Grave's disease TSH receptor antibodies or thyroid stimulating immunoglobulins are elevated.

Treatment options include anti-thyroid medications, radioactive iodine 131 (I131), and thyroidectomy. Anti-thyroid medications are generally considered first line therapy in children. However, in older children, above age 10 years, some will consider I131 as a first line alternative. Under age 5 years, I131 is generally

not considered an option. Surgery should be considered in centers with highly skilled and experienced surgeons due to its complexity (Rivkees 2014; Lee and Hwang 2014).

Reports on remission rates for children on anti-thyroid medications vary in different studies but appear to be less than 30% after two years of treatment. Many advocate for definitive therapy with radioactive I131 or surgery if there is no remission after a couple years of medical therapy. One of the more recent studies looking at remission rates in children on medical therapy, showed 20% remission after 4 years, 37% after 6 years, 45% after 8 years, and 49% after 10 years (Leger et al. 2012). While these are lower early remission rates than some of the older studies, the study does advocate for a benefit of longer-term treatment. High TSH receptor antibodies, younger age and large goiter size are historically described as indicators of poor likelihood of remission and increased relapse. However, the reliability of these predictors is variable and their usefulness in clinical decision making is debatable (Lee and Hwang 2014; Kamath et al. 2012).

An important recent update in the management of hyperthyroidism in children is the recent statements warning against using propylthiouracil (PTU) in children. This followed reports of severe and aggressive hepatotoxicity in children receiving PTU with some requiring transplant (Karras et al. 2012; Rivkees and Szarfman 2010). The FDA has placed a black box label warning against the use of PTU in children. Therefore methimazole or carbimazole is the recommended antithyroid medication in children and PTU should not be used except in special circumstances such as short-term use in patients with adverse reactions to methimazole preparing for radioactive I131 or surgery (Rivkees 2014; Lee and Hwang 2014).

References

Abreu AP, Dauber A, Macedo DB, Noel SD, Brito VN, Gill JC, et al. Central precocious puberty caused by mutations in the imprinted gene MKRN3. *N Engl J Med.* 2013;368(26):2467–75. PubMed PMID:

23738509. Pubmed Central PMCID: PMC3808195. Epub 2013/06/07. eng
- Addison T. On the constitutional and local effects of disease of the supra-renal capsules. Special ed. Birmingham: Classics of Medicine Library; 1980.
- Albanese A, Kewley GD, Long A, Pearl KN, Robins DG, Stanhope R. Oral treatment for constitutional delay of growth and puberty in boys: a randomised trial of an anabolic steroid or testosterone undecanoate. *Arch Dis Child.* 1994;71(4):315–7. PubMed PMID: 7979523. Pubmed Central PMCID: PMC1030008. Epub 1994/10/01. eng
- Allen DB, Cuttler L. Clinical practice. Short stature in childhood—challenges and choices. *N Engl J Med.* 2013;368(13):1220–8. PubMed PMID: 23534561. Epub 2013/03/29. eng
- Bellone J, Valetto MR, Aimaretti G, Segni M, Volta C, Cardinale G, et al. Effects of phenylalanine, histidine, and leucine on basal and GHRH-stimulated GH secretion and on PRL, insulin, and glucose levels in short children. Comparison with the effects of arginine. *J Pediatr Endocrinol Metab.* 1996;9(5):523–31. PubMed PMID: 8961128. Epub 1996/09/01. eng
- Berglund A, Gravholt CH, Olsen MS, Christiansen JS, Stochholm K. Growth hormone replacement does not increase mortality in patients with childhood-onset growth hormone deficiency. *Clin Endocrinol.* 2015;83(5):677–83. PubMed PMID: 26147754. Epub 2015/07/07. eng
- Binder G, Schweizer R, Haber P, Blumenstock G, Braun R. Accuracy of endocrine tests for detecting hypogonadotropic hypogonadism in girls. *J Pediatr.* 2015;167(3):674–8. e1. PubMed PMID: 26095287. Epub 2015/06/23. eng
- Biro FM, Galvez MP, Greenspan LC, Succop PA, Vangeepuram N, Pinney SM, et al. Pubertal assessment method and baseline characteristics in a mixed longitudinal study of girls. *Pediatrics.* 2010;126(3):e583–90. PubMed PMID: 20696727. Pubmed Central PMCID: PMC4460992. Epub 2010/08/11. eng
- Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, et al. Diagnosis and treatment of primary adrenal insufficiency: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab.* 2016;101(2):364–89. PubMed PMID: 26760044. Pubmed Central PMCID: PMC4880116. Epub 2016/01/14. eng
- Butler MG, Lee J, Manzardo AM, Gold JA, Miller JL, Kimonis V, et al. Growth charts for non-growth hormone treated Prader-Willi syndrome. *Pediatrics.* 2015;135(1):e126–35. PubMed PMID: 25489013. Pubmed Central PMCID: PMC4279067. Epub 2014/12/10. eng
- Cai Y, Xu M, Yuan M, Liu Z, Yuan W. Developments in human growth hormone preparations: sustained-release, prolonged half-life, novel injection devices, and alternative delivery routes. *Int J Nanomedicine.* 2014;9:3527–38. PubMed PMID: 25114523. Pubmed Central PMCID: PMC4122423. Epub 2014/08/13. eng

- Carel JC, Tresca JP, Letrait M, Chaussain JL, Lebouc Y, Job JC, et al. Growth hormone testing for the diagnosis of growth hormone deficiency in childhood: a population register-based study. *J Clin Endocrinol Metab.* 1997;82(7):2117–21. PubMed PMID: 9215281. Epub 1997/07/01. eng
- Carel JC, Ecosse E, Landier F, Meguellati-Hakkas D, Kaguélidou F, Rey G, et al. Long-term mortality after recombinant growth hormone treatment for isolated growth hormone deficiency or childhood short stature: preliminary report of the French SAGhE study. *J Clin Endocrinol Metab.* 2012;97(2):416–25. PubMed PMID: 22238382. Epub 2012/01/13. eng
- Chen M, Eugster EA. Central precocious puberty: update on diagnosis and treatment. *Paediatr Drugs.* 2015;17(4):273–81. PubMed PMID: 25911294. Epub 2015/04/26. eng
- Chi CH, Durham E, Neely EK. Pharmacodynamics of aqueous leuprolide acetate stimulation testing in girls: correlation between clinical diagnosis and time of peak luteinizing hormone level. *J Pediatr.* 2012;161(4):757–9. e1. PubMed PMID: 22809662. Epub 2012/07/20. eng
- Cohen LE. Idiopathic short stature: a clinical review. *JAMA.* 2014;311(17):1787–96. PubMed PMID: 24794372. Epub 2014/05/06. eng
- Cohen P, Rogol AD, Deal CL, Saenger P, Reiter EO, Ross JL, et al. Consensus statement on the diagnosis and treatment of children with idiopathic short stature: a summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop. *J Clin Endocrinol Metab.* 2008;93(11):4210–7. PubMed PMID: 18782877. Epub 2008/09/11. eng
- Coutant R, de Casson FB, Rouleau S, Douay O, Mathieu E, Gatelais F, et al. Divergent effect of endogenous and exogenous sex steroids on the insulin-like growth factor I response to growth hormone in short normal adolescents. *J Clin Endocrinol Metab.* 2004;89(12):6185–92. PubMed PMID: 15579776. Epub 2004/12/08. eng
- DeBoer MD, Denson LA. Delays in puberty, growth, and accrual of bone mineral density in pediatric Crohn's disease: despite temporal changes in disease severity, the need for monitoring remains. *J Pediatr.* 2013;163(1):17–22. PubMed PMID: 23522861. Pubmed Central PMCID: PMC3692567. Epub 2013/03/26. eng
- Dunkel L. Treatment of idiopathic short stature: effects of gonadotropin-releasing hormone analogs, aromatase inhibitors and anabolic steroids. *Horm Res Paediatr.* 2011;76(Suppl 3):27–9. PubMed PMID: 21912156. Epub 2011/09/23. eng
- Ferguson KK, Peterson KE, Lee JM, Mercado-Garcia A, Blank-Goldenberg C, Tellez-Rojo MM, et al. Prenatal and peripubertal phthalates and bisphenol A in relation to sex hormones and puberty in boys. *Reprod Toxicol (Elmsford, NY).* 2014;47:70–6. PubMed PMID: 24945889. Pubmed Central PMCID: PMC4117729. Epub 2014/06/20. eng
- Freriks K, Sas TC, Traas MA, Netea-Maier RT, den Heijer M, Hermus AR, et al. Long-term effects of previous oxandrolone treatment in adult women with Turner syndrome. *Eur J Endocrinol.* 2013;168(1):91–9. PubMed PMID: 23076845. Epub 2012/10/19. eng
- Fuld K, Chi C, Neely EK. A randomized trial of 1- and 3-month depot leuprolide doses in the treatment of central precocious puberty. *J Pediatr.* 2011;159(6):982–7. e1. PubMed PMID: 21798557. Epub 2011/07/30. eng
- Giustina A, Scalvini T, Tassi C, Desenzani P, Poiesi C, Wehrenberg WB, et al. Maturation of the regulation of growth hormone secretion in young males with hypogonadotropic hypogonadism pharmacologically exposed to progressive increments in serum testosterone. *J Clin Endocrinol Metab.* 1997;82(4):1210–9. PubMed PMID: 9100598. Epub 1997/04/01. eng
- van Gool SA, Kamp GA, Visser-van Balen H, Mul D, Waelkens JJ, Jansen M, et al. Final height outcome after three years of growth hormone and gonadotropin-releasing hormone agonist treatment in short adolescents with relatively early puberty. *J Clin Endocrinol Metab.* 2007;92(4):1402–8. PubMed PMID: 17284626. Epub 2007/02/08. eng
- Harrington J, Palmert MR. Clinical review: distinguishing constitutional delay of growth and puberty from isolated hypogonadotropic hypogonadism: critical appraisal of available diagnostic tests. *J Clin Endocrinol Metab.* 2012;97(9):3056–67. PubMed PMID: 22723321. Epub 2012/06/23. eng
- Herman-Giddens ME, Steffes J, Harris D, Slora E, Hussey M, Dowshen SA, et al. Secondary sexual characteristics in boys: data from the Pediatric Research in Office Settings Network. *Pediatrics.* 2012;130(5):e1058–68. PubMed PMID: 23085608. Epub 2012/10/23. eng
- Hilczer M, Smyczynska J, Lewinski A. Limitations of clinical utility of growth hormone stimulating tests in diagnosing children with short stature. *Endocr Regul.* 2006;40(3):69–75. PubMed PMID: 17100548. Epub 2006/11/15. eng
- Joint LWPES/ESPE CAH Working Group. Consensus statement on 21-hydroxylase deficiency from the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology. *J Clin Endocrinol Metab.* 2002;87(9):4048–53. PubMed PMID: 12213842. Epub 2002/09/06. eng
- Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, et al. Guidelines for the treatment of hypothyroidism: prepared by the american thyroid association task force on thyroid hormone replacement. *Thyroid.* 2014;24(12):1670–751. PubMed PMID: 25266247. Pubmed Central PMCID: PMC4267409. Epub 2014/10/01. eng
- Kamath C, Adlan MA, Premawardhana LD. The role of thyrotrophin receptor antibody assays in graves' disease. *J Thyroid Res.* 2012;2012:525936. PubMed PMID: 22577596. Pubmed Central PMCID: PMC3345237. Epub 2012/05/12. eng

- Kapadia CR, Nebesio TD, Myers SE, Willi S, Miller BS, Allen DB, et al. Endocrine effects of inhaled corticosteroids in children. *JAMA Pediatr.* 2016;170(2):163–70. PubMed PMID: 26720105. Epub 2016/01/01. eng
- Karras S, Memi E, Kintiraki E, Krassas GE. Pathogenesis of propylthiouracil-related hepatotoxicity in children: present concepts. *J Pediatr Endocrinol Metab.* 2012;25(7–8):623–30. PubMed PMID: 23155684. Epub 2012/11/20. eng
- Koch HM, Wittassek M, Bruning T, Angerer J, Heudorf U. Exposure to phthalates in 5–6 years old primary school starters in Germany—a human biomonitoring study and a cumulative risk assessment. *Int J Hyg Environ Health.* 2011;214(3):188–95. PubMed PMID: 21371937. Epub 2011/03/05. eng
- Kuczumski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, et al. 2000 CDC growth charts for the United States: methods and development. *Vital Health Stat 11.* 2002;246:1–190. PubMed PMID: 12043359. Epub 2002/06/05. eng
- Lafranchi S. Thyroiditis and acquired hypothyroidism. *Pediatr Ann.* 1992;21(1):29–39. PubMed PMID: 1549397. Epub 1992/01/01. eng
- Lawrence S, Cummings E, Chanoine JP, Metzger DL, Palmert M, Sharma A, et al. Canadian Pediatric Endocrine Group extension to WHO growth charts: why bother? *Paediatr Child Health.* 2013;18(6):295–7. PubMed PMID: 24421695. PubMed Central PMCID: PMC3680249. Epub 2014/01/15. eng
- Lawrence S, Cummings E, Chanoine JP, Metzger D, Palmert M, Sharma A, et al. Use of growth charts in Canada: A National Canadian Paediatric Surveillance Program survey. *Paediatr Child Health.* 2015;20(4):185–8. PubMed PMID: 26038634. PubMed Central PMCID: PMC4443823. Epub 2015/06/04. eng
- Lazar L, Frumkin RB, Battat E, Lebenthal Y, Phillip M, Meyerovitch J. Natural history of thyroid function tests over 5 years in a large pediatric cohort. *J Clin Endocrinol Metab.* 2009;94(5):1678–82. PubMed PMID: 19240148. Epub 2009/02/26. eng
- Lee HS, Hwang JS. The treatment of Graves' disease in children and adolescents. *Ann Pediatr Endocrinol Metab.* 2014;19(3):122–6. PubMed PMID: 25346915. PubMed Central PMCID: PMC4208256. Epub 2014/10/28. eng
- Lee PA, Klein K, Mauras N, Lev-Vaisler T, Bacher P. 36-Month treatment experience of two doses of leuprolide acetate 3-month depot for children with central precocious puberty. *J Clin Endocrinol Metab.* 2014;99(9):3153–9. PubMed PMID: 24926950. Epub 2014/06/14. eng
- Leger J, Gelwane G, Kaguelidou F, Benmerad M, Alberti C. Positive impact of long-term antithyroid drug treatment on the outcome of children with Graves' disease: national long-term cohort study. *J Clin Endocrinol Metab.* 2012;97(1):110–9. PubMed PMID: 22031519. Epub 2011/10/28. eng
- Lewis KA, Goldyn AK, West KW, Eugster EA. A single histrelin implant is effective for 2 years for treatment of central precocious puberty. *J Pediatr.* 2013;163(4):1214–6. PubMed PMID: 23809043. PubMed Central PMCID: PMC4063525. Epub 2013/07/03. eng
- Lomniczi A, Wright H, Castellano JM, Sonmez K, Ojeda SR. A system biology approach to identify regulatory pathways underlying the neuroendocrine control of female puberty in rats and nonhuman primates. *Horm Behav.* 2013;64(2):175–86. PubMed PMID: 23998662. PubMed Central PMCID: PMC3933372. Epub 2013/09/04. eng
- Marin G, Domene HM, Barnes KM, Blackwell BJ, Cassorla FG, Cutler GB Jr. The effects of estrogen priming and puberty on the growth hormone response to standardized treadmill exercise and arginine-insulin in normal girls and boys. *J Clin Endocrinol Metab.* 1994;79(2):537–41. PubMed PMID: 8045974. Epub 1994/08/01. eng
- Martin DD, Wit JM, Hochberg Z, Savendahl L, van Rijn RR, Fricke O, et al. The use of bone age in clinical practice – part 1. *Horm Res Paediatr.* 2011a;76(1):1–9. PubMed PMID: 21691054. Epub 2011/06/22. eng
- Martin DD, Wit JM, Hochberg Z, van Rijn RR, Fricke O, Werther G, et al. The use of bone age in clinical practice – part 2. *Horm Res Paediatr.* 2011b;76(1):10–6. PubMed PMID: 21691055. Epub 2011/06/22. eng
- Mauras N, Gonzalez de Pijem L, Hsiang HY, Desrosiers P, Rapaport R, Schwartz ID, et al. Anastrozole increases predicted adult height of short adolescent males treated with growth hormone: a randomized, placebo-controlled, multicenter trial for one to three years. *J Clin Endocrinol Metab.* 2008;93(3):823–31. PubMed PMID: 18165285. PubMed Central PMCID: PMC2266949. Epub 2008/01/01. eng
- Mericq MV, Eggers M, Avila A, Cutler GB Jr, Cassorla F. Near final height in pubertal growth hormone (GH)-deficient patients treated with GH alone or in combination with luteinizing hormone-releasing hormone analog: results of a prospective, randomized trial. *J Clin Endocrinol Metab.* 2000;85(2):569–73. PubMed PMID: 10690857. Epub 2000/02/26. eng
- Midyett LK, Moore WV, Jacobson JD. Are pubertal changes in girls before age 8 benign? *Pediatrics.* 2003;111(1):47–51. PubMed PMID: 12509553. Epub 2003/01/02. eng
- Morishima A, Grumbach MM, Simpson ER, Fisher C, Qin K. Aromatase deficiency in male and female siblings caused by a novel mutation and the physiological role of estrogens. *J Clin Endocrinol Metab.* 1995;80(12):3689–98. PubMed PMID: 8530621. Epub 1995/12/01. eng
- Mul D, Wit JM, Oostdijk W, Van den Broeck J. The effect of pubertal delay by GnRH agonist in GH-deficient children on final height. *J Clin Endocrinol Metab.* 2001;86(10):4655–6. PubMed PMID: 11600521. Epub 2001/10/16. eng
- Murray PG, Dattani MT, Clayton PE. Controversies in the diagnosis and management of growth hormone deficiency in childhood and adolescence. *Arch Dis Child.* 2016;101(1):96–100. PubMed PMID: 26153506. Epub 2015/07/15. eng

- Natale V, Rajagopalan A. Worldwide variation in human growth and the World Health Organization growth standards: a systematic review. *BMJ Open*. 2014;4(1):e003735. PubMed PMID: 24401723. Pubmed Central PMCID: PMC3902406. Epub 2014/01/10. eng
- Owen BM, Bookout AL, Ding X, Lin VY, Atkin SD, Gautron L, et al. FGF21 contributes to neuroendocrine control of female reproduction. *Nat Med*. 2013;19(9):1153–6. PubMed PMID: 23933983. Pubmed Central PMCID: PMC3769455. Epub 2013/08/13. eng
- Palmert MR, Dunkel L. Clinical practice. Delayed puberty. *N Engl J Med*. 2012;366(5):443–53. PubMed PMID: 22296078. Epub 2012/02/03. eng
- Perry R, Kecha O, Paquette J, Huot C, Van Vliet G, Deal C. Primary adrenal insufficiency in children: twenty years experience at the Sainte-Justine Hospital, Montreal. *J Clin Endocrinol Metab*. 2005;90(6):3243–50. PubMed PMID: 15811934. Epub 2005/04/07. eng
- Phelan N, Conway SH, Llahana S, Conway GS. Quantification of the adverse effect of ethinyl-estradiol containing oral contraceptive pills when used in conjunction with growth hormone replacement in routine practice. *Clin Endocrinol*. 2012;76(5):729–33. PubMed PMID: 22098528. Epub 2011/11/22. eng
- Poidvin A, Touze E, Ecosse E, Landier F, Bejot Y, Giroud M, et al. Growth hormone treatment for childhood short stature and risk of stroke in early adulthood. *Neurology*. 2014;83(9):780–6. PubMed PMID: 25122206. Epub 2014/08/15. eng
- Punthakee Z, Legault L, Polychronakos C. Prednisolone in the treatment of adrenal insufficiency: a re-evaluation of relative potency. *J Pediatr*. 2003;143(3):402–5. PubMed PMID: 14517528. Epub 2003/10/01. eng
- Quigley CA, Wan X, Garg S, Kowal K, Cutler GB Jr, Ross JL. Effects of low-dose estrogen replacement during childhood on pubertal development and gonadotropin concentrations in patients with Turner syndrome: results of a randomized, double-blind, placebo-controlled clinical trial. *J Clin Endocrinol Metab*. 2014;99(9):E1754–64. PubMed PMID: 24762109. Pubmed Central PMCID: PMC4154082. Epub 2014/04/26. eng
- Radetti G, Maselli M, Buzi F, Corrias A, Mussa A, Cambiaso P, et al. The natural history of the normal/mild elevated TSH serum levels in children and adolescents with Hashimoto's thyroiditis and isolated hyperthyrotropinaemia: a 3-year follow-up. *Clin Endocrinol*. 2012;76(3):394–8. PubMed PMID: 21981142. Epub 2011/10/11. eng
- Raman S, Grimberg A, Waguespack SG, Miller BS, Sklar CA, Meacham LR, et al. Risk of neoplasia in pediatric patients receiving growth hormone therapy—a report from the Pediatric Endocrine Society Drug and Therapeutics Committee. *J Clin Endocrinol Metab*. 2015;100(6):2192–203. PubMed PMID: 25839904. Epub 2015/04/04. eng
- Rivkees SA. Pediatric Graves' disease: management in the post-propylthiouracil Era. *Int J Pediatr Endocrinol*. 2014;2014(1):10. PubMed PMID: 25089127. Pubmed Central PMCID: PMC4118280. Epub 2014/08/05. eng
- Rivkees SA, Szarfman A. Dissimilar hepatotoxicity profiles of propylthiouracil and methimazole in children. *J Clin Endocrinol Metab*. 2010;95(7):3260–7. PubMed PMID: 20427502. Epub 2010/04/30. eng
- Rivkees SA, Sklar C, Freemark M. Clinical review 99: the management of Graves' disease in children, with special emphasis on radioiodine treatment. *J Clin Endocrinol Metab*. 1998;83(11):3767–76. PubMed PMID: 9814445. Epub 1998/11/14. eng
- Rodd C, Metzger DL, Sharma A. Extending World Health Organization weight-for-age reference curves to older children. *BMC Pediatr*. 2014;14:32. PubMed PMID: 24490896. Pubmed Central PMCID: PMC3922078. Epub 2014/02/05. eng
- Rose SR, Vogiatzi MG, Copeland KC. A general pediatric approach to evaluating a short child. *Pediatr Rev*. 2005;26(11):410–20. PubMed PMID: 16264029. Epub 2005/11/03. eng
- Rose SR, Brown RS, Foley T, Kaplowitz PB, Kaye CI, Sundararajan S, et al. Update of newborn screening and therapy for congenital hypothyroidism. *Pediatrics*. 2006;117(6):2290–303. PubMed PMID: 16740880. Epub 2006/06/03. eng
- Rothenbuhler A, Ormieres B, Kalifa G, Bougneres P. A pilot study of growth hormone administration in boys with predicted adult short stature and near-ending growth. *Growth Hormone IGF Res*. 2015;25(2):96–102. PubMed PMID: 25641639. Epub 2015/02/03. eng
- Saggese G, Federico G, Barsanti S, Fiore L. The effect of administering gonadotropin-releasing hormone agonist with recombinant-human growth hormone (GH) on the final height of girls with isolated GH deficiency: results from a controlled study. *J Clin Endocrinol Metab*. 2001;86(5):1900–4. PubMed PMID: 11344181. Epub 2001/05/10. eng
- Sas TC, Gault EJ, Bardsley MZ, Menke LA, Freriks K, Perry RJ, et al. Safety and efficacy of oxandrolone in growth hormone-treated girls with Turner syndrome: evidence from recent studies and recommendations for use. *Horm Res Paediatr*. 2014;81(5):289–97. PubMed PMID: 24776783. Epub 2014/04/30. eng
- Schroor EJ, van Weissenbruch MM, Knibbe P, Delemarrevan de Waal HA. The effect of prolonged administration of an anabolic steroid (oxandrolone) on growth in boys with constitutionally delayed growth and puberty. *Eur J Pediatr*. 1995;154(12):953–7. PubMed PMID: 8801102. Epub 1995/12/01. eng
- Selva KA, Mandel SH, Rien L, Sesser D, Miyahira R, Skeels M, et al. Initial treatment dose of L-thyroxine in congenital hypothyroidism. *J Pediatr*. 2002;141(6):786–92. PubMed PMID: 12461494. Epub 2002/12/04. eng
- Selva KA, Harper A, Downs A, Blasco PA, Lafranchi SH. Neurodevelopmental outcomes in congenital hypothyroidism: comparison of initial T4 dose and time to reach target T4 and TSH. *J Pediatr*. 2005;147(6):775–80. PubMed PMID: 16356430. Epub 2005/12/17. eng

- Seminara SB. Kisspeptin in reproduction. *Semin Reprod Med.* 2007;25(5):337–43. PubMed PMID: 17710729. Epub 2007/08/22. eng
- Seminara SB, Messager S, Chatzidaki EE, Thresher RR, Acierno JS Jr, Shagoury JK, et al. The GPR54 gene as a regulator of puberty. *N Engl J Med.* 2003;349(17):1614–27. PubMed PMID: 14573733. Epub 2003/10/24. eng
- Shulman DI, Palmert MR, Kemp SF. Adrenal insufficiency: still a cause of morbidity and death in childhood. *Pediatrics.* 2007;119(2):e484–94. PubMed PMID: 17242136. Epub 2007/01/24. eng
- Silverman LA, Neely EK, Kletter GB, Lewis K, Chitra S, Terleckyj O, et al. Long-term continuous suppression with once-yearly histrelin subcutaneous implants for the treatment of central precocious puberty: a final report of a phase 3 multicenter trial. *J Clin Endocrinol Metab.* 2015;100(6):2354–63. PubMed PMID: 25803268. Pubmed Central PMCID: PMC4504932. Epub 2015/03/25. eng
- Smith DW, Truog W, Rogers JE, Greitzer LJ, Skinner AL, McCann JJ, et al. Shifting linear growth during infancy: illustration of genetic factors in growth from fetal life through infancy. *J Pediatr.* 1976;89(2):225–30. PubMed PMID: 940016. Epub 1976/08/01. eng
- Smith EP, Boyd J, Frank GR, Takahashi H, Cohen RM, Specker B, et al. Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man. *N Engl J Med.* 1994;331(16):1056–61. PubMed PMID: 8090165. Epub 1994/10/20. eng
- Stanley TL, Levitsky LL, Grinspoon SK, Misra M. Effect of body mass index on peak growth hormone response to provocative testing in children with short stature. *J Clin Endocrinol Metab.* 2009;94(12):4875–81. PubMed PMID: 19890023. Pubmed Central PMCID: PMC2795667. Epub 2009/11/06. eng
- Swerdlow AJ, Higgins CD, Adlard P, Preece MA. Risk of cancer in patients treated with human pituitary growth hormone in the UK, 1959–85: a cohort study. *Lancet (London).* 2002;360(9329):273–7. PubMed PMID: 12147369. Epub 2002/07/31. eng
- Tarquino DC, Jones MC, Jones KL, Bird LM. Growth charts for 22q11 deletion syndrome. *Am J Med Genet A.* 2012;158A(11):2672–81. PubMed PMID: 22887711. Epub 2012/08/14. eng
- Touwslager RN, Gielen M, Derom C, Mulder AL, Gerver WJ, Zimmermann LJ, et al. Determinants of infant growth in four age windows: a twin study. *J Pediatr.* 2011a;158(4):566–72. e2. PubMed PMID: 21147487. Epub 2010/12/15. eng
- Touwslager RN, Gielen M, Mulder AL, Gerver WJ, Zimmermann LJ, Fowler T, et al. Changes in genetic and environmental effects on growth during infancy. *Am J Clin Nutr.* 2011b;94(6):1568–74. PubMed PMID: 22071713. Epub 2011/11/11. eng
- Weise M, Drinkard B, Mehlinger SL, Holzer SM, Eisenhofer G, Charmandari E, et al. Stress dose of hydrocortisone is not beneficial in patients with classic congenital adrenal hyperplasia undergoing short-term, high-intensity exercise. *J Clin Endocrinol Metab.* 2004;89(8):3679–84. PubMed PMID: 15292287. Epub 2004/08/05. eng
- WHO Multicentre Growth Reference Study Group. Assessment of differences in linear growth among populations in the WHO Multicentre Growth Reference Study. *Acta Paediatr (Oslo 1992).* 2006;450:56–65. PubMed PMID: 16817679. Epub 2006/07/05. eng
- Wickman S, Sipila I, Ankarberg-Lindgren C, Norjavaara E, Dunkel L. A specific aromatase inhibitor and potential increase in adult height in boys with delayed puberty: a randomised controlled trial. *Lancet (London).* 2001;357(9270):1743–8. PubMed PMID: 11403810. Epub 2001/06/14. eng
- Wit JM, Oostdijk W. Novel approaches to short stature therapy. *Best Pract Res Clin Endocrinol Metab.* 2015;29(3):353–66. PubMed PMID: 26051296. Epub 2015/06/09. eng
- Wit JM, Hero M, Nunez SB. Aromatase inhibitors in pediatrics. *Nat Rev Endocrinol.* 2012;8(3):135–47. PubMed PMID: 22024975. Epub 2011/10/26. eng
- Wittassek M, Koch HM, Angerer J, Bruning T. Assessing exposure to phthalates - the human biomonitoring approach. *Mol Nutr Food Res.* 2011;55(1):7–31. PubMed PMID: 20564479. Epub 2010/06/22. eng
- Xie C, Zhao Y, Gao L, Chen J, Cai D, Zhang Y. Elevated phthalates' exposure in children with constitutional delay of growth and puberty. *Mol Cell Endocrinol.* 2015;407:67–73. PubMed PMID: 25770461. Epub 2015/03/17. eng
- Xie C, Epstein LH, Eiden RD, Shenassa ED, Li X, Liao Y, et al. Stunting at 5 years among SGA newborns. *Pediatrics.* 2016;137(2):e20152636. PubMed PMID: 26772663. Epub 2016/01/17. eng
- Yanovski JA, Rose SR, Municchi G, Pescovitz OH, Hill SC, Cassorla FG, et al. Treatment with a luteinizing hormone-releasing hormone agonist in adolescents with short stature. *N Engl J Med.* 2003;348(10):908–17. PubMed PMID: 12621135. Epub 2003/03/07. eng
- Yazdani P, Lin Y, Raman V, Haymond M. A single sample GnRH α stimulation test in the diagnosis of precocious puberty. *Int J Pediatr Endocrinol.* 2012;2012(1):23. PubMed PMID: 22809285. Pubmed Central PMCID: PMC3438042. Epub 2012/07/20. eng
- Zemel BS, Pipan M, Stallings VA, Hall W, Schadt K, Freedman DS, et al. Growth charts for children with down syndrome in the United States. *Pediatrics.* 2015;136(5):e1204–11. PubMed PMID: 26504127. Epub 2015/10/28. eng



Update in Pediatric Gastroenterology, Hepatology and Nutrition

10

A. Jay Freeman, Tatyana Hofmekler, John-Paul Berauer, and Sirish Palle

Reflux

Gastroesophageal reflux (GER), the physiological passage of gastric contents into the esophagus, occurs in over two-thirds of otherwise healthy infants with daily “spitting-up” and represents a common topic of parental concern at well child visits within the first year (Lightdale and Gremse 2013). Gastroesophageal reflux disease (GERD), is reflux associated with troublesome symptoms and is estimated to occur in 10–20% of infants and 5–8% of children in North America (Nelson et al. 2000; Dent et al. 2005). Peak incidence of GERD occurs for most patients around 4 months of age with only 5–10% of patients continuing to experience symptoms at 12 months (Martin et al. 2002). GERD can present in a variety of manners depending on age (see Table 10.1), and should be monitored closely in populations that are high-risk for GERD associated complications (e.g. patients which are neurologically impaired, obese, preterm infants and/or have chronic respiratory conditions) (Hassall et al. 2007).

Established and proposed extra-esophageal manifestations of GERD must be considered

A.J. Freeman (✉) • T. Hofmekler • J.-P. Berauer
S. Palle
Division of Pediatric Gastroenterology, Hepatology
and Nutrition, Emory University School of Medicine,
Atlanta, GA, USA
e-mail: afreem6@emory.edu

and evaluated for in patients suspected of having GERD. However, care must be exercised to not overestimate the effects of reflux on certain conditions. Specifically, recent systematic reviews have failed to show significant evidence associating GERD with apnea or the crying/irritable infant (Smits et al. 2014; Gieruszczak-Białek et al. 2015). Additionally, while GERD may effect wheezing and asthma, recent publications suggest the impact is much less than previously thought and additional pulmonary care for uncontrolled asthma and/or wheezing should not be delayed even with the addition GERD therapy (Sheikh et al. 1999; Littner et al. 2005; American Lung Association Asthma Clinical Research Centers et al. 2009; Kiljander et al. 2010, 2013).

Table 10.1 Common GERD symptoms by age

| Infants | Older children and adolescents |
|---|---|
| Feeding refusal/inadequate volumes by mouth | Abdominal/chest pain (heartburn) |
| Recurrent emesis | Recurrent emesis |
| Poor weight gain/failure to thrive | Dysphasia |
| Irritability | Asthma |
| Sleep disturbances | Recurrent pneumonia |
| Respiratory symptoms/cough | Upper airway symptoms (cough, hoarse voice) |

Modified and adapted from Lightdale and Gremse (2013)

Diagnostic Considerations

GERD is a clinical diagnosis and diagnostic testing is not generally required. Despite the development and validation of a number of GERD questionnaires, there remains no single symptom, cluster of symptoms or subjective tool to diagnose or predict esophagitis, other complications of GERD and/or determine which patients will respond to therapy. As no single test definitively diagnoses or excludes GERD, testing should be conducted only to exclude other diagnosis that may explain the patient's symptoms, evaluate for complications of GERD, to establish a causal relationship between GERD and other symptoms and/or monitor therapy effectiveness (Lightdale and Gremse 2013). Despite its wide-spread use, Upper GI tract radiographic imaging serves no role in the evaluation of reflux but rather may be useful in ruling out anatomical causes of persistent emesis (Vandenplas et al. 2009). Multiple intraluminal impedance (MII) has replaced traditional pH probes due to their ability to detect not only acid but also non-acidic reflux. This allows MII to access a number of key variables including; (1) antegrade and retrograde esophageal boluses, (2) volume, speed and length of reflux event, (3) temporal association between reflux event and specific symptom(s) and (4) effectiveness of GERD therapy. Lastly, endoscopy with esophageal biopsies may be used to determine the extent of mucosal damage secondary to GERD, evaluate for anatomical abnormalities and/or Barrett esophagus and exclude other conditions that may mimic GERD including EoE and infectious esophagitis (Hassall 2002).

Management

Life style modifications should be attempted as first line therapy against GERD. Milk protein sensitivity is often overlooked as a condition that can mimic GERD and a 2- to 4-week trial of maternal exclusion of milk and eggs is recommended for breastfeeding infants, or partially hydrolyzed or amino acid formula in formula fed infants assuming adequate weight gain and no

respiratory compromise (Vandenplas et al. 2009). Additional overfeeding, seated or supine positions and environmental tobacco smoke should be avoided. Thickening of the infants formula with rice cereal (1 tablespoon per ounce) may also be attempted but all thickening agents should be avoided in preterm infants given the risk of developing necrotizing enterocolitis (Clarke and Robinson 2004). Although data suggests that reflux is decreased in infants in the prone position, the risk of sudden infant death syndrome far outweighs the benefits and therefore prone position should only be considered when the child is awake or directly observed (Vandenplas et al. 2009). In older children, dietary avoidance of caffeine, alcohol, spicy foods and other food triggers may be sufficient to control symptoms (Lightdale and Gremse 2013).

If lifestyle modifications fail, acid suppression with histamine₂ receptor antagonists (H₂RAs) or proton pump inhibitors (PPIs) are often effective. Several studies have shown clinical benefit of H₂RAs but they are often limited in their long-term use by either tachyphylaxis or patient tolerance making PPIs a better choice in those patients expected to be on longer acid suppressive therapy (Gremse 2004). PPIs are generally considered safe for long periods of time with highest efficacy when taken ~30 min before a meal (Rudolph et al. 2001; Chan et al. 2011; Kierkus et al. 2014). Additionally, children tend to metabolize PPIs faster than adults and often need higher per kilogram dosing or twice a day dosing (Kierkus et al. 2014). For break through symptoms while on acid suppression medication, over the counter antacids may be used to provide relief.

Prokinetic agents such as metoclopramide and erythromycin have become trendy in GERD therapy but there is insufficient data at this time to support their routine use in infants or older children (Vandenplas et al. 2009).

In patients with severe GERD in which lifestyle changes and medical therapy have failed and also have either; (1) growth failure or (2) risk for significant aspiration or other respiratory compromise, then transpyloric feeds via a nasojunal tube or surgical management may be required, typically a fundoplication. Ideally a

patient should be seen by both a pediatric gastroenterology and a pediatric surgeon to ensure medical management has been optimized prior to undergoing surgery due to its risks and long-term complications.

Eosinophilic Esophagitis

Previously thought of as an extremely rare condition, eosinophilic esophagitis (EoE) is now known to be one of the most commonly diagnosed conditions during the assessment of feeding difficulties in children (Straumann et al. 2008). EoE has been described worldwide and affects all age groups with a prevalence between 1 and 5 per 10,000 persons in the United States and Europe, most commonly affecting white males with an onset from school age to midlife (Furuta and Katzka 2015). Among those patients undergoing endoscopic assessment for food impaction, prevalence rates of EoE increase dramatically to nearly 55% (Desai et al. 2005).

Pathogenesis

The exact cause of EoE remains unclear but increasing prevalence of disease has led to focused attention on environmental exposures. Several risk factors have been identified supporting environmental influences to the development of EoE including birth by cesarean section, prematurity, early antibiotic exposure during infancy, food allergies, lack of breast feeding, smoking exposure and residency in low population density areas (Jensen et al. 2013, 2014; Slae et al. 2015). Additionally, clustering amongst families, male predominance, strong twin concordance and genome-wide association studies (GWAS) all suggest a genetic component as well (Furuta and Katzka 2015). At the cellular level, it is believed that impaired barrier function (dilated interepithelial spaces, increased epithelial permeability and down-regulation of proteins associated with barrier function and molecular adhesion) along with increased activity of type 2 helper T (Th2) cells represents the underlying cause of

disease (Furuta and Katzka 2015). Repeated case series have shown environmental and food hypersensitivities, with symptomatic and mucosal responses to elimination of exposure and subsequent relapse upon reintroduction of antigen, further supporting the role of food and environmental hypersensitivity as an important component of the pathophysiology of EoE (Markowitz et al. 2003).

Presentation

Reflux symptoms are a common initial presentation for all patients with EoE, but other symptoms may be more non-specific and vary by age. Adolescents are more likely to present with classic symptoms of dysphasia and food impaction while younger children are more likely to present with feeding difficulties, nausea, emesis and failure to thrive. Due to patient accommodation, symptoms may be subtle including slow oral intake, cutting food into very small pieces, excessive lubrication of foods with sauces, diluting foods with increased fluid intake, fear of eating in public and avoidance of pills and/or certain foods which may cause dysphasia (Furuta and Katzka 2015).

Endoscopic evaluation is necessary for the diagnosis of EoE with an increased number of eosinophils in the esophageal epithelium representing the histologic hallmark of disease. Utilizing a cutoff value of 15 eosinophils per high-powered field results in a sensitivity of 100% and specificity of 96%, although patients with classic phenotypic features and lower levels of eosinophilia have been described (Ravi et al. 2011; Dellon et al. 2015). Although not diagnostic, the most common gross findings on endoscopy include white specks/exudate, mucosal edema, linear furrowing, esophageal rings and esophageal stricturing (see Fig. 10.1). Barium esophagography may also have a role in the evaluation of patients with EoE as up to 55% of children who had no signs of stricturing at time of endoscopy have been found to have esophageal narrowing on esophagography (Menard-Katcher et al. 2015).

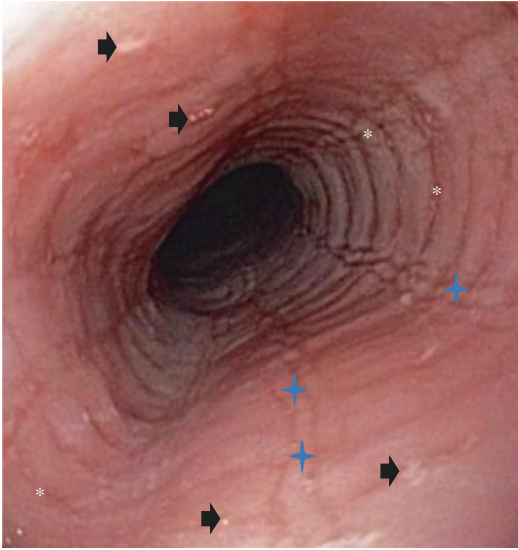


Fig. 10.1 Common histological appearance of EoE. Classic appearance of EoE with white specks/exudate (*black arrow head*), vertical furrowing (*blue stars*) and esophageal rings, also known as furrowing (*white asterisk*)

Management

The management of EoE can be summarized as the “3 D-approach”: Diet, Drugs and Dilation (D’Alessandro et al. 2015). Although the goal of therapy is clinical and histological remission, this is rare and clinical improvement along with significant reduction of mucosal eosinophilia are considered signs of effective therapeutic response (Dellon et al. 2013).

Diet

An elemental diet represents the therapy with the highest clinical response with nearly 90% of children demonstrating clinical improvement and is associated with histological remission. Patients are placed on an amino-acid based formula for 4–6 weeks. If clinical and histological response is seen, foods are slowly reintroduced one-food group at a time every 5–7 days. If no reoccurrence of symptoms is seen, endoscopic evaluation is performed to ensure histological disease progression is not seen before reintroducing each new food group. If a specific food elicits clinical symptoms or increased mucosal eosinophilia,

Table 10.2 Overview of EoE therapies

| Therapy | Recommendation or dosage |
|---|--|
| Elemental diet therapy | Amino-acid based formula for 4–6 weeks |
| Elimination diet therapy | |
| Six-food elimination | Elimination of milk, wheat, eggs, soy, seafood and nuts |
| Four-food elimination | Elimination of milk, wheat, eggs and soy |
| Allergy testing-based | Not recommended |
| Proton pump inhibitors (Omeprazole ^a) | 10–20 kg body weight: 10 mg twice a day >20 kg body weight: 20 mg twice a day |
| Glucocorticosteroids | |
| Fluticasone | 220–440 µg twice a day |
| Budesonide | 0.25–0.5 mg twice a day |

Modified and adapted from Furuta and Katzka (2015)

^aAn alternative, equivalent PPI may be used

then that food should be excluded from the patient’s diet (Peterson and Boynton 2014; D’Alessandro et al. 2015).

In older children a 4- or 6-food elimination diet may be attempted and has been shown to have an approximately 70% rate of clinical response (see Table 10.2). Similar to the elemental diet, selected foods are eliminated from the diet and are only reintroduced after clinical and histological response are confirmed by endoscopy with those foods eliciting clinical symptoms and/or increased mucosal eosinophilia removed from the patient’s diet (Rodríguez-Sánchez et al. 2014).

Allergy, skin-prick driven therapy has been shown to have much poorer response rates with only 45% of patients showing sustained response and therefore is not routinely recommended (Arias et al. 2014).

Drugs

Proton-pump Inhibitor (PPI) use is a mainstay of EoE therapy. As essentially all patients experience reflux-like symptoms, lack of PPI response is the only current method to rule out gastro-esophageal reflux as a cause of the patient’s

symptoms (Furuta and Katzka 2015). Additionally, nearly 40% of patients with histologically confirmed EoE experience a clinical response to PPI therapy alone and therefore is considered first-line therapy in all patients with EoE (Molina-Infante et al. 2015).

The use of systemic corticosteroids results in high rates of remission but long-term use is limited by relapse after tapering of the medication and side effects. Therefore, systemic steroids may be used to rapidly induce remission but should not be considered as a long-term therapeutic option (Mukkada and Furuta 2014). Topical steroids (fluticasone and budesonide) have also shown significant response rates with much lower side effect profiles as compared to systemic steroids and is now considered first-line therapy after a PPI trial (Contreras and Gupta 2014; Gupta et al. 2015). The preferred route of administration is via an oral viscous solutions with sucralose creating a slurry consistency, although several alternatives to sucralose have been shown to be effective as well including applesauce and honey (Lee et al. 2016).

Dilation

Strictures are a common finding among patients with EoE with several studies showing endoscopic dilation to be safe and efficacious (D'Alessandro et al. 2015). Although dilation may result in rapid symptom relief, it does not affect esophageal inflammation and should be considered an adjunct therapy only to appropriate dietary and/or medical interventions (Kavitt et al. 2014).

Celiac Disease

Introduction and Epidemiology

Prevalence of celiac disease in pediatric patients is similar to that of adults, effecting approximately 1% of the population (Newton and Singer 2012). Celiac disease is defined as “chronic small intestinal immune-mediated enteropathy precipitated by exposure to dietary

gluten in genetically predisposed individuals” (Ludvigsson et al. 2013). Classic celiac disease presents with symptoms suggestive of malabsorption: diarrhea, steatorrhea, weight loss, and/or growth failure (Ludvigsson et al. 2013). However, there has been an increasing number of non-classical cases that present with a number of intestinal and extra-intestinal manifestations (Rampertab et al. 2006).

Pathogenesis and Immunology

The pathogenesis of Celiac disease is linked to a combination of genetic, environmental and immunological risk factors, although no clear pathway for each has ever been defined (Tran 2014). The microbiome has been studied extensively with mixed results both in favor and opposed to its role in the development of Celiac disease (de Meij et al. 2013).

Genetics and Risk Factors

The common human leukocyte antigen (HLA) class II gene (DR3, DR5/DR7, or DR4) known as HLA-DQ2 and HLA-DQ8 located on chromosome 6p21 is associated with Celiac disease (Gutierrez-Achury et al. 2011). HLA typing is not helpful in establishing a diagnosis of Celiac disease but can be useful to exclude the diagnosis in high-risk patients or group of patients. Patients that do not have the HLA-DQ2 or HLA-DQ8 molecules have a negative predictive value near 100%, thus essentially ruling out the diagnosis of celiac. It is important to remember that many children with the proper HLA typing may not have celiac disease at the time of testing, but are still at risk to develop the disease later in life (Tran 2014).

Multiple risk factors have been associated with having an increased risk of gluten intolerance (see Table 10.3) and if present should prompt screening for Celiac disease (see diagnosis section below) (Husby et al. 2012). Alternatively, breast feeding has been suggested to be protective (Størdal et al. 2013).

Table 10.3 Factors associated with an increased risk for Celiac disease

| | |
|--|--|
| <i>Signs</i> | |
| Unexplained elevated transaminases without known liver disease | |
| Iron deficiency anemia | |
| Pubertal delay | |
| Poor growth | |
| <i>Diagnoses</i> | |
| Type I DM | |
| Selective IgA deficiency | |
| Down's syndrome | |
| Autoimmune liver disease | |
| Dermatitis herpetiformis | |
| Intussusceptions | |
| Eosinophilic esophagitis | |
| Irritable bowel syndrome | |
| <i>Behaviors/family</i> | |
| Introduction of gluten after age 6 months | |
| Relatives with celiac disease | |

Diagnosis

In addition to patients with increased risk factors, patients with symptoms of diarrhea, poor growth, stunting, delayed puberty, amenorrhea, nausea or vomiting, chronic abdominal pain, fatigue and/or recurrent aphthous stomatitis should be screened for Celiac disease (Husby et al. 2012). Patients are most commonly screened for celiac disease with serological tests and this should be done while the patient is consuming a gluten containing diet. Celiac panels are particularly expensive, and generally not as helpful. It is better to select specific serological tests to check in patients (Hill et al. 2016). Immunoglobulin A (IgA) anti-tissue transglutaminase (TTG) can have a sensitivity of 98% if done in a reliable lab with an established upper limit of normal. Endomysial antibody IgA should be done in a lab with reference standards of a pediatric population (Husby et al. 2012). Deaminated gliadin peptide (DGP IgG) has comparable specificity and lower sensitivity as the EMA IgA. In children under age 2, the TTG IGA and EMA have a higher chance of being inaccurate. For this reason in kids <2 years, they should have a TTG IGA and DGP IGG tested. False negatives will occur with IgA deficiency so total IgA is usually collected when a screening TTG-IgA is collected for the first time for any patient (Hill et al. 2016).

An esophagogastroduodenoscopy is usually preformed to confirm the diagnosis in patients

with concerning serology. Biopsies are taken from duodenal bulb and affected tissue will be patchy. The degree of villous atrophy is graded on the Marsh criteria (3c being most severe and 0 being normal). In patients where the routine pathology is inconclusive, anti T-cell receptor gamma delta (TCR $\gamma\delta$) positive intraepithelial lymphocytes detection can be performed on formalin fixed paraffin imbedded in small bowel biopsies. The (TCR $\gamma\delta$) will remain elevated even on gluten free diet (Tran 2014).

Although not routinely the standard of care within the United States, in 2012 the European society of Pediatric Gastroenterology, Hepatology and Nutrition offered times when endoscopy could be avoided for a diagnosis. Pediatric patients with signs or symptoms suggestive of celiac, high anti-TTG IGA titers (>10 times the ULN) should be offered a second blood test to check for EMA. If it is positive, then the diagnosis of celiac can be made without endoscopic confirmation. It is also advised to check for HLA types in these patients (Husby et al. 2012).

Treatment

The treatment for celiac disease is a gluten free diet. Unfortunately, about 25% of patients continue to experience symptoms despite a gluten free diet (Paarlahti et al. 2013). Patients should plan to have less than 20 parts per million (ppm; 6 mg equivalent) of gluten per day. Some patients require new appliances that have been gluten free. Following a gluten free diet can add additional stress to all family members involved as this frequently affects the entire family. Gluten free diets tend to be higher in fat and should be avoided unless a diagnosis of celiac disease is made.

Functional Gastrointestinal Disorders

Background

Functional GI Disorders (FGID) are better defined as *Disorders of the Gut-Brain Interaction* and can affect anyone from young age through

adulthood. FGIDs did not always receive scientific rigor until the last several decades and so scientific historic data is lacking. However, with increasing categorization and scientific interest, research is suggesting several complex processes such as microbial dysbiosis, altered mucosal immune function, visceral hypersensitivity and central nervous system dysregulation all contributing to the etiology of FGIDs (Drossman and Hasler 2016). With emerging understanding, it is important to keep in mind that functional disorders can coexist, or even be worsened, with other underlying gastrointestinal pathologies (Hyams et al. 2016).

Most recently, the Rome IV criteria were published in the *Journal of Gastroenterology* (Drossman and Hasler 2016), updating the typical definitions and treatments of FGIDs. The full list of pediatric FGIDs is seen in Table 10.4. Here

Table 10.4 Pediatric functional gastrointestinal disorders

| |
|--|
| G. Childhood functional GI disorders: neonate/toddler |
| G1. Infant regurgitation |
| G2. Rumination syndrome |
| G3. Cyclic vomiting syndrome (CVS) |
| G4. Infant colic |
| G5. Functional diarrhea |
| G6. Infant dyschezia |
| G7. Functional constipation |
| H. Childhood functional GI disorders: child/adolescent |
| H1. Functional nausea and vomiting disorders |
| H1a. Cyclic vomiting syndrome (CVS) |
| H1b. Functional nausea and functional vomiting |
| H1b1. Functional nausea |
| H1b2. Functional vomiting |
| H1c. Rumination syndrome |
| H1d. Aerophagia |
| H2. Functional abdominal pain disorders |
| H2a. Functional dyspepsia |
| H2a1. Postprandial distress syndrome |
| H2a2. Epigastric pain syndrome |
| H2b. Irritable bowel syndrome (IBS) |
| H2c. Abdominal migraine |
| H2d. Functional abdominal pain—NOS |
| H3. Functional defecation disorders |
| H3a. Functional constipation |
| H3b. Nonretentive fecal incontinence |

Table adapted from Drossman and Hasler (2016)

we will focus on functional diarrhea, functional constipation and functional abdominal pain.

Neonate/Toddler Functional GI Disorders

Functional symptoms in infants and toddlers can be a result of normal development, as in the case of infant regurgitation, or it can be a “maladaptive behavioral response to an internal or external stimuli”, as in the case of functional constipation. Young children cannot distinguish between emotional and physical distress, and both can result in similar behavior. Because young children are unable to express themselves clearly, physicians must rely on caregiver’s history and clinical insight for diagnosis and treatment. For this reason, in the management of functional disorders, it is of the utmost importance that clinicians develop a trusting relationship between the caregivers and themselves. Conversations should include the assessment of family dynamic and inquiry on how disruptive the FGID is to the family relationship. Treatments and interventions should certainly be targeted to the child, but should also consider and attend to the family as well.

Functional Diarrhea

Diagnostic criteria for functional diarrhea are in Table 10.5. Physiologically, children with functional diarrhea maintain normal hydration, electrolyte balance and glucose absorption, and there is no steatorrhea (Milla et al. 1978). Etiology is typically nutritional: overfeeding, excessive fruit juice intake, excessive fructose intake, low fat diet, and/or excessive sorbitol intake. Stools can become progressively less formed throughout the day and may have undigested food or

Table 10.5 Diagnostic criteria for functional diarrhea

| |
|--|
| Must include all of the following: |
| 1. Daily painless, recurrent passage of 4 or more large, unformed stools |
| 2. Symptoms last more than 4 weeks |
| 3. Onset between 6 and 60 months of age |
| 4. No failure to thrive if caloric intake is adequate |

Table adapted from Benninga, et al. (2016)

mucous. If the patient is growing well, malabsorption is unlikely. No specific treatment is indicated other than reassurance (Benninga et al. 2016).

Functional Constipation

Functional constipation (FC) is the result of a child having repeated voluntary attempts to withhold feces in an attempt to avoid defecation due to a fear. The fear can be due to a previous discomfort, pain, or other negative experience associated with defecation (Tabbers et al. 2014). In children, one episode of painful stool due to a diet change can be the initial negative experience that can result in withholding in the future. Continued retention of feces in the colon results in continued water absorption from the stool causing the fecal matter to become harder and more painful to evict. Diagnostic criteria for FC are listed in Table 10.6.

Differential diagnosis for FC in childhood should include anatomical obstruction, Hirschsprung's disease, spinal problems, metabolic and neuroenteric abnormalities. Hirschsprung's disease should be suspected in those infants that did not pass meconium passage in the first 24 h of life. Barium enemas may be unhelpful until after 4–6 weeks of life and colonic distention has taken place. Rectal suction biopsy is the gold standard for diagnosis although anorectal manometry is sometimes appropriate if

extreme short segment Hirschsprung's disease is suspected (Benninga et al. 2016).

Treatment for FC should include education of the caregivers, reassurance, and implanting interventions early when symptoms start. Duration of treatment can be months to years in certain situations. Pharmacological treatments should include stool softeners such as polyethylene glycol, lactulose or milk of magnesia. Stool softeners will soften the actual stool making it less painful for the child. Over time, the goal would be to minimize the discomfort and normalize defecation for the child. Although these medications are commonly prescribed in children, there is no large well-designed randomized trial studying these interventions. Additionally, no randomized control studies exist that study dietary supplement or laxatives in infants and toddlers (Benninga et al. 2016). However, laxatives such as senna, are frequently added in combination with stool softeners. There is all together limited data on probiotics in children. Reports evaluating cow milk allergy causing constipation have been inconsistent with conflicting data (Iacono et al. 2006; Kiefte-de Jong et al. 2010). It is reasonable to consider a 2–4 week trial of hypoallergenic formula in infants and toddlers in whom laxative treatment failed (Tabbers et al. 2014). Behavior techniques such as strict toilet training should be avoided due to potential to cause additional anxiety. For preschoolers, reward system with “stars” can work to provide incentive.

Table 10.6 Diagnostic criteria for functional constipation

Must include 1 month of at least 2 of the following in infants up to 4 years of age:

1. 2 or fewer defecations per week
2. History of excessive stool retention
3. History of painful or hard bowel movements
4. History of large-diameter stools
5. Presence of a large fecal mass in the rectum.

In toilet-trained children, the following additional criteria may be used:

1. At least 1 episode/week of incontinence after the acquisition of toileting skills
2. History of large-diameter stools that may obstruct the toilet

Table adapted from Benninga, et al. (2016)

Functional Disorders of Childhood and Adolescence

Functional Nausea and Functional Vomiting

Functional Nausea and Vomiting are new diagnoses that present in the Rome IV criteria. Diagnostic criteria are listed in Table 10.7. Their inclusion was based on clinical experience with having patients complaining of these symptoms without underlying pain that would otherwise make the diagnoses of functional dyspepsia. These patients may experience autonomic symptoms such as dizziness, sweating, pallor and tachycardia. Postural orthostatic tachycardia

Table 10.7 Diagnostic criteria for functional nausea and vomiting

| |
|--|
| H1b1. Functional nausea |
| Must include all of the following fulfilled for the last 2 months: |
| 1. Bothersome nausea as the predominant symptom, occurring at least twice per week, and generally not related to meals |
| 2. Not consistently associated with vomiting |
| 3. After appropriate evaluation, the nausea cannot be fully explained by another medical condition |
| H1b2. Functional vomiting |
| Must include all of the following: |
| 1. On average, 1 or more episodes of vomiting per week |
| 2. Absence of self-induced vomiting or criteria for an eating disorder or rumination |
| 3. After appropriate evaluation, the vomiting cannot be fully explained by another medical condition |

Table adapted from Hyams et al. (2016)

^aCriteria fulfilled for at least 2 months before diagnosis

should be considered during the workup. Additionally, anatomical variations (such as malrotation), gastroparesis, and pseudo-obstruction should also be considered and evaluated for if necessary. Electrolytes, calcium, cortisol and thyroid hormone levels should all be evaluated. Psychological evaluations are important in these children (Hyams et al. 2016).

There is no established treatment for patients with nausea and vomiting. Cognitive behavioral therapy and/or hypnotherapy can be helpful. Cyproheptadine has been shown to be helpful in functional dyspepsia with nausea. Gastric electric stimulation can be considered in severe cases under the guidance of a specialized neurogastroenterologist (Benninga et al. 2016).

Functional Abdominal Pain Disorder and Irritable Bowel Syndrome

Previously known as “abdominal pain related functional gastrointestinal disorder” the term has now been changed to “functional abdominal pain disorders”. There is emphasis to use specific names to differentiate between various functional disorders (Table 10.4) and to acknowledge that more than one functional disorder may occur at the same time (Hyams et al. 2016).

Irritable bowel syndrome is a type of functional abdominal pain disorder and it is divided into diarrhea predominant, constipation predominant, constipation and diarrhea predominant, and unspecified. Diagnosis criteria are in Table 10.8. For patients with constipation and abdominal pain, it is recommended to treat constipation first. If there is continued discomfort, then patient should be treated for irritable bowel syndrome—constipation predominant (Hyams et al. 2016).

Etiology for IBS is still thought to be a disease of the brain gut syndrome. Sensitizing medical events such as abdominal distention, inflammatory processes (infections and allergies), and motility problems superimposed with a potential genetic predisposition can lead to changes in pain processing and develop visceral hypersensitivity. Visceral hypersensitivity in combination with sensitizing psychosocial events such as depression, family stressors, coping problems and secondary gains can all lead to abdominal pain and other gastrointestinal complaints (Iovino et al. 2009; Saps et al. 2009). During evaluation of IBS, other pathologies causing a mucosal disease and/or malabsorption should be considered. Alarm symptoms listed in Table 10.9 should be warrant further investigation for etiologies such as celiac, inflammatory bowel disease, and other (Hyams et al. 2016). Fecal calprotectin is being used increasingly to evaluate for mucosal inflammation that is commonly present in patients with

Table 10.8 Diagnostic criteria for irritable bowel syndrome

| |
|---|
| Must include all of the following: |
| 1. Abdominal pain at least 4 days per month associated with one or more of the following: |
| (a) Related to defecation |
| (b) A change in frequency of stool |
| (c) A change in form (appearance) of stool |
| 2. In children with constipation, the pain does not resolve with resolution of the constipation (children in whom the pain resolves have functional constipation, not irritable bowel syndrome) |
| 3. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition |

Criteria fulfilled for at least 2 months before diagnosis

Table adapted from Hyams et al. (2016)

Table 10.9 Potential alarm features in children with chronic abdominal pain

| |
|---|
| Family history of inflammatory bowel disease, celiac disease, or peptic ulcer disease |
| Persistent right upper or right lower quadrant pain |
| Dysphagia |
| Odynophagia |
| Persistent vomiting |
| Gastrointestinal blood loss |
| Nocturnal stools |
| Arthritis |
| Perirectal disease |
| Involuntary weight loss |
| Deceleration of linear growth |
| Delayed puberty |
| Unexplained fever |

Clinical judgment should be exercised, putting what might be considered an alarm sign into the whole context of the history and physical exam

Table adapted from Hyams and Di Lorenzo *Gastro*; 1456–1468

inflammatory bowel disease (Henderson et al. 2012).

There are few randomized control studies for IBS. However, there is evidence to try probiotics (Zhang et al. 2016), peppermint oil (Pittler and Ernst 1998; Grigoleit and Grigoleit 2005; Khanna et al. 2014), FODMAP (Fermentable, Oligo-, Di, Mono-saccharides And Polyols) diet (Halmos et al. 2014). In addition to pharmacotherapy and food interventions, cognitive behavior therapy, relaxation techniques, biofeedback and hypnotherapy have all been found to be helpful (Bursch 2008).

Functional Constipation

Functional constipation in childhood and adolescents is similar to that in toddlerhood. As in the younger child, the triggering event is frequently a painful experience with defecation or social occurrences that become more meaningful at this age. Repeated withholding leads to continued absorption of water from the feces while they are in the colon and thus resulting in a hard stool mass. This mass becomes more painful to pass and causes a continued cycle of withholding due to the associated pain (Hyams et al. 2016).

Diagnosis of constipation should ideally be made by history and physical exam. Digital rectal

exam are frequently, but not always useful in evaluations degree of stool burden in the rectum. Regular abdominal x-rays should be avoided except in those patients where physical exam and history are not sufficient. Barium enemas should not be used early in the evaluation process. Laboratory screening with hypothyroidism, celiac and hypercalcemia are not indicated without other concerning symptoms (Hyams et al. 2016).

Treatment should comprise of rectal disimpaction and then a routine regiment to avoid reaccumulation. Disimpactions can either be done by large amounts of polyethylene glycol or rectal enemas. Routine regiments should include small amounts of polyethylene glycol as a stool softener and/or a stimulant such as Senna. Unfortunately, those children that suffer with fecal incontinence require long term follow up without always full resolution of symptoms (Hyams et al. 2016). At 2 year follow up, 29% of patients with fecal incontinence were free of soiling at 2 years following intensive therapy (Tabbers et al. 2014). High fiber diets have not been shown to improve constipation.

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is an emerging inflammatory condition of the gastrointestinal (GI) tract in children that includes Crohn's disease (CD) and ulcerative colitis (UC). UC and CD are grouped together as they have similar epidemiology, immunologic, genetic, clinical features and diagnostic features but they differ in treatment and prognostic approach. In this section, we will use a common IBD approach where appropriate but differentiate CD from UC whenever necessary.

Epidemiology

Worldwide, population studies show that IBD is unevenly distributed with the highest disease rates occurring in developed nations like Europe and North America (Lashner 1995; Lakatos

2006). However recent many small series on IBD epidemiology published from Asia, Eastern Europe and South America show increased incidence. Data published from Canada and United Kingdom show an increased incidence of IBD in second and third generation immigrants especially from South Asia. Based on few systematic, population-based studies the incidence of IBD in the pediatric population is estimated to be around 7–12 per 100,000 children in North America (Kugathasan et al. 2003). IBD in children differs from adults with more cases seen among males patients and CD comprises about 2/3 of all new IBD diagnosis, where as in adults prevalence of CD and UC are equal (Perminow et al. 2006).

Pathophysiology

The underlying etiology of IBD is not well understood. Environmental, genetic, microbial and immune factors have been proposed as underlying causes (Oliva-Hemker and Fiocchi 2002). Over 200 genetic loci have been discovered that are linked to IBD suggesting an underlying genetic component, yet the changing epidemiology of IBD implies that, in addition to genetic susceptibility for disease, environmental triggers such as diet and commensal microbiota signatures may likely impact disease presentation and ultimate phenotypic expression.

Clinical Presentation

UC and CD are both chronic inflammatory diseases of the gastrointestinal tract with periods of remission and flares. Although UC and CD share many similarities, they each have distinguishing characteristics depending on location of involvement, disease extent and extra intestinal manifestations (Baldassano and Piccoli 1999). In UC, inflammation is continuous starting in the rectum and extending proximally to varying extents and this inflammation only involves mucosa of the colon. In contrast, CD typically exhibits transmural inflammation and can be located anywhere in the GI tract, from mouth to anus. Additionally,

inflammation in CD is often patchy which can be helpful in distinguishing UC from CD. The most common site of involvement for Crohn's disease is the terminal ileum but more than 2/3 pediatric patients have some colonic involvement and up to 10–15% have only colonic disease. In approximately 10% of cases it is difficult to distinguish UC from CD and these patients are diagnosed with "indeterminate colitis".

The most common presentation of UC is diarrhea, rectal bleeding and abdominal pain while CD is more likely to present with more subtle and varied abdominal pain, diarrhea, poor appetite, and weight loss. The insidious onset and nonspecific presentation can often cause a delay in the diagnosis of CD.

Abdominal pain is the single most common presenting symptom in IBD, but may have several other less obvious presentations such as growth failure, anemia, arthralgias and rashes without notable GI symptoms (Fish and Kugathasan 2004; Heuschkel et al. 2008). Knowing the varied presentations of IBD can aid in early referral and initiation of treatment (see Table 10.10).

Extra-intestinal Manifestations

Although usually more rare, many extra-intestinal manifestations have been reported in the literature. Up to 25–30% of patients exhibit extra-intestinal manifestations that cause varying degree of morbidity and mortality. The exact etiology of these conditions is unknown but autoimmune reactions, induction of immune complexes and inflammatory response, and genetic factors are all postulations. Extra-intestinal manifestations can correlate with GI symptoms but some will be present even in GI remission. The most common extra-intestinal manifestations are listed in Table 10.11.

Evaluation

If IBD is suspected, laboratory tests that should be ordered to include complete blood count

Table 10.10 Potential “red flags” on history and exam suspicious for inflammatory bowel disease

| History | Physical exam |
|--|----------------------------|
| Abdominal Pain | Pallor/anemia |
| Distant from umbilicus | |
| Interferes with sleep | |
| Discrete, acute episodes | |
| Precipitated by eating | |
| Dysphasia/Odynophagia | |
| Involuntary weight loss | Decreased growth velocity |
| Rectal bleeding | Delayed puberty/maturation |
| Nocturnal stooling | Oral ulcerations |
| Extra-intestinal manifestations | Abdominal tenderness/mass |
| Recurrent low-grade fevers | |
| Erythema nodosum | |
| Pyoderma gangrenosum | |
| Joint pain/swelling | |
| Severe eye pain/ Persistent conjunctivitis | |
| Unexplained jaundice | |
| Strong family history of IBD | Perianal fistula/fissures |

Table 10.11 Extra-intestinal manifestations of IBD

| Extra-intestinal locations | Symptoms |
|----------------------------|--------------------------------------|
| Skin | Erythema nodosum |
| | Pyoderma gangrenosum |
| Mouth | Aphthous stomatitis |
| | Gingivitis |
| Eye | Uveitis |
| | Episcleritis |
| Bone | Spondyloarthritis/axial arthritis |
| | Osteoporosis/osteopenia |
| | Finger clubbing |
| Hepatobiliary | Sclerosing cholangitis |
| | Chronic hepatitis |
| | Fatty liver |
| | Pancreatitis |
| Blood | Anemia |
| | Thrombocytosis |
| Vascular | Thromboembolism |
| | Deep vein thrombosis |
| Kidney | Renal calculi (oxalate or uric acid) |
| | Amyloidosis |

(CBC), erythrocyte sedimentation rate (ESR), albumin, aminotransferases, C reactive protein (CRP), iron studies, and stool calprotectin. The four lab tests that are most commonly abnormal

and good indicators of the presence of IBD are the elevated ESR (>20 mm/h) or CRP, thrombocytosis (>400,000), decreased albumin level (2.0–3.5 g/dL), and decreased haemoglobin level indicating iron deficiency anemia. If any of these labs are abnormal, referral to a specialist should be made in a timely manner so that the diagnosis is confirmed with further work up (Mack et al. 2007).

Serologic markers such as anti-Saccharomyces cervisiae (ASCA), pANCA (anti-neutrophil cytoplasmic antibodies), antibody to outer membrane protein (Anti-OmpC) and others are used by few clinicians to identify IBD subtypes in cases where there is a significant overlap in the results after conventional diagnostic work up. Currently there is no sufficient evidence in use of these serological markers for therapeutic strategies or monitoring treatment response of IBD patients (Zholudev et al. 2004).

The diagnosis of inflammatory bowel disease is dependent on endoscopic, histological, and radiological findings. Radiography is necessary at diagnosis to determine extent of disease, location of disease, and severity. In the past, upper gastrointestinal series (UGI) with small bowel follow through was the “gold standard”. However, technology has made great strides in the last

decade and other modalities like magnetic resonance imaging (MRI) and computed tomography scans (CT) are now standard of care with pelvic MRI the imaging modality of choice for perianal disease (Sauer et al. 2016). Most children with IBD receive multiple radiological exams throughout their life, increasing their lifetime exposure, making MRI especially promising in the pediatric population because of the lack of ionizing radiation (Fig. 10.2).

Video Capsule Endoscopy (VCE) has been a crucial addition in imaging in IBD. VCE allows small bowel visualization with no radiation and is well tolerated in the pediatric population. In most cases it requires no sedation; in the young/small child endoscopy may be necessary to place the capsule in the small bowel via endoscopy but in larger/older children this is not necessary. This technology has made evaluation of the small bowel more sensitive and can aid in diagnosing suspected IBD and distinguishing between UC and CD.

Endoscopy with biopsy is the most sensitive and specific evaluation of the colon and terminal

part of ileum for evidence of IBD. Endoscopy aids in diagnosing IBD, differentiating between UC and CD, and assessing extent and severity of disease. After diagnosis, it is used to monitor response to therapy (mucosal healing), for cancer surveillance, and to perform therapeutic procedures, such as stricture dilatation (Beattie et al. 1996). Several studies showed that performing an esophagogastroduodenoscopy during the work-up for pediatric IBD resulted in higher rates of confirming a diagnosis and is now considered standard practice. Macroscopic findings may include patchy or continuous inflammation, ulcerations, nodularity, and strictures (Fig. 10.3).

Histology

Combined together with macroscopic appearance of the mucosa, biopsies aid in the diagnosis of IBD and differentiation between UC and CD. During endoscopy and colonoscopy,

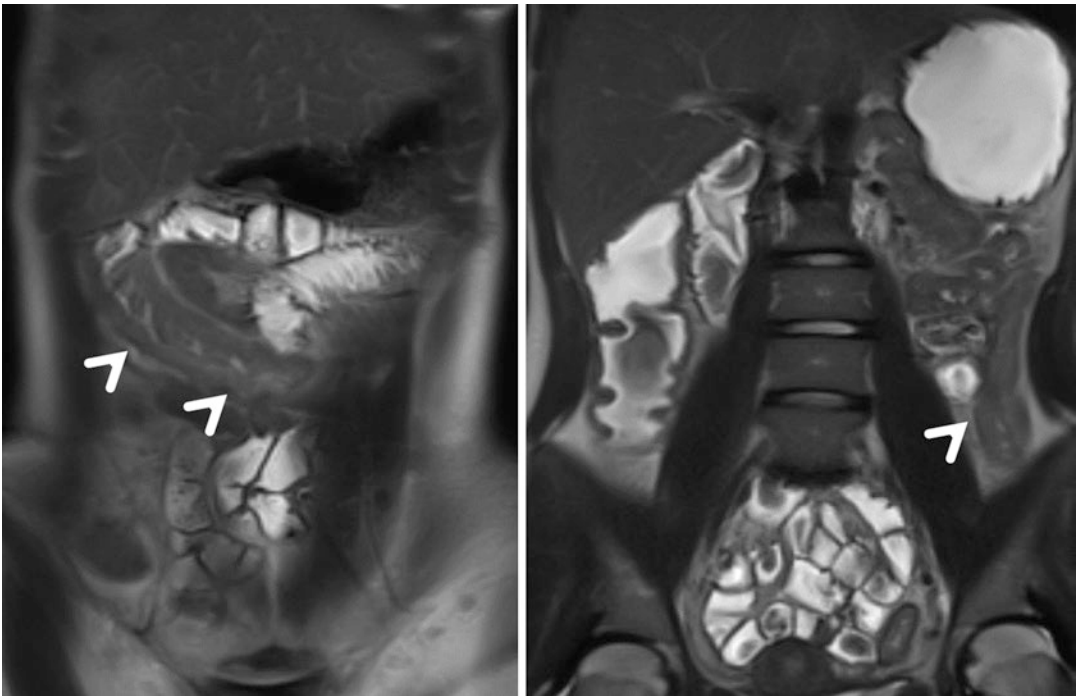


Fig. 10.2 MRE of patient with Ulcerative Colitis. MRE of ulcerative colitis—sequential coronal T2 weighted showing thickened transverse colon and featureless thick walled descending colon

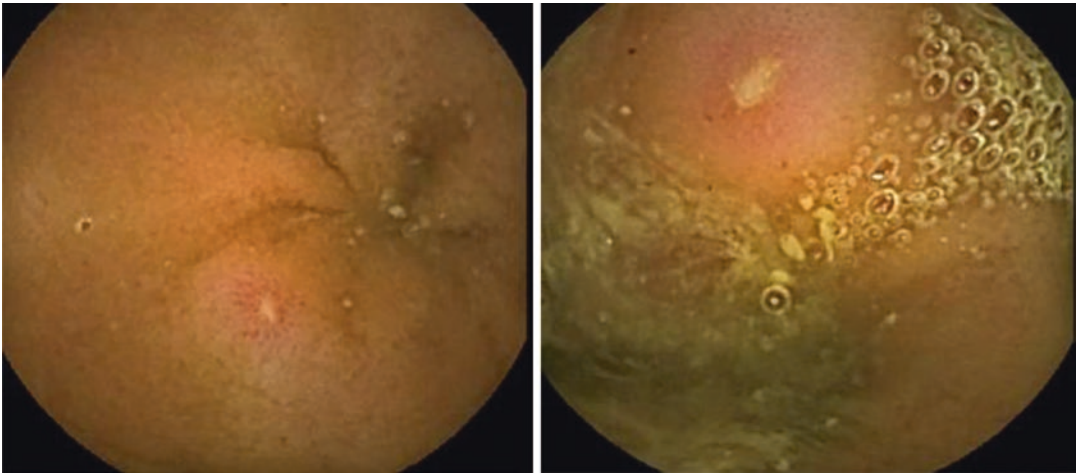


Fig. 10.3 Video capsule endoscopy images of ulcers in the small bowel suggestive of Crohn's disease. Video capsule endoscopy showing large ulcers with erythematous base in the small bowel of a patient with CD

biopsies are usually obtained from all areas, even in the absence of obvious lesions because histological abnormalities, sometimes granulomas, can be present in biopsies of “normal” appearing tissue. Certain histological findings are helpful in confirming an IBD diagnosis and distinguishing between UC and CD. Presences of noncaseating granulomas are pathognomonic for CD; however, 60% of the times biopsies will not show granulomas and the diagnosis is made based on radiological, histological, or endoscopic findings.

Management

Before the year 2000 the main therapy was corticosteroids, with few other options. Currently classes of drugs used to treat IBD include amino salicylates, immunomodulators and biologics. These classes have allowed practitioners to greatly decrease their dependence on steroids. There is a recent increased focus on IBD pathways and genetics which will ideally allow focussed targeting of disease pathways in the future with hopes that such targeting will lead to better outcomes with fewer adverse effects. Many treatment medications overlap between UC and CD but there are some clear indications that differ.

Corticosteroids

Corticosteroids still remains the main therapy for the induction of remission in moderate to severe CD and UC by providing rapid improvement of inflammation (Beattie et al. 1996). There is not much evidence to suggest that they provide mucosal healing, hence they should not be used as maintenance therapy. They are typically started along with a maintenance therapy to induce remission; while the maintenance drug takes effect, the steroids are gradually weaned. IV steroids can be used in severe UC and CD to induce remission. Rectal steroid enemas can be used for proctitis and sigmoid disease with no systemic side effects (Wang et al. 2016). The other formulations of steroids like oral budesonide, which has first pass metabolism, can be used to minimize systemic adverse effects. Systemic steroids have many adverse effects in children, particularly the effects on growth, immunity and adrenal suppression. For these reasons, plus lack of efficacy in maintenance of remission and mucosal healing in IBD, they should be used only as short period of time, ideally less than 3 months.

Aminosalicylates

Aminosalicylates (ASAs) are a wide group of medications that all contain a 5-aminosalicylate (5-ASA) moiety. These medications have shown to be effective in induction and maintenance of

remission in mild to moderate UC and are the first line of therapy in these cases (Wang et al. 2016). They may also have some benefit in maintenance of remission in mild CD. Because ASAs have varying delivery systems which determine the segment of bowel targeted, it is imperative to understand disease location prior to initiation of this therapy. In general these therapies are well tolerated. Main adverse effects are headache and rash; rare but serious side effects include pancreatitis, hepatitis, colitis and low sperm count in males.

Immunomodulators

Azathioprine and its metabolite 6-mercaptopurine (6-MP) are primarily used for steroid refractory CD and as maintenance of remission in moderate to severe UC and CD (Markowitz et al. 2000; Hyams et al. 2007; Turner et al. 2011). These drugs are not used in the induction of remission because they act slowly and may take up to 3 months to reach maximal effect. Most often they are started in conjunction with steroids in moderate to severe disease and when used in this way can minimize the steroid use. Adverse effects of these drugs are idiosyncratic and dose dependent. Idiosyncratic adverse effects are pancreatitis, fevers, and myalgias. Dose dependent adverse effects include infection, bone marrow suppression, and elevated liver enzymes (Kirschner 1998). Patients must be monitored for these side effects.

Methotrexate has shown to be effective in inducing and maintaining remission in adult patients with CD (Turner et al. 2011). So far, there have been no controlled trials of methotrexate use in paediatric CD but reports from retrospective reviews have shown good remission rates in patients that fail 6-MP or are intolerant to azathioprine. Methotrexate is a known teratogen, so birth control counselling must be given to all females of childbearing age who are started on this therapy.

Biologic Therapies

Biologics have revolutionized the treatment and management of IBD dramatically. One class of these drugs is the anti-tumour necrosis factor

alpha (TNF alpha) agents. TNF alpha is a cytokine involved in systemic inflammation and can stimulate the acute phase reaction. Infliximab blocks the action of TNF α by preventing it from binding to its receptor in the cell and was the first in this class to be approved in paediatric IBD. This biologic is used in children with moderate to severe UC and CD (Hyams et al. 2007; Turner et al. 2011). Infliximab is also effective in fistulising and perianal CD (Bernstein et al. 2010). Since infliximab is chimeric, it can cause formation of antibodies against the drug and decrease efficacy. The most common adverse effects for infliximab include infusion reactions, infections, and ALT elevations. Infusion reactions are usually mild and respond to antihistamine therapy.

Another anti-TNF agent, adalimumab, has been approved for treatment of IBD in adults and recently approved for paediatrics CD (Sandborn et al. 2012). Adalimumab has decreased occurrence of antibody formation and is given as a subcutaneous injection. Biologic therapies can reactivate latent *Mycobacterium tuberculosis* and all patients must have a documented negative PPD or quantiferon gold before starting therapy. Other more serious complications with anti-TNF drugs are increased risk for malignancy. Infliximab has a black box warning regarding hepatosplenic T-cell lymphoma (Kotlyar et al. 2011), which is a rare and often fatal T-cell lymphoma that has been reported in approximately 12 US cases. All patients had IBD and predominantly were young males. All these patients had received infliximab in conjunction with azathioprine and/or 6-mercaptopurine. For this reason, these agents should not be used concurrently in young males, until other options are exhausted and the benefits outweigh the risks. Other malignancies that have been associated with anti-TNF agents include lymphoma and leukaemia.

Surgical Management

IBD first line treatment remains medical therapy. Indications for surgery are relatively similar between ulcerative colitis and Crohn's disease, however, the approach and the outcomes differ. Indications for surgery include fulminant colitis,

massive haemorrhage, perforation, stricture, abscess, fistula (in Crohn's disease), toxic megacolon, failure of medical therapy, steroid dependency, and dysplasia. Additional indications for surgery in paediatric patients include growth and pubertal delay as children often demonstrate post operative catch up growth.

The current standard surgical procedure for UC is total colectomy followed by ileoanal pull-through with anal anastomosis (IPAA) (Tilney et al. 2006). The majority of patients with Crohn's disease will need surgery during their life, although this number is decreasing due to advances in medical therapy. As recurrence rates of CD are very high within 5 years of surgery the aim of the surgery is to resect as little bowel as possible. This is also the reason CD is a relative contraindication to IPAA.

Outcomes

IBD is a relapsing disease that has high morbidity but low mortality. Most children with IBD lead active normal lives, with no limitations. However, patients with IBD are at increased risk for some malignancies. In UC the greatest risk is colonic dysplasia/cancer. The risk has been estimated to be up to 25% after 30 years of disease. Risk factors for development of colorectal cancer in UC patients are long duration of disease, early onset, chronic inflammation, family history of colorectal cancer, and primary sclerosing cholangitis. Patients with colonic CD share the same risk factors as UC patients. CD patients are known to have slight increased risk of lymphoma over their lifetime.

Nutrition

One primary area of progress in pediatric nutrition has been a unifying effort to define pediatric malnutrition better. The World Health Organization (WHO) defines malnutrition as "the cellular imbalance between the supply of nutrients and energy and the body's demand for them to ensure growth, maintenance, and specific func-

tions" (de Onís et al. 1993). In pediatric children, the repercussion of malnutrition can be profound because of child's need for growth and development (Mehta et al. 2013). International studies have linked malnutrition to majority of childhood deaths in developing countries (Pelletier et al. 1993, 1995). However, in developed countries, there is less precise data. One problem has been a lack of unifying definition. The American Society of Parenteral and Enteral Nutrition (A.S.P.E.N) working group put forth guidelines to use five domains to help define malnutrition. The five domains include anthropometric parameters, growth, chronicity of malnutrition, etiology and pathogenesis, and developmental or functional outcomes (Fig. 10.4) (Mehta et al. 2013).

Anthropometric measurements should include a weight, height, body mass index (BMI) (for children 2 years and older) and mid arm circumference (MAUC) on admission to a hospital. Triceps skin fold (TSF) and mid-arm muscle circumference (MAMC) measurements can be considered. Serial measurements should be collected throughout an admission and plotted on appropriate growth charts. Head circumference should be measured for children under age 2 years. Ideally a single trained individual would be doing these measurements. Children under age 2 should have their lengths measured lying down on a length board. For older children that cannot stand, tibia lengths, knee height and/or arm span can be used. Infants and young children should be weighted with minimal clothing. Children that cannot be moved should be weighed in beds with special technology especially designed for this. Because using the proper growth chart is important, children under 2 years should be plotted on the WHO growth chart. The CDC growth chart should be used for children 2–20 years. Premature children should have their corrected age used while plotting their growth up until age 3 years. Z-scores should be used to express individual variables in relation to the population (Mehta et al. 2013).

Growth should be assessed with dynamic changes in weight and length velocity over time. A decline in the z-score by more than 1 can be an indication of failing growth. Once growth failure is established, etiology and interventions should

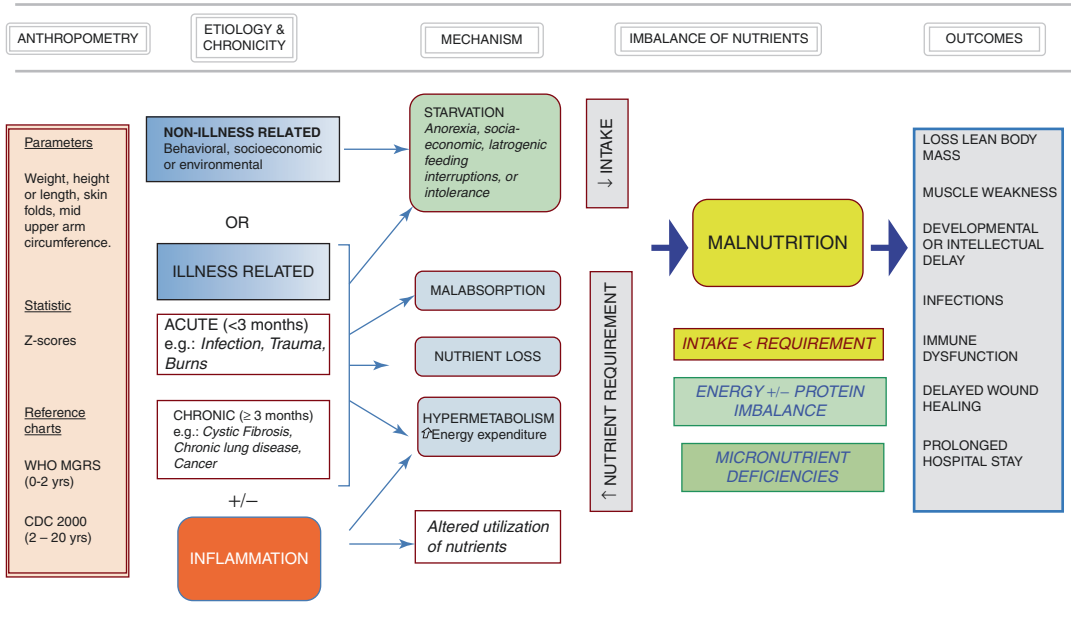


Fig. 10.4 Defining malnutrition. Adapted from Mehta et al. (2013)

be discussed and interventions provided based on the diagnosis. Chronicity of malnutrition needs to be established. Children with malnutrition for less than 3 months are considered to have acute malnutrition. Malnutrition for 3 or more months is considered chronic. Chronic malnutrition can be characterized by stunting, which may be irreversible and may present before 3 months if the degree of malnutrition is severe (Mehta et al. 2013).

If a disease process is directly responsible for malnutrition, it should be identified. Additionally, the mechanism(s) leading to malnutrition should be described. For example, if the malnutrition is due to decreased intake/starvation, increased requirement, excessive losses or failure to absorb. Because inflammation can increase the need for calories and decrease the bioavailability of nutrition, inflammatory makers should be measured when they are applicable. Development is a critical part to all pediatric patients. Developmental assessment should be considered in patients with chronic malnutrition. Muscle mass measurements should also be done via anthropometric measurements or body composition measurements. Measures of muscle strength are impor-

tant but are not always uniform or reproducible with physical exams (Mehta et al. 2013).

Intestinal Rehab and Short Gut Syndrome

Definition and Pathogenesis

Intestinal failure results when patients cannot depend on their intestines to maintain protein-energy, fluid, electrolyte or micronutrient balance. This can be the consequence of obstruction, dysmotility, congenital defects, diseases associated with loss of absorption, or surgical resection resulting in short gut syndrome (O’Keefe et al. 2006). More recently, other definitions have been suggested, including measurements of fecal energy loss, amount of parenteral nutrition needed for growth, and amount of functional remaining gut mass, however measurements are still in early stages and not accepted clinically (Ruemmele et al. 2006). While short gut syndrome as a consequence of necrotizing enterocolitis in infancy has historically been the most common cause of intestinal failure in pediatric

patients, gastroschisis is now becoming a more common diagnosis (Fig. 10.5). However, many patients continue to have multiple underlying factors contributing to their intestinal failure making them have a spectrum of underlying pathologies to address (Fig. 10.6).

General Management Approach

Management of intestinal failure individuals needs to be centered to the underlying pathogenesis and cause of intestinal failure. In most cases of short gut syndrome and dysmotility, efforts need to be centered to promote gut adaptation or process by which the residual bowel increases absorption of fluids, electrolytes and nutrients to compensate for the loss of functional bowel. Structural adaptation should occur by which the absorptive area physically increases in size. Functional adaption should occur as the intestine slows the transit of time to allow for more absorption (Thompson et al. 2011). Adaptation will be

promoted by maximizing general nutrition and enteral exposure to complex nutrients and minimizing infections. Adaptation in infants is maximized in the 3–4 years after bowel resection. For this reason, it is important to maximize parenteral nutrition to have overall growth, encourage gut exposure to nutrition, and minimize central line infections, which these patients are at increased risk for.

Parenteral Nutrition Management

Parenteral nutrition should be managed carefully by experienced individuals. Ideal growth should be maintained at approximately the 25th percentile. Multidisciplinary teams are ideal for this oversight to provide maximal input in ordering proper components. Intravenous drug shortages are common and require expertise in maneuvering the various components in parenteral nutrition to least affect the patient. In general there have been few new additions to be able to add to

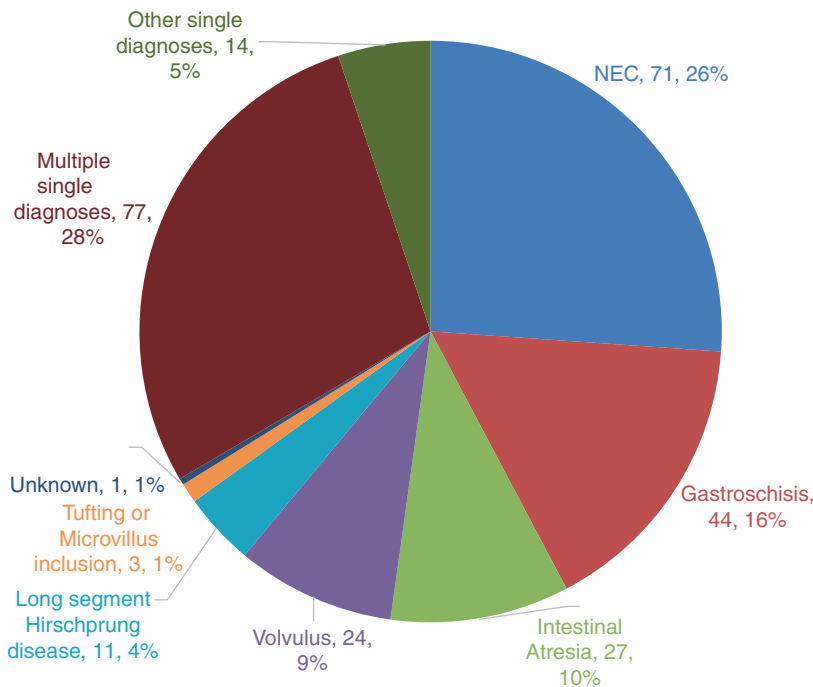


Fig. 10.5 Primary diagnosis of patients with intestinal failure. Primary diagnoses of patients with intestinal failure from the pediatric intestinal failure consortium (N = 272) (Adapted from Squires et al. (2012))

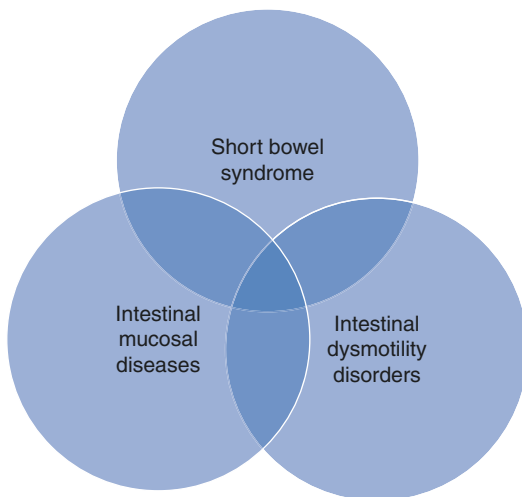


Fig. 10.6 Underlying causes of intestinal failure. Spectrum of underlying causes that cause intestinal failure in pediatric patients. Examples of short bowel syndrome include consequences of surgical resection due to congenital defects and necrotizing enterocolitis. Examples of intestinal mucosal disease include microvillus inclusion disease, tufting enteropathy, autoimmune enteropathy. Examples of Intestinal dysmotility include chronic internal pseudo obstruction syndrome. Hirschsprung's disease can be a dysmotility disorder but also result in short gut syndrome based on the extent of bowel involved. Aggressive Crohn's disease may result in surgical short bowel syndrome along with intestinal mucosal disease

parenteral nutrition in the recent past. Best advances have been in understanding how to best utilize the components of parenteral nutrition that we have.

As an example, over the last 10 years new insight has been made in how to utilize soy based lipids in parenteral nutrition. Parenteral nutrition associated liver disease (PNALD) is one of the most worrisome complications of chronic parenteral nutrition and lipid minimization of soy based oil emulsions to 1 or 0.5 mg/kg/day has been shown to decrease PNLD. Long-term studies are still needed to determine the final outcome of patients receiving lipid minimization. Extreme lipid minimization may precipitate essential fatty acid deficiencies and this should be monitored for by the triene to tetraene ratio. By decreasing the amount of lipid in parenteral nutrition, dextrose quantities have needed to be increased to compensate for the calories. Unfortunately, high

concentration of dextrose, which may also be hepatotoxic over time, and GIR is recommended to be maintained below 15 mg/kg/min. For this reason, there must be closer attention to patient's clinical changes in adjusting the parenteral nutrition.

Fish oil based lipid infusions are not available outside of clinical trials in the United States. However, in countries where it is available, the preparation is also known to prevent PNALD. More longitudinal studies are needed, but there is current evidence showing similar results of preventing liver disease as in lipid minimization.

In addition to macronutrients, micronutrient must also be carefully tracked. Despite having micronutrients added directly to parenteral nutrition, Yang et al. (2011) showed that 50% of patients still experience micronutrient deficiencies with copper, iron and selenium being among the most common deficiencies. Regular micronutrient monitoring should take place for any patient on chronic parenteral nutrition.

Enteral Nutrition Management

No consensus exists on types of formulas that would be most appropriate for infants with intestinal failure. In general, consideration needs to be placed on the remaining gut and degree of functionality of the remaining gut. Increased exposure to enteral nutrition is known to improve adaptation by stimulating hyperplasia, promoting peristalsis and stimulates flow of GI secretions and secretion of humoral factors. However, it is not known whether continuous or bolus feeds are best. Breast milk is known to bolster the immune system and contain immunoglobulins, nutrients, hormones and growth factors to help with intestinal growth (Andorsky et al. 2001; Raphael and Duggan 2012). When breast milk is not available, formula should be used. There is no consensus on types of formulas to use but more complex nutrients are associated with improved adherence. Higher Medium Chain Triglyceride formulas have been theorized to improve absorption by bypassing the lymphatics and are able to be absorbed in the colon.

However, they have not shown to decrease time on parenteral nutrition and create a higher osmotic load to patients that could result in increased stooling. Long chain fatty acids are known to produce adaptation better but are less efficiently absorbed (Jeppesen and Mortensen 1998; Raphael and Duggan 2012). Thus formulas must be geared to the individual patient.

Central Access Preservation

Central lines become the lifeline for intestinal failure patients. Preventing central line associated infections (CLABSI) is critical in preserving vascular access. Patients enrolled in multidisciplinary clinics for intestinal failure patients have shown to have lower rates of CLABSI. Ethanol lock therapies have been established as a novel practice associated with decreasing CLABSI. There have been studies that showed increased line breaks with some regimens of ethanol lock therapy, but more studies are needed to understand if this is only seen in higher concentrations or more frequent use of ethanol.

Surgery

Bowel lengthening surgery should be preserved only for the situations when a patient is unable to be advanced in their feeds. The Serial Transverse Enteroplasty procedure is the most common bowel lengthening surgery and could be done in areas of dilated bowel. However, in patients with underlying dysmotility disorder such as gastroschisis, outcomes may be guarded since it is dysmotile bowel that is being lengthened. Thus, although the length is increased, the functionality may still be poor.

Transplant

Transplantation for small bowel or dual small bowel and liver are rare in the United States. On average less than 100 occur per year due to advances in careful parenteral nutrition preparation and avoidance of PNALD. Nevertheless,

patients should be evaluated if they have limited vascular access, advancing PNALD, or no chance of coming off parenteral nutrition.

Neonatal Cholestasis

Background

Neonatal cholestasis, characterized clinically by the prolonged occurrence of jaundice in the newborn period, is defined physiologically as a decrease in bile formation or flow due to impaired hepatobiliary membrane transport systems or mechanical obstruction of bile flow (Balistreri 1985). The resulting accumulation of biliary constituents within the liver and bloodstream are important pathophysiologic mechanisms implicated in both acquired and hereditary forms of cholestasis. While neonatal jaundice due to unconjugated hyperbilirubinemia is common, affecting up to 84% of term newborns (Kelly and Stanton 1995; Bhutani et al. 2013), and not usually harmful to infants, cholestatic jaundice (conjugated hyperbilirubinemia) must always be considered a pathological state signifying hepatobiliary dysfunction. With an incidence of approximately 1 in 2500 live births (Balistreri 1985), cholestatic liver diseases comprise a rare, yet critical, group of disorders. Left untreated, many of these disorders lead to progressive fibrosis of the liver and, ultimately, cirrhosis. Timely differentiation of neonatal cholestasis from simple unconjugated hyperbilirubinemia is one of the major challenges facing clinicians during the evaluation of the jaundiced infant because in the early stage, the infants can look very healthy except for their jaundice. Early recognition by the primary care provider and prompt referral to a pediatric gastroenterologist who can perform an appropriate diagnostic evaluation to identify the cause may ameliorate potentially catastrophic outcomes related to delayed diagnosis.

Pathogenesis

Decreased canalicular secretion of a broad range of biliary constituents that are normally excreted

into bile and retention of these potentially noxious substances within the liver is the fundamental pathophysiologic defect in all forms of cholestasis (Trauner et al. 1998). These substances include bile salts, glucuronide conjugates (e.g. bilirubin diglucuronide), heavy metals (e.g. copper), inorganic anions (e.g. bicarbonate and chloride), phospholipids, exogenous drugs, and environmental toxins (Boyer 2007). Disturbances of normal hepatobiliary transport and bile composition due to alterations in the uptake, conjugation, or excretion of these compounds result in the formation of “toxic bile” and subsequent hepatocellular and/or bile duct injury (Trauner et al. 1998, 2008). Moreover, retention of bile acids within the hepatocyte cause damage to intracellular membrane component, mitochondrial dysfunction, and hepatocyte cell death by apoptosis and necrosis. Secondary effects of cholestasis result from a deficiency of micelle-forming bile acids within the intestinal lumen that are essential for dietary lipid and fat-soluble vitamin absorption.

Presentation

The hepatic and systemic effects of chronic cholestasis are profound and widespread. Most infants with cholestatic liver disease present during the first month of life with jaundice often the most readily apparent sign of liver disease (Suchy et al. 2002). While jaundice occurs more commonly in the neonatal period than at any other time of life, neonatal jaundice due to a physiological delay in maturation of the bilirubin conjugation pathway or in association with breastmilk feeding is common in the first 2 weeks of life, whereas neonatal cholestasis must be considered in any infant who remains jaundiced beyond the age of 14–21 days or who develops jaundice within the first month of life. Pale or acholic stools are the hallmark sign of cholestasis and suggest an obstructive process such as biliary atresia but may not be present with partial or evolving biliary obstruction. The presence of deeply pigmented stools makes biliary atresia unlikely. Parental reports of the stool color often overestimate the degree of pigmentation; there-

fore, medical practitioners should directly observe the stool (Matsui and Ishikawa 1994). Dark urine (normally colorless in the newborn) is a common non-specific indicator of conjugated hyperbilirubinemia, but is not pathognomonic.

The impact of bile acid deficiency may result in steatorrhea, poor weight gain, or fat-soluble vitamin deficiency from dietary lipid and fat-soluble vitamin malabsorption. Vitamin D deficiency can cause rickets and some infants present with bleeding or bruising secondary to coagulopathy caused by liver failure or vitamin K deficiency. Some causes of neonatal cholestasis have specific abnormalities associated with their underlying etiology, such as dysmorphic facies and congenital heart disease (e.g. Alagille’s syndrome), skin lesions and chorioretinitis (e.g. CMV, HSV, toxoplasma), abdominal mass (e.g. choledochal cyst), and hypotonia or abnormal reflexes (e.g. mitochondrial disorders). Hepatosplenomegaly can occur in infants who have storage diseases or cirrhosis. In some cases, progression to end-stage liver disease can cause serious life-threatening complications such as portal hypertension, variceal bleeding, ascites and peripheral edema, or hepatic encephalopathy although these are less common during the neonatal period.

Etiologies

In the 1970s, up to 65% of infants presenting with cholestasis were diagnosed with “idiopathic neonatal hepatitis” (Balistreri 1985). By the turn of the century, improved diagnostic methods and advances in molecular genetics have decreased this category to no more than 15% (Balistreri and Bezerra 2006). Biliary atresia remains the most common cause, consistently accounting for approximately one third of all cases in multiple reports over several decades (Suchy 2004; Balistreri and Bezerra 2006; Hoerning et al. 2014). Various forms of inherited cholestasis syndromes occur in 10–20% of cases. Approximately 10% are caused by alpha1-antitrypsin deficiency. Other inborn errors of metabolism comprise about 20% of all cases. Congenital infections, including the so-called “TORCH” infections, account for only 5% of cases.

Diagnosis

The initial detection of neonatal cholestasis lies in the domain of the primary care provider and depends primarily on the recognition of prolonged jaundice. A thorough physical examination and direct observation of urine color, and, most importantly, stool color, is an essential aspect of the primary assessment of the jaundiced infant, as acholic stool and dark urine often indicate the presence of conjugated hyperbilirubinemia.

To differentiate benign causes of jaundice from neonatal cholestasis, the American Academy of Pediatrics and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition recommend measurement of total and direct (conjugated) serum bilirubin levels if jaundice is accompanied by dark urine or light stool or if it persists beyond 2 weeks of age (American Academy of Pediatrics Subcommittee on Hyperbilirubinemia 2004; Fawaz et al. 2016). Breast-fed infants who can be reliably monitored and who have an otherwise normal history (i.e. no dark urine or light stools) and physical examination may be asked to return at 3 weeks of age and, if jaundice persists, have the serum bilirubin fractionated at that time. Considering the clinical complexity to determine whether or not a direct fraction exceeds a percentage of the total bilirubin level, a direct bilirubin value greater than 1.0 mg/dL, regardless of the total bilirubin level, should be considered abnormal (Rosenthal et al. 1986). Any infant with cholestatic jaundice should be immediately referred to a pediatric gastroenterologist who can conduct a diagnostic evaluation to identify a specific cause.

Of note, ultrasonography is useful to identify anatomic abnormalities such as choledochal cysts. The diagnosis of biliary atresia cannot be made reliably with an ultrasound scan, although the finding of an absent or atretic gallbladder is suggestive.

Management

Prompt identification of infants who have medically treatable forms of cholestasis (e.g. UTI, galactosemia, hereditary tyrosinemia, congenital

hypothyroidism) as well as those amenable to surgical intervention (e.g. biliary atresia, choledochal cyst) is crucial to avoid irreversible end-organ dysfunction. The quintessential example is the timing of hepatopertoenterostomy in patients who have biliary atresia. In a recent report from the Japanese Biliary Atresia Registry, the likelihood of success of the Kasai procedure and survival with native liver was highest in children who underwent the procedure in the first 30 days of life (Nio et al. 2003). Even when specific therapy is not available, infants who have cholestasis may benefit from early medical management to prevent long-term complications associated with chronic liver disease. Additionally, advanced experience of the center in caring for complex liver disease in neonates has been shown to correlate with improved outcomes (Kelly and Davenport 2007). Therefore it is imperative that primary care providers identify a center of excellence in order to refer patients in which complex neonatal liver disease is suspected.

Malnutrition secondary to impaired absorption of fats, impaired metabolism of proteins and carbohydrates, and increased hepatic metabolism is common in cholestatic infants and adversely affects their outcome, and should be monitored by frequent anthropometric assessment. Nutritional support and supplementation with fat-soluble vitamins is recommended in all children with cholestasis. Caloric intake should be approximately 125% of the recommended dietary allowance based on ideal body weight (Suchy 2004). If breast feeding does not promote growth, cholestatic infants should receive a formula containing medium-chain triglycerides such as Pregestimil® or Alimentum®, because these triglycerides can be directly absorbed from the small intestine into the portal circulation without requiring modification by bile acids (Fawaz et al. 2016). Specialized infant formula and diets may have a role in select cases (e.g. galactosemia, hereditary fructose intolerance, and hereditary tyrosinemia). For infants with continued poor growth, formulas can be concentrated or have additional carbohydrates or fats added to increase caloric density (Fawaz et al. 2016). Oral feeding is the preferred route of formula intake; however, if patients are unable to

ingest the needed calories, nasogastric tube feeding should be initiated, generally continuous overnight feeding. Parenteral nutrition is rarely necessary; however, if there is severe protein-energy malnutrition, feeding intolerance, and/or malabsorption, provision of parenteral nutrition, in combination with enteral nutrition, improves nutrient delivery and does not invariably worsen cholestasis (Fawaz et al. 2016).

Infants with cholestasis require supplementation with fat-soluble vitamins administered orally as water-soluble preparations (Suchy et al. 2002). Doses of at least 2–4 times the recommended daily allowance are typically required to produce therapeutic plasma concentrations. Serum levels should be routinely monitored to guide dosing. No single multivitamin preparation is adequate for all cholestatic infants; most will need additional vitamins K and E, and many will need vitamins D and A beyond a multivitamin preparation. Occasionally, intramuscular vitamin D is required. Vitamin supplementation should be continued for at least 3 months after resolution of jaundice (Venigalla and Gourley 2004).

Ursodeoxycholic acid (UDCA), a hydrophilic bile acid, has been found to have beneficial effects on many forms of cholestasis. Although its mode of action is not completely understood. UDCA is generally used as first-line therapy for pruritus due to cholestasis, parenteral nutrition-induced cholestasis, α 1-antitrypsin deficiency, and after successful surgery for biliary atresia (Dani et al. 2015). The most common side effect is diarrhea, which usually responds to dose reduction. UDCA can be discontinued when cholestasis has resolved. In infants with moderate to severe pruritus due to cholestasis, cholestyramine (240 mg/kg/day), a bile acid sequestrant, or rifampicin (5–10 mg/kg/day) may also be recommended.

Nonalcoholic Fatty Liver Disease

Background

With the rapidly increasing prevalence of childhood obesity around the world, morbidity and mortality related to its complications is on the

rise (2000). During the past 30 years, the percentage of children in the United States (U.S.) aged 6–11 years who were obese nearly tripled from 6.5% in 1980 to 17.7% in 2012 (National Center for Health Statistics (US) 2012; Ogden et al. 2014). Over the same time period, the percentage of adolescents aged 12–19 years who were obese quadrupled from 5% to 20.5%. Racial and ethnic disparities exist, with higher rates observed among African-American and Hispanic children compared to Caucasian children and the highest rate for 6–11 year old Hispanic boys (48.7% are overweight or obese).

Concurrent with the national epidemic of childhood obesity, epidemiologic data collected from 1988 to 2010 demonstrate that the prevalence of nonalcoholic fatty liver disease (NAFLD) among adolescents increased in parallel, becoming the most common cause of chronic liver disease in both adults and children in the past decade (Younossi et al. 2011; Welsh et al. 2013). Currently, NAFLD affects approximately 10% of the pediatric population in the U.S., reaching rates as high as 38% among obese children and adolescents (Schwimmer et al. 2006). This represents an estimated seven million children with chronic liver disease who are at increased risk of liver failure, cardiovascular disease, and liver cancer in adulthood.

According to the United Network for Organ Sharing database, nonalcoholic steatohepatitis (NASH)-related cirrhosis was the third most common indication for liver transplantation in patients younger than 65 years of age during the period from 2007 to 2010 (Kemmer et al. 2013). Although most liver transplants were not performed before the age of 18 years, many of these cases were likely the consequence of childhood NAFLD. Due to the alarming trends in childhood obesity and the improved management of chronic viral hepatitis, NAFLD is expected to become the most common indication for liver transplantation in the near future (Charlton et al. 2011). Improving our understanding of the etiopathogenesis of NAFLD, early identification of patients through non-invasive diagnostic methods, and the development of targeted therapies may reduce the burden of disease and eliminate the need for liver transplantation.

Pathogenesis

NAFLD encompasses a broad histological spectrum of disease activity ranging from simple steatosis, which is mostly non-progressive, to NASH, a state characterized by hepatic necroinflammation and/or fibrosis with variable risks for progression to cirrhosis and hepatocellular carcinoma (Adams et al. 2005; Vernon et al. 2011). While the pathogenesis of liver injury remains uncertain, a growing body of literature suggests a role for genetic and epigenetic factors in the development and progression of NAFLD. In the majority of patients, NAFLD is also associated with metabolic risk factors such as insulin resistance and atherogenic dyslipidemia; it is thus considered the hepatic manifestation of the metabolic syndrome (Adams et al. 2005). Although both excessive body mass index (BMI) and central obesity are common and well-documented risk factors for NAFLD, neither is necessary for the development of NAFLD. Familial clustering as well as racial and ethnic differences in the prevalence of NAFLD indicates that genetic factors influence the development and progression of NAFLD, but environmental factors are also likely to influence development and progression as well (Kitamoto et al. 2013).

Knowledge about the natural history and evolution of histologic changes in pediatric NAFLD is still evolving. Based on the currently available evidence from adult natural history studies, patients with simple steatosis exhibit very slow, if any, histologic progression, while approximately 20% of patients with NASH ultimately develop cirrhosis, usually over an average of 21.3 years (Singh et al. 2015). However, NAFLD in children may be more severe compared to that in adulthood and a subset of patients rapidly progress (Molleston et al. 2002; Holterman et al. 2013). Children as young as 2 years of age have been reported with NAFLD, and NASH-related cirrhosis has been reported as early as 8 years of age (Schwimmer et al. 2005). In addition to liver-related complications, NAFLD is associated with extrahepatic morbidity and mortality. Nonhepatic associations include cardiovascular, metabolic, pulmonary, and psychological disorders. Cardiovascular disease is the most common cause of death in NAFLD patients (Chacko and Reinus 2016).

Presentation

During the pre-cirrhotic stage, most children with NAFLD are asymptomatic (Lewis and Mohanty 2010). Typically, NAFLD is first suspected in a person found incidentally to have elevated serum aminotransferases or abnormalities suggestive of hepatic steatosis on routine imaging while undergoing evaluation for unrelated reasons such as abdominal pain (Mofrad et al. 2003; Farrell and Larter 2006). Rarely, patients may present with fatigue, malaise, or vague abdominal discomfort due to hepatomegaly and stretching of the hepatic capsule (Choudhury and Sanyal 2004).

Physical examination may reveal acanthosis nigricans, which indicates the presence of insulin resistance, or hepatomegaly, which is often difficult to appreciate due to central obesity (Schwimmer et al. 2003). Once a patient develops cirrhosis, they may display cutaneous stigmata of liver disease (e.g. palmar erythema, spider nevi) or features of hepatic decompensation, which include jaundice, pruritus, ascites, edema, variceal bleeding, and encephalopathy.

Diagnosis

The diagnostic criteria for NAFLD include: (1) presence of hepatic steatosis detected either by imaging or histology, (2) absence of significant alcohol consumption, and (3) appropriate exclusion of other causes for hepatic steatosis and co-existing chronic liver disease (Chalasanani et al. 2012). Competing etiologies for hepatic steatosis include viral hepatitis, particularly hepatitis C virus, severe malnutrition, provision of parenteral nutrition, autoimmune hepatitis, and use of steatogenic medications such as anabolic steroids. Given the relatively young age at diagnosis, consideration to the possibility of genetic disorders such as alpha-1 antitrypsin deficiency, Wilson's disease, cystic fibrosis, and various inborn errors of metabolism are more relevant for children. It is important to recognize that, because of the high prevalence of childhood obesity, NAFLD can co-exist with other chronic liver diseases (Nascimbeni et al. 2013).

Laboratory Evaluation

In clinical practice, serum alanine aminotransferase (ALT) concentration is most commonly used as the initial screening test for NAFLD, despite suboptimal sensitivity and specificity (Schwimmer et al. 2013). Even in the presence of significant histological abnormalities, a substantial number of NAFLD patients have normal transaminase levels (Molleston et al. 2014), indicating that ALT alone is not an ideal screening test for NAFLD. Elevations of aspartate aminotransferase (AST), alkaline phosphatase, and gamma-glutamyl transpeptidase (GGT) are common but not useful as screening tools for NAFLD (Mofrad et al. 2003).

In persons with suspected NAFLD, exclusion of other causes of chronic liver disease often includes virological testing for hepatitis viruses A, B, and C, EBV, and CMV, a battery of serologic markers for autoimmune hepatitis (e.g. ANA, anti-LKM-1, anti-SMA, p-ANCA, and IgG), determination of alpha-1 antitrypsin phenotype and serum ceruloplasmin concentration in addition to other specific tests as directed by the clinical history and physical examination (Vajro et al. 2012). In the absence of autoimmune hepatitis, autoantibodies are positive in a significant proportion of children with NAFLD (Patton et al. 2008). Although their clinical significance is uncertain, their presence requires liver biopsy to discriminate between the two conditions. In patients with NAFLD, it is reasonable to assess for dyslipidemia and diabetes mellitus, because NAFLD may indicate the presence of these diseases.

Radiologic Evaluation

Imaging studies including ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI) are useful in demonstrating hepatic steatosis, at least when hepatic fat accumulation is moderate to severe (Saadeh et al. 2002). However, these tests cannot detect the differences between NASH and NAFLD. Transabdominal US is acceptable as the first-line imaging modality for NAFLD because of its universal availability, affordability, and lack of radiation exposure. However, its relatively low sensitivity for detecting mild steatosis, operator-dependency, and poor image quality in obese patients are major limitations (Mottin et al.

2004). Newer US-based methodologies such as transient elastography or FibroScan®, which measure liver stiffness noninvasively, have shown promising ability to stage liver fibrosis but are not available outside of large academic medical centers (Yoneda et al. 2008). Both MR spectroscopy (MRS) and MRI-proton density fat fraction (MRI-PDFF) accurately detect and quantify steatosis (Schwimmer et al. 2015). At this time, MR-based methods are not widely used for screening because of the high cost, limited availability, and lack of validated thresholds for diagnosis of NAFLD. CT is highly sensitive and specific, but its cost together with radiation exposure prevents its widespread application.

Histologic Evaluation

Despite its invasiveness, liver biopsy remains the gold standard for the diagnosis and staging of NAFLD (Vos 2016). Histopathologic evaluation of the liver is the only diagnostic test that reliably identifies and quantifies hepatic steatosis, steatohepatitis, and fibrosis, thereby distinguishing NAFLD from NASH as well as other forms of liver disease.

While controversy remains about who should have a liver biopsy and when in the diagnostic evaluation liver biopsy should be used, there is universal agreement that liver biopsy should not be performed in all patients. The clinical practice guidelines on NAFLD from the American Association for the Study of Liver Diseases, North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), and European Society for Pediatric Gastroenterology, Hepatology and Nutrition suggest that a liver biopsy be obtained when the diagnosis is uncertain, before pharmacological or surgical treatment is undertaken, and in cases of clinically suspected advanced liver disease (Chalasanani et al. 2012; Vos 2016).

Screening

Early diagnosis of NAFLD in children may help prevent the development of chronic liver disease during adulthood (Schwimmer et al. 2013). The American Academy of Pediatrics and NASPGHAN, in their most recent guidelines,

recommend screening for NAFLD with ALT levels beginning between ages 9–11 years for all children whose BMI is \geq 95th percentile and for those with a BMI between the 85th and 94th percentile with additional risk factors (e.g. central adiposity, insulin resistance, diabetes, dyslipidemia, sleep apnea, or family history of NAFLD) (BarlowExpert Committee 2007; Vos 2016). Screening can be considered in younger patients with risk factors such as severe obesity or a family history of NAFLD or hypopituitarism. When the initial screening test is normal, repeat screening should be performed every 2–3 years if risk factors remain unchanged or sooner if clinical risk factors increase in number or severity.

Management

The management of pediatric NAFLD is aimed at preventing progression toward more advanced forms of disease, regression of steatosis, and improvement in any underlying metabolic risk factors. Currently, the principal treatment for NAFLD is lifestyle modification by diet (directed by a registered dietician) and exercise (Vos 2016). Recommendations regarding pharmacological therapy are limited by a small number of randomized controlled trials (RCTs) and insufficient information to assess the risk-benefit ratio. Regardless of age, behavioral and/or pharmacological therapy should commence immediately after the diagnosis of NAFLD for all children. Taking into consideration the severity of NAFLD, the degree of obesity, and the presence of comorbidities, the clinician must individualize treatment accordingly. Comorbidities such as obesity, diabetes mellitus type 2, hypertension, and dyslipidemia are managed concurrently as part of the therapy for NAFLD (Chalasanani et al. 2012). It should be highlighted that the pharmacological treatment of metabolic risk factors, particularly with statins, is not contraindicated in NAFLD (Chalasanani 2005). If the patient becomes cirrhotic, standard treatment of cirrhosis, including liver transplantation in the decompensated state, is offered.

Weight loss surgery (WLS) is a hot topic but is not recommended as a primary treatment for NAFLD but is becoming more common for severely obese (BMI \geq 35 kg/m²) adolescents with non-cirrhotic NAFLD and other serious obesity-related health conditions (Chalasanani et al. 2012; Vos 2016). NAFLD has been proposed as a criterion for WLS in several published adolescent bariatric surgery guidelines (Nobili et al. 2015). However, no studies have examined the histological outcomes of WLS in the pediatric NAFLD population, and only one has reported on the progression of liver disease post-operatively, using ALT as a surrogate marker (Holterman et al. 2012). Therefore, the impact of bariatric surgery on NAFLD outcomes in children is difficult to quantify. In addition, there is concern for subacute liver failure secondary to massive steatohepatitis as a result of rapid weight loss after bariatric surgery (D'Albuquerque et al. 2008). Therefore, bariatric surgery referral should never be considered without the direct input of an experienced pediatric hepatologist.

Viral Hepatitis

Viral hepatitis is a broad term that describes inflammation of the liver from any viral source. Thousands of viruses may be implicated in inducing hepatic inflammation and likely represents an under diagnosed cause of nonspecific transaminase elevation. The mass majority of cases result in spontaneous, and often unrecognized, resolution of hypertransaminemia but in rare cases may progress to acute liver failure (ALF). In the largest studied cohort of pediatric patients experiencing ALF, Squires, et al. reported 20% of pediatric patients presenting in ALF where ultimately diagnosed with a viral etiology. A further 49% of patients had an indeterminate cause of their ALF, many of which may have been secondary to an undiagnosed viral causes (Squires et al. 2006). With the exception of Herpes simplex virus, therapy is symptomatic with liver transplant reserved for the most severe cases in which hepatic synthetic function appears to be irreversibly compromised.

While a seemingly innumerable number of viruses may lead to an acute hepatitis, chronic viral hepatitis in children is almost exclusively caused by either Hepatitis B or C. However, the landscape of these two diseases is rapidly and radically evolving as improved hygiene practices, blood supply monitoring and the widespread use of vaccines has greatly impacted the prevalence rates of Hepatitis B, while unprecedented success rates of Hepatitis C antiviral drugs is sure to lead to decreased chronic carrier rates as well as long-term complications such as cirrhosis and hepatocellular carcinoma (HCC) (Corte et al. 2016).

Hepatitis B

The majority of cases of chronic Hepatitis B (defined as positive Hepatitis B surface Antigen, or HBsAg, for 6 months or longer) occur via maternal transmission as risk of chronicity is highest among newborns who contract the virus (90%) as compared to children less than 5 years of age (25–30%) and adolescents or adults (<5%) (McMahon et al. 1985; Tassopoulos et al. 1987). The disease course in children is typically asymptomatic with preserved growth and psychological development, but close monitoring is required as 3–5% of children will develop cirrhosis and 0.01–0.03% developing HCC during childhood (Chang et al. 1995, 2005).

Prevention

Vaccination is the most effective measure to prevent the transmission and spread of Hepatitis B (Sokal et al. 2013). Administration of monovalent vaccine within the first 24 h of life followed by 2 or 3 (preterm infants <2000 g) doses of monovalent or combined vaccine with a minimum interval of 4 weeks results in about 95% seroprotective response (anti-HBs ≥ 10 mIU/ml) (WHO Publication 2010). If mother is a chronic carrier, vaccination alone is not sufficient to avoid vertical transmission and hepatitis B immunoglobulin (HBIG) is recommended in addition to vaccine, resulting in 90% protection rate in newborns born to Hepatitis B e Antigen (HBeAg) positive mothers (98% if HBeAg negative) (Lee et al. 2006;

WHO Publication 2010). Breastfeeding has not been shown to be a significant risk in transmission of the virus from mother to newborn who have received proper immunoprophylaxis and in the absence cracked and/or bleeding nipples, should be encouraged to breastfeed (Shi et al. 2011).

Monitoring and Therapy

The decision to start therapy for children with chronic hepatitis B is based on ALT levels, HBeAg positivity, DNA levels, liver histology, family history of HCC and a possible co-existing liver disease (Sokal et al. 2013). Serum ALT, viral DNA load and HBeAg/Anti-HBe levels should be obtained every 6 months and HCC surveillance with hepatic ultrasound should be performed yearly. ALT levels ($1.5\times$ upper level or normal or >60 IU/L, whichever is lower) for over 6 months, high DNA levels ($>20,000$ IU/ml), family history of HCC and/or evidence of cirrhosis should all prompt evaluation by an experienced pediatric hepatologist to determine the possible need for therapy (Sokal et al. 2013). Given the evolving landscape of antiviral therapies with numerous ongoing clinical trials, treatment strategies are beyond the scope of this review and should be determined by an experienced hepatologist.

Hepatitis C

There is an estimated 3.5 million people infected with hepatitis C (HCV) in the United States with nearly half of all infected people unaware (Holmberg et al. 2013; Denniston et al. 2014). Higher incidence rates of disease during the 1970s and 1980s has resulted in updated guidelines from the Center for Disease Control and Prevention (CDC) resulting in broader screening mechanisms to detect those patients with undiagnosed, asymptomatic HCV infection (Mahajan et al. 2013). Given that the most common source of infection among children is via vertical transmission, an increased recognition of disease burden among adults/parents has prompted an increase in screening of children of infected

mothers with early recognition of disease in many instances (Corte et al. 2016).

Screening

Any child born to a HCV positive mother, regardless of the child’s age or clinical condition, should be screened for HCV infection. While the mother’s viral load at time of delivery directly effects transmission rates, generally speaking about 1 in 20 children born to a HCV positive mother will contract the virus (Corte et al. 2016). Although less common in children, other populations in which to consider HCV screening include; patients with prolonged elevation of their serum ALT levels, history of illegal injected drug use, and needle stick, sharp accident or mucosal exposure to a HCV positive individual.

Initial screening lab of choice is a serum HCV antibody (IgG). There are some limitations to this screening test though in that it does not become positive until 6–8 weeks after acquisition and thus not an appropriate choice in acute liver failure screening, does not differentiate acute versus chronic disease and is not useful in patients <18 months of age when maternal antibodies are still present in the blood (Mack et al. 2012). All patients with a positive HCV antibody screen or are being evaluated for acute liver failure should undergo testing with HCV RNA to confirm or rule-out infection. In all patients with positive HCV RNA testing, referral to an experienced hepatologist is indicated for further workup including determine virus genotype, consideration of possible of co-infections and decision on whether therapy is indicated or not.

Monitoring

The invention of direct-acting antiviral agents has revolutionized the therapy of HCV in both adults and children with multiple pediatric studies showing sustained viral remission rates >90%, far superior and with less side effects than previous interferon and ribavirin based therapies (Corte et al. 2016). However, given that 20% of patients will spontaneously clear the virus in the first 3 years of life and only 2% of patients will progress to cirrhosis by the end of adolescents, therapy may be delayed in many instances

(Bortolotti et al. 2008). In these instances routine screening and anticipatory guidance become imperative. Patients should undergo annual examination with a focus on education and anticipatory guidance (see Table 10.12) and

Table 10.12 General guidelines for patients with hepatitis C

| Topic | Recommendations |
|------------------------|--|
| Household contacts | Okay to share: sharing food, drink, utensils, clothes/towels, toilet seats Avoid sharing: toothbrush, nail clippers, shaving supplies, glucometers, any personal item that may be contaminated with blood |
| Non-household contacts | No contraindication to attending day care, school, camps, playgrounds, community pool or participating in contact and non-contact sports |
| Casual contact | No contraindication to kissing, hugging or holding-hands |
| Sexual contact | Monogamous sexual contact is non contraindicated while unprotected sexual activity with multiple partners is highly discouraged |
| Other activities | Tattoos, body piercing, illicit drug use and use of alcohol should be avoided |
| Blood spills | Gloves should be worn to clean all spills. Thoroughly clean with a dilution of 1 part household bleach to 10 parts water (refer to www.CDC.gov) |
| Minor cuts | Universal precautions |
| Vaccines | Should receive all age-appropriate vaccines including Hepatitis A & B |
| Obesity | Obesity may further burden hepatic health and affect response to HCV therapy |
| Pregnancy | Universal screening is not recommended and transmission rates similar between vaginal or cesarean deliveries. Prolonged rupture of membranes and use of fetal scalp probes should be avoided as they may increase transmission rates |
| Breastfeeding | Not contraindicated unless mastitis or bleeding is present |

General guidelines for parents of and children with hepatitis C (adapted from Mack et al. (2012)

laboratory evaluation of serum aminotransferases, total and direct bilirubin, albumin, HCV RNA level, complete blood count with platelets and prothrombin time/international normalized ratio (Mack et al. 2012). Additionally, annual to biannual screening for HCC should be performed via abdominal ultrasound or serum alpha-fetoprotein. Any abnormalities and/or concerns should be communicated with an experienced hepatologist.

Pediatric Acute Liver Failure

The liver is the second-largest organ in the human body and performs more than 500 vital functions including gluconeogenesis, synthesis of plasma proteins and coagulation factors, drug metabolism, and conversion of ammonia into urea (Boyer et al. 2011). Specialized macrophages located in the hepatic sinusoids known as Kupffer cells are intimately involved in the liver's response to infection, toxins, ischemia, and other stresses (Bilzer et al. 2006). The liver is also the body's largest gland, responsible for the production and secretion of bile, an alkaline compound that aids in digestion via the emulsification of lipids, and cholesterol, which serves as a precursor for the biosynthesis of steroid hormones and bile acids (Boyer et al. 2011).

Liver failure occurs when massive destruction of the hepatic parenchyma results in impairment of any one of these critical functions (Bucuvalas et al. 2006). Fortunately, a significant proportion of hepatocytes must be damaged before liver failure occurs and spontaneous recovery is possible, owing to the liver's unique regenerative ability. However, the outcome of pediatric acute liver failure (PALF) is generally poor, and one-half of patients die or require liver transplantation (LT) (Squires et al. 2006). According to the PALF Study Group, PALF is defined as coagulopathy not corrected by the administration of vitamin K with an International Normalized Ratio (INR) >1.5 in patients with hepatic encephalopathy, or >2.0 in patients without encephalopathy, within 8 weeks of onset of symptoms in the absence of preexisting liver disease (Squires et al. 2006).

Pathogenesis

Acute liver failure (ALF) results from rapid death or injury to a large proportion of hepatocytes, leaving insufficient hepatic parenchymal mass to sustain liver function. The pathophysiological mechanisms that lead to ALF are yet to be fully elucidated. However, acute hepatic necrosis is the most common mechanistic pathway of a variety of insults to the liver (Taylor and Whittington 2016). In 1999, the PALF Study Group was formed to develop a database that would facilitate an improved understanding of the etiopathogenesis, treatment and outcome of ALF in children. A report of the first 348 patients enrolled in the PALF registry found that the etiologic categories of non-acetaminophen-induced ALF in children were similar to adults and included metabolic, infectious, and immune-mediated conditions as well as drug injury (Squires et al. 2006).

Acute acetaminophen (APAP) toxicity was the most common identifiable cause of ALF in children ≥ 3 years (21%) (McGill et al. 2012). Non-APAP drug-related ALF was recognized primarily in older children. In most of these cases, the mechanism of injury leading to ALF is thought to be an idiosyncratic drug reaction. An infectious etiology was identified in 6% of patients, with herpes simplex virus (HSV) and Epstein-Barr virus (EBV) the most common identifiable infections in children <3 years and ≥ 3 years, respectively (Squires et al. 2006). Autoimmune hepatitis (AIH) also accounted for 6% of patients and occurred in all age groups. A metabolic cause for ALF was established in 18% of children <3 years of age. This group of diseases can lead to structural liver damage as a result of acute or progressive accumulation of toxic metabolites within the liver (Hansen and Horslen 2008). Unfortunately, an indeterminate cause of ALF was assigned to 54% of children <3 years of age and 49% overall (Taylor and Whittington 2016). Replacement of hepatic parenchyma with nonfunctioning tissue is an occasional cause of PALF with hepatic hemangioma, leukemia, and various other liver tumors representing the most prominent etiologies. Hypoxic-ischemic liver injury is an uncommon cause of ALF, but never in the absence of other

major organ dysfunction. Gestational alloimmune liver disease (GALD), the most common cause of neonatal ALF, is caused by transplacental passage of maternal alloantibody that activates fetal complement and leads to the formation of a membrane attack complex, resulting in hepatocyte injury (Whittington 2012).

It is unclear why some individuals recover from ALF spontaneously while others die or require LT. The final outcome is likely dependent on the underlying etiology, modifying effects of host factors, and whether or not the massive parenchymal loss can be compensated by liver progenitor cell (LPC)-mediated regeneration. Due to the rapid and severe course of the disease, several factors may determine whether LPC-dependent liver regeneration can save the failing liver, including the number of activated cells, speed of cell proliferation, and direction of cell differentiation (Weng et al. 2015). These critical issues are awaiting further investigation.

Presentation

Jaundice is the presenting symptom in most children with ALF. A prodromal phase indistinguishable from that of acute viral hepatitis, associated with non-specific symptoms of malaise, nausea, vomiting, anorexia, and abdominal discomfort, may precede the appearance of jaundice. As the disease progresses, most patients develop hepatic encephalopathy (HE), a complex neuropsychiatric syndrome that encompasses a spectrum of disease ranging from excessive sleepiness or confusion to severe psychomotor retardation or loss of consciousness. HE is classified into four grades based on the degree of impairment reflected by neurologic, psychiatric and physical findings (Ferenci et al. 2002). HE is particularly difficult to assess in young children and neonates. Infants may present initially with poor feeding, irritability, inconsolable crying, and altered sleep patterns, with frank features of HE manifesting late in the course of the disease.

Coagulation abnormalities related to decreased synthesis of clotting factors as well as qualitative platelet abnormalities are seen in ALF and may

result in gastrointestinal or mucocutaneous bleeding (Kurtovic et al. 2005). The bleeding tendency accounts for increased risk of morbidity and mortality in patients with ALF undergoing diagnostic or therapeutic invasive procedures. Multiple organ failure is a complication of ALF with substantial renal dysfunction occurring in more than 50% of patients with ALF (Bernal and Wendon 2014). ALF often results in impaired glycogen storage and a diminished ability for gluconeogenesis. Therefore, ALF should be considered in children who are hypoglycemic and, likewise, children who are diagnosed with ALF should be monitored closely for hypoglycemia (Krasko et al. 2003). Findings on physical examination may include jaundice, hepatosplenomegaly, ascites, dilated abdominal veins secondary to portal hypertension, and cutaneous stigmata of chronic liver disease (e.g. spider nevi, palmar erythema, and leukonychia).

Diagnosis

Encephalopathy may be absent, late, or unrecognized in children (Chen et al. 2003). Therefore, the diagnostic emphasis in PALF is placed on the presence of coagulopathy that is not correctable by the administration of parenteral vitamin K. The PALF Study Group used an INR > 2.0 as the primary defining feature of ALF in young children where hepatic encephalopathy cannot be reliably determined (Squires et al. 2006). Because ALF progresses rapidly, patients require prompt medical evaluation and treatment, preferably in a tertiary referral center that performs liver transplantation and is experienced in treating pediatric liver disease. The diagnostic evaluation of these critically ill patients is challenged by many factors, including the lack of consensus on an age-appropriate evaluation, the short time interval between presentation and outcome, and limitations on the maximum allowable blood draw volume.

A wide range of laboratory studies is required to determine the etiology, severity, and prognosis in pediatric patients with ALF. The initial laboratory evaluation can be divided into three areas:

(1) basic screening tests to assess hematological, renal, and electrolyte abnormalities; (2) liver-specific biochemical and function tests; and (3) diagnostic tests indicated for signs and symptoms suggestive of a specific pathology. Proactive coordination of these tests is necessary to ensure that high-priority tests are performed expeditiously.

Serum aminotransferase levels do not correlate with the severity of the disease (Giannini et al. 2005). Their degree of elevation varies during the course of injury and may depend on the mechanism. It is important to note that a decrease in aminotransferase levels alone does not have prognostic value, since both resolution and massive hepatic necrosis may cause a similar biochemical picture. Both direct and indirect serum bilirubin levels are usually elevated. Typically, conjugated hyperbilirubinemia is present. Hypoalbuminemia, prolongation of the prothrombin time, and hypoglycemia are markers of synthetic liver dysfunction. Serum creatinine levels have been recognized as strong predictors of survival and the need for LT. The correlation between ammonia levels and the severity of HE remains controversial (Ong et al. 2003).

A comprehensive summary of the specific diagnostic tests for the cause of ALF is beyond the scope of this review. Unfortunately, the tendency is to attempt to rule out every known cause of liver disease with exhaustive and expensive testing. A well-thought workup is far more useful. Priority should be guided by the age of the patient and those conditions amenable to specific therapies. Even if no specific therapy exists, establishing a diagnosis may have important implications regarding the decision to proceed with LT and/or offer genetic counseling for heritable diseases that predispose to early cirrhosis (Whittington and Hibbard 2004). While some disorders such as GALD and galactosemia have characteristic clinical presentations, a detailed history and physical examination cannot be overlooked or abbreviated. Exposure to contacts with infectious hepatitis, accurate medication reconciliation, or a family history of Wilson's disease, α -1 antitrypsin deficiency, infectious hepatitis, infant deaths, or autoimmune conditions might

lead to a specific diagnosis. Despite recent improvements, current practice indicates that the diagnostic evaluation in children with ALF is often insufficient and the precise etiology remains unidentified in approximately 50% of cases (Narkewicz et al. 2009).

Management

In the absence of a condition known to respond to specific therapy (e.g. acute APAP toxicity, HSV, GALD, tyrosinemia, galactosemia, AIH), the medical management of PALF is largely supportive (Squires et al. 2006). Medical treatment is focused on monitoring and supporting the physiological functions of the liver as well as prompt identification and treatment of complications as a bridge to spontaneous recovery or LT. A multidisciplinary approach and early referral to a pediatric liver transplantation center with an experienced hepatologist, transplant surgeon, and intensivist are essential.

Vital signs, including continuous blood oxygen saturation, should be carefully monitored. Metabolic, hematologic, and coagulation parameters should be monitored daily, or more frequently in an unstable child, until the patient becomes stable. Serial neurologic examinations performed at regular intervals are essential to characterize the degree and progression of HE. The use of benzodiazepines and other sedative medications must be avoided in non-intubated patients to prevent worsening or interference with assessment of the neurological status. If sedation is required, agents with a short half-life such as midazolam, propofol, or dexmedetomidine are preferred. Placement of a central venous catheter allows for measurement of central venous pressure, administration of fluids, medications, and blood products, and frequent laboratory monitoring. Any child who has grade III or IV encephalopathy should be intubated (Pediatric Gastroenterology Chapter of Indian Academy of Pediatrics et al. 2013).

General supportive care includes correction of any fluid, electrolyte, and acid-base disturbances. Intravenous fluids should be tailored to the

clinical status of the patient and restricted to 85–90% of maintenance volumes to avoid fluid overload (Squires 2008). The classic signs and symptoms of hypoglycemia are often obscured, especially in the presence of encephalopathy; therefore, blood glucose levels should be monitored regularly. Oral or enteral nutrition is preferred to parenteral nutrition if it can be done in a safe manner and there is a functional gastrointestinal tract. Protein restriction is not recommended for children with HE. If a metabolic condition is suspected, all nutrition should be discontinued for 24 h and then restarted keeping the specific condition in mind (Pediatric Gastroenterology Chapter of Indian Academy of Pediatrics et al. 2013).

One of the most serious complications of ALF is intracranial hypertension as a result of cerebral edema and HE, which can cause irreversible neurologic damage, and death (Cochran and Losek 2007). Classic signs of intracranial hypertension, such as papilledema and loss of pupillary reflexes are not always clinically apparent and radiographic evidence of cerebral edema frequently occurs late and does not reliably detect intracranial hypertension (Hirsch et al. 2000). Direct intracranial pressure (ICP) monitoring is the most accurate method to monitor changes in intracranial pressure in ALF patients. However, ICP monitoring is not routinely recommended due to the risk of local complications and lack of survival benefit (Vaquero et al. 2005). Management of intracranial hypertension often reflects the preferences of individual centers and may include positioning the head of the patient at $>30^\circ$ from horizontal, hyperventilation of intubated patients to a PCO_2 of <35 mmHg, infusion of hypertonic saline to maintain serum sodium at 145–155 mmol/L, mannitol infusions for surges of ICP exceeding 20 mmHg, maintenance of mild-moderate hypothermia, and bowel decontamination with lactulose or neomycin to reduce ammonia levels. If lactulose is administered, care should be taken to avoid over distension of the abdomen, which can interfere with a liver transplant procedure, if required.

Routine correction of coagulopathy with fresh frozen plasma (FFP) and other procoagulation

products such as recombinant factor VIIa is not recommended, as they often obscure the trend of INR as a prognostic marker and impair medical decision making regarding LT. However, replacement is indicated in patients with clinically significant bleeding or prior to invasive procedures (Rahman and Hodgson 2001). Risks associated with FFP include volume overload and transmission of infectious agents via large donor pools. Cryoprecipitate may be helpful in patients with significant hypofibrinogenemia (<100 mg/dL). Platelet transfusion is not recommended unless a threshold platelet count of $10\text{--}20 \times 10^9 \text{ L}^{-1}$ is reached or there is significant bleeding and platelet count $<50 \times 10^9 \text{ L}^{-1}$ (Drews and Weinberger 2000). Prophylactic use of proton pump inhibitors aid in the prevention of gastrointestinal bleeding (Polson et al. 2005).

Due to impaired immune function, bacterial and fungal infections are common and a leading cause of mortality (Wade et al. 2003). An active uncontrolled infection is also a relative contraindication for LT. Surveillance cultures should be obtained upon admission and with any unexplained deterioration in clinical status. Empiric administration of broad-spectrum antibiotics is recommended when the likelihood of impending sepsis is high (Stravitz et al. 2007). Empiric antibiotics are also recommended for patients with ALF listed for LT, since immunosuppression after liver transplant is imminent. Fluconazole or amphotericin should be added for suspected or proven fungal infection.

Renal dysfunction occurs in many patients with ALF and is usually multifactorial with components of acute tubular necrosis, hypovolemia and even hepatorenal syndrome. Avoidance of nephrotoxic agents, including aminoglycosides and non-steroidal anti-inflammatory drugs is critical. If progressive renal failure ensues, continuous venovenous hemofiltration is preferred over standard hemodialysis due to less dramatic fluid shifts. Use of plasmapheresis and therapeutic plasma exchange have been advocated in children with ALF to improve coagulopathy and prevent bleeding complications while allowing for adjustments of fluid, electrolyte, and acid-base balance (Singer et al. 2001).

Because ALF in children can progress rapidly, a timely decision to proceed to LT is needed to prevent sequelae. Unfortunately, existing prognostic scoring systems based on biochemical markers and/or clinical features, including the King's College Criteria, have not been shown to be useful for predicting survival or death in PALF (Shanmugam and Dhawan 2011).

Approximately 10–15% of pediatric liver transplants are performed for ALF (Squires et al. 2006). Although post-transplant survival in PALF remains lower than that observed for children who receive liver transplants for other causes, pediatric liver transplant recipients have the highest survival rate for any solid organ (Baliga et al. 2004). Contraindications to LT are active uncontrollable sepsis, severe cardiopulmonary disease, multisystem organ failure, extrahepatic malignancy, and severe neurological impairment. Artificial and bioartificial liver support devices such as the Molecular Absorbent Recirculating System (MARS) and Extracorporeal Liver Assist Device (ELAD), which temporarily perform normal hepatocyte functions, are currently undergoing development for PALF as a means of bridging patients to either transplantation or spontaneous recovery during native liver regeneration.

Pancreatitis

Over the last two decades the incidence of pancreatitis among children has been on the rise. A lack of historical pediatric data represents a major limitation in determining the degree of this increase but several studies out of the United States, Mexico and Australia have all shown a significant increase in the number of hospital admission for pediatric pancreatitis (Bai et al. 2011). Establishing the true incidence of pediatric pancreatitis is further complicated by a vast difference in incidence reports amongst hospitals which is felt to be due to variations in institutional management of acute abdominal pain, particularly in emergency units (Zsoldos et al. 2016). Despite the likely under reporting of acute pancreatitis (AP) in children, retrospective analysis suggests the true incidence of disease to be

approximately 13.2 cases per 100,000 children in the United States (Morinville et al. 2010).

Although the increase in disease burden is well recognized for pediatric pancreatitis, data on pathophysiology, etiologies, management and clinical outcomes is continuing to take shape. The majority of available data is based almost exclusively from the adult literature, yet pancreatitis among adults is likely a very different disease than that seen in children given the differences in etiological backgrounds (Abu-El-Haija et al. 2014). Among adult patients with AP, alcohol and biliary etiologies predominate while genetic, anatomic, metabolic and toxic causes are much more prevalent amongst pediatric patients (Husain et al. 2016). Fortunately, a greater amount of attention has been focused recently on addressing pediatric specific pancreatitis concerns with large, pediatric-centered consortium such as INSPPIRE (International Study Group of Pediatric Pancreatitis: In Search for a Cure) and PINEAPPLE (Pain in Early Phase of Pediatric Pancreatitis) already significantly increasing our understanding of the disease process and burden.

Presentation

Abdominal pain is the most common initial presentation of AP affecting 80–95% of patients, with nausea or vomiting noted in up to 80% of cases (Bai et al. 2011). Importantly though, infants and toddlers are less likely to present with abdominal pain (43–93%) and/or emesis (29–76%), but have a higher likelihood of presenting with abdominal distention (16%) or fever (40%), both of which are rare in older patients (Kandula and Lowe 2008; Park et al. 2010). Biochemical presentation may also differ by age. In older patients the sensitivity of amylase to detect AP ranges from 50% to 85% with lipase felt to be approximately 75% more sensitive (Park et al. 2010). However, among infants and toddlers, studies suggest 100% of patients will have elevated lipase levels with only approximately 50% having elevated amylase levels (Kandula and Lowe 2008). Amylase remains an important marker in the detection of AP though as several

reports exist of patients with radiographic evidence of pancreatitis with isolated elevation of their amylase seen (Werlin et al. 2003; Bai et al. 2011).

Etiologies

While the pathophysiology remains obscure and largely theoretical, several risk factors are known to increase a patient's risk of developing AP. Risk factors typically fit into one of the following four categories: (1) Metabolic, (2) Environmental, (3) Genetic, or (4) Anatomical/Obstructive.

Metabolic

Hypertriglyceridemia, hypercalcemia and chronic renal failure are all considered significant risk factors for the development of AP and acute recurrent pancreatitis (ARP). Triglyceride levels >1000 mg/dL represent an absolute risk, while levels >500 mg/dL represent an absolute risk for the development of AP (Bălănescu et al. 2013; Christian et al. 2014). A threshold for hypercalcemia imparting a risk for AP has yet to be established but hypercalcemia associated with primary hyperparathyroidism, high IV calcium during cardiac surgery or parenteral nutrition administration, and ectopic secretion of calcium-mobilizing hormones such as seen acute lymphoblastic leukemia have all been associated with the development of pancreatitis (Husain et al. 2016). Autopsy studies have shown significant pancreatic disease among patients with end stage renal disease. However, determining the diagnosis of pancreatitis in patients with chronic renal failure may be difficult due to the impaired clearance of amylase and lipase leading to the recommendation that levels 3× ULN are needed in order to make diagnosis in this specific patient population (Husain et al. 2016).

Environmental

To date no studies have shown a clear association between smoking and/or alcohol use and the development of pancreatitis among children, although as one might imagine data on the subject is scarce (Husain et al. 2016; Kumar et al. 2016). Drug-induced pancreatitis is felt to repre-

sent a small proportion of all pancreatitis cases (0.3–2%) but is an important consideration for patients on certain medications which include certain antibiotics, nonsteroidal anti-inflammatory agents, immunomodulators, certain chemotherapeutic agents, antiepileptic drugs, antihypertensives, antihyperglycemics and antiviral therapies (Nitsche et al. 2012). Directly establishing drug-induced pancreatitis is often difficult requiring a withdrawal and monitor approach. Utilization of drug-induced pancreatitis algorithms, such as that proposed by Trivedi, may be of use to the clinician to more accurately recognize drug-induced pancreatitis (Trivedi and Pitchumoni 2005).

Genetic

Cystic fibrosis transmembrane conductance regulator (CFTR), pancreatic secretory trypsin inhibitor (SPINK1), cationic trypsinogen (PRSS1) and chymotrypsin C (CTRC) represent the major genetic causes of ARP and chronic pancreatitis (CP) in children. A recent review of the INSPPIRE database showed 48% of patients with ARP and 73% of patients with CP had at least one mutation on one of these pancreatitis-associated genes. The most common mutation associated with ARP was CFTR (34% of patients) while PRSS1 was the most commonly seen mutation among patients with CP (46%) (Kumar et al. 2016).

Anatomic/Obstructive

Approximately 1/3 of patients with ARP or CP are felt to have an anatomic or obstructive etiology (Kumar et al. 2016). Although surgical intervention is required in certain anatomical conditions, many obstructive etiologies may safely be managed by ERCP, which has been shown to be safe and effective in pediatric patients (Enestvedt et al. 2013; Halvorson et al. 2013; Saito et al. 2014).

Management

Historically, management of pancreatitis has been based on adult recommendations but more recently pediatric driven data is emerging suggesting new approaches may be warranted.

Acute Pancreatitis

Pain management is an integral part of AP management with narcotics often considered the drug of choice. However, determining when to introduce enteral nutrition and how aggressive to be with IV hydration have been highly debated topics in pediatric AP research. Recent pediatric studies have shown that aggressive IV hydration (1.5–2× maintenance) over the first 48 hours and early enteral nutrition (within 48 h) were not only safe but also resulted in shortened hospital stays and decreased risk of developing severe AP (Szabo et al. 2015). Additionally, those patients who consumed a high fat intake experienced lower pain scores as compared to those placed on a fat restricted diet (Abu-El-Haija et al. 2016).

Chronic

Pain control is the mainstay of therapy for patients with CP and without proper oversight may result in narcotic addiction. Therefore, neuropathic pain control with tricyclic antidepressants, gabapentin or pregabalin are preferred (Pohl and Uc 2015). The use of proton-pump inhibitors, antioxidants and pancreatic enzymes for pain control have been proposed but none have been thoroughly studied or shown to be of benefit in pediatric pancreatitis. In severe cases of ARP and CP in which pain becomes unmanageable, total pancreatectomy with islet autotransplantation may be a viable option (Bellin et al. 2016).

Endoscopy

Pediatric esophagogastroduodenoscopy (EGD) was first described in the 1970's and has transformed from an infrequently performed procedure with significant risk to the routine, often outpatient procedure that it is viewed as today (Friedt and Welsch 2013). The majority of Advances in pediatric endoscopy have resulted in physicians becoming less reliant on invasive surgical measures and advancing imaging techniques such as CT and MRI, which are frequently less sensitive and specific, to diagnose and treat a variety of gastrointestinal disorders. Future advancements promise to further decrease the need of invasive procedures requiring sedation

and/or anesthesia while simultaneously improving diagnostic and therapeutic efficacy.

Esophagogastroduodenoscopy

From 1985 to 2005 there was over a 12-fold increase in the number of pediatric EGD's performed (Franciosi et al. 2010). Expanding diagnostic and therapeutic indications for EGD has resulted in further growth of the field with EGD becoming viewed as a routine procedure in many larger institutions (see Table 10.13 for common indications for EGD). Growth in interventional technologies has been particularly influential in changing the way we treat a number of conditions including, but not limited to, foreign body ingestions and acute gastrointestinal bleeding.

Foreign Body Ingestion

Although patients with a retained foreign body may present with drooling, pain, stridor, refusal to eat, dysphasia, stridor, wheezing or respiratory distress, approximately 50% of pediatric foreign body ingestions will present without symptoms (Temiz 2015). Coins represent the most common accidental ingestion in children in the western hemisphere, accounting for ~70% of ingestions (Peters et al. 2015). While a number of other toys, jewelry, food products (e.g. bones) and other common objects can be ingested, special attention must be shown to any object stuck in the esophagus for over 24 h, button batteries and high-powered Neodymium magnets (e.g. Buckyballs®) given the potential risk of bowel perforation and should prompt immediate referral to a pediatric center with advanced endoscopy capabilities (see Fig. 10.7).

Upper Gastrointestinal Bleeding

Life threatening gastrointestinal bleeding is a rare occurrence in pediatrics and is best treated by an advanced endoscopist at a pediatric tertiary care center. Interventions are dependent upon the size of the child, the site of the bleed and the judgment of the endoscopist (Rahman et al. 2015). Bleeding is typically characterized as variceal or non-variceal. Variceal bleeding is

Table 10.13 Common indications for pediatric EGD

| Diagnostic | Therapeutic |
|---|-------------------------------|
| Abdominal pain/functional disorders | Foreign body/Bezoar removal |
| Weight loss/failure to thrive | Enteral tube placement |
| Dysphasia/odynophagia | Dilation |
| Diarrhea/malabsorption | Banding/injection of varices |
| Emesis/hematemesis | Non-variceal bleeding control |
| Iron deficiency anemia | Polypectomy |
| Enteropathy/suspected celiac disease | Botox/other injections |
| Suspected/surveillance inflammatory bowel disease | |

Common diagnostic and therapeutic indications for performing an EGD in pediatric patients (Adapted from Rahman et al. (2015))

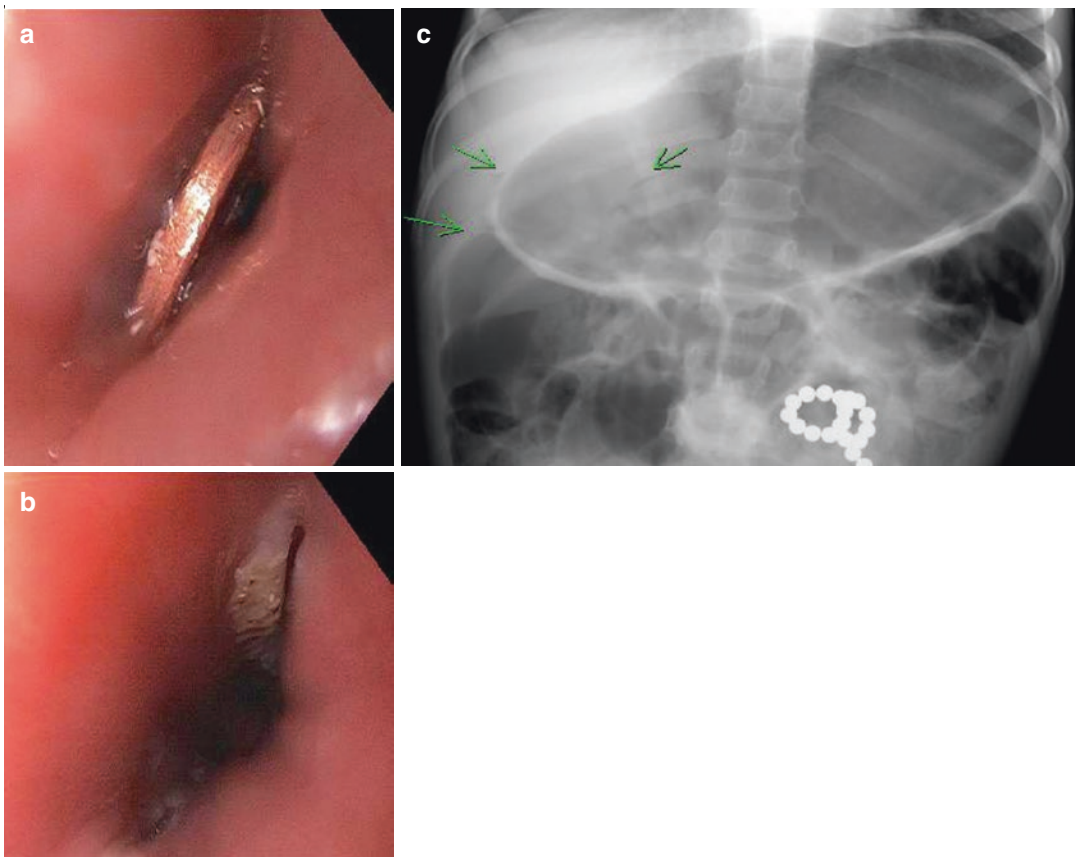


Fig. 10.7 Coin and neodymium magnet ingestions. (a) EGD image of penny ingested in a 2 year old >30 h before presentation to the emergency room with resulting linear ulcer (*B-blue asterix*) after extraction. (c) Shows abdomi-

nal x-ray of a neodymium magnet ingestion in a 5 year old with free air seen below the diaphragm (*green arrows*) from resulting intestinal perforation

typically managed with IV octreotide and endoscopic banding or sclerotherapy (Thomson and Belsha 2016). Non-variceal bleeding is typically treated with two of the following classes of inter-

ventions; (1) injection therapy (e.g. adrenaline, sclerosing agents, fibrin glue or normal saline), (2) Mechanical therapy (e.g. endoscopic hemoclips) or (3) Thermo-coagulation (e.g. hot biopsy

forceps, gold probe or argon plasma coagulation) (Thomson and Belsha 2016).

Future Directions

A specific focus of endoscopic research has been to decrease the need for surgical intervention in patients with severe gastroesophageal reflux disease (GERD). Two exciting techniques that have been developed are endoluminal gastroplication and iatrogenic stricture formation through radio-frequency energy as replacements for surgical funduplications (Rahman et al. 2015). While initial results are promising, years more research is required before these modalities will be determined to have any potential use in pediatric reflux therapy.

Endoscopic Retrograde Cholangiopancreatography (ERCP)

ERCP has been established as an effective diagnostic and therapeutic tool for pancreaticobiliary disorders in pediatrics. The invention of smaller diameter duodenoscopes in the late 1980s allowed for ERCP use in the pediatric population with several studies reporting outcomes in pediatrics is not statistically different than that seen in the adult population (Enestvedt et al. 2013; Halvorson et al. 2013; Troendle et al. 2015; Giefer and Kozarek 2015; Yıldırım et al. 2016). The primary impediment to pediatric ERCP is finding a pediatric endoscopist trained in ERCP or an adult endoscopist with appropriate sized duodenoscopes and access to a center with experience performing ERCP in children.

Evaluation of the Small Intestine

Previously felt to be “unreachable”, the invention of video capsule endoscopy (VCE) and balloon enteroscopy has provided advanced endoscopist two new tools to access for mucosal changes in the small intestine. With balloon enteroscopy, the endoscopist also has the added capability to perform biopsies of distal small bowel and perform therapeutic measures similar to those that are

capable with EGD. Investigation of obscure GI bleeds or unexplained anemia, investigation of IBD and surveillance of polyposis syndromes are the main indications for both modalities (Zevit and Shamir 2015). Like many of the other interventions outlined in this section, VCE and balloon enteroscopy are best performed at pediatric tertiary centers by pediatric gastrointestinal providers with experience utilizing these modalities. Future directions include VCE dedicated to evaluate the esophagus and colon in order to decrease the number of endoscopy procedures that require anesthesia.

Colonoscopy

While a number of advancements have occurred in upper endoscopy and small bowel imaging, colonoscopy has remained essentially unchanged and continues to serve more as a diagnostic tool. The main pediatric indications for colonoscopy remain: (1) Hematochezia, (2) Abdominal pain, (3) Diarrhea and (4) Polypectomy/polyp screening (Park 2010).

References

- Abu-El-Haija M, Lin TK, Palermo J. Update to the management of pediatric acute pancreatitis: highlighting areas in need of research. *J Pediatr Gastroenterol Nutr.* 2014;58:689–93. <https://doi.org/10.1097/MPG.0000000000000360>.
- Abu-El-Haija M, Wilhelm R, Heinzman C, et al. Early enteral nutrition in children with acute pancreatitis. *J Pediatr Gastroenterol Nutr.* 2016;62:453–6. <https://doi.org/10.1097/MPG.0000000000001013>.
- Adams LA, Lymp JF, St Sauver J, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology.* 2005;129:113–21.
- American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics.* 2004;114:297–316.
- American Lung Association Asthma Clinical Research Centers, Mastrorade JG, Anthonisen NR, et al. Efficacy of esomeprazole for treatment of poorly controlled asthma. *N Engl J Med.* 2009;360:1487–99. <https://doi.org/10.1056/NEJMoa0806290>.
- Andorsky DJ, Lund DP, Lillehei CW, et al. Nutritional and other postoperative management of neonates

- with short bowel syndrome correlates with clinical outcomes. *J Pediatr*. 2001;139:27–33. <https://doi.org/10.1067/mpd.2001.114481>.
- Arias A, González-Cervera J, Tenias JM, Lucendo AJ. Efficacy of dietary interventions for inducing histologic remission in patients with eosinophilic esophagitis: a systematic review and meta-analysis. *Gastroenterology*. 2014;146:1639–48. <https://doi.org/10.1053/j.gastro.2014.02.006>.
- Bai HX, Lowe ME, Husain SZ. What have we learned about acute pancreatitis in children? *J Pediatr Gastroenterol Nutr*. 2011;52:262–70. <https://doi.org/10.1097/MPG.0b013e3182061d75>.
- Bălănescu NR, Topor L, Ulici A, Djendov FB. Acute pancreatitis secondary to hyperlipidemia in an 11-year-old girl: a case report and review of literature. *J Med Life*. 2013;6:2–6.
- Baldassano RN, Piccoli DA. Inflammatory bowel disease in pediatric and adolescent patients. *Gastroenterol Clin N Am*. 1999;28:445–58.
- Baliga P, Alvarez S, Lindblad A, et al. Posttransplant survival in pediatric fulminant hepatic failure: the SPLIT experience. *Liver Transpl*. 2004;10:1364–71. <https://doi.org/10.1002/lt.20252>.
- Balistreri WF. Neonatal cholestasis. *J Pediatr*. 1985;106:171–84.
- Balistreri WF, Bezerra JA. Whatever happened to "neonatal hepatitis"? *Clin Liver Dis*. 2006;10:27–53v. <https://doi.org/10.1016/j.cld.2005.10.008>.
- Barlow SE, Expert Committee. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. *Pediatrics*. 2007;120(Suppl 4):S164–92. <https://doi.org/10.1542/peds.2007-2329C>.
- Beattie RM, Nicholls SW, Domizio P, et al. Endoscopic assessment of the colonic response to corticosteroids in children with ulcerative colitis. *J Pediatr Gastroenterol Nutr*. 1996;22:373–9.
- Bellin MD, Kerdsirichairat T, Beilman GJ, et al. Total pancreatectomy With islet autotransplantation improves quality of life in patients with refractory recurrent acute pancreatitis. *Clin Gastroenterol Hepatol*. 2016; <https://doi.org/10.1016/j.cgh.2016.02.027>.
- Benninga MA, Faure C, Hyman PE, et al. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterology*. 2016;(150):1443–1455.e2. <https://doi.org/10.1053/j.gastro.2016.02.016>.
- Bernal W, Wendon J. Acute liver failure. *N Engl J Med*. 2014;370:1170–1. <https://doi.org/10.1056/NEJMc1400974>.
- Bernstein CN, Fried M, Krabshuis JH, et al. World Gastroenterology Organization practice guidelines for the diagnosis and management of IBD in 2010. *Inflamm Bowel Dis*. 2010;16:112–24.
- Bhutani VK, Stark AR, Lazzaroni LC, et al. PredischARGE screening for severe neonatal hyperbilirubinemia identifies infants who need phototherapy. *J Pediatr*. 2013;162:477–482.e1. <https://doi.org/10.1016/j.jpeds.2012.08.022>.
- Bilzer M, Roggel F, Gerbes AL. Role of Kupffer cells in host defense and liver disease. *Liver Int*. 2006;26:1175–86. <https://doi.org/10.1111/j.1478-3231.2006.01342.x>.
- Bortolotti F, Verucchi G, Cammà C, et al. Long-term course of chronic hepatitis C in children: from viral clearance to end-stage liver disease. *Gastroenterology*. 2008;134:1900–7. <https://doi.org/10.1053/j.gastro.2008.02.082>.
- Boyer JL. New perspectives for the treatment of cholestasis: lessons from basic science applied clinically. *J Hepatol*. 2007;46:365–71. <https://doi.org/10.1016/j.jhep.2006.12.001>.
- Boyer TD, Wright T, Manns MP. Zakim and Boyer's hepatology: a textbook of liver disease. Berlin: Elsevier Health Sciences; 2011.
- Bucuvalas J, Yazigi N, Squires RH. Acute liver failure in children. *Clin Liver Dis*. 2006;10:149–68vii. <https://doi.org/10.1016/j.cld.2005.10.006>.
- Bursch B. Psychological/cognitive behavioral treatment of childhood functional abdominal pain and irritable bowel syndrome. *J Pediatr Gastroenterol Nutr*. 2008;47:706–7. <https://doi.org/10.1097/01.mpg.0000338967.47679.e9>.
- Chacko KR, Reinus J. Extrahepatic complications of nonalcoholic fatty liver disease. *Clin Liver Dis*. 2016;20:387–401. <https://doi.org/10.1016/j.cld.2015.10.004>.
- Chalasan N. Statins and hepatotoxicity: focus on patients with fatty liver. *Hepatology*. 2005;41:690–5. <https://doi.org/10.1002/hep.20671>.
- Chalasan N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology*. 2012;55:2005–23.
- Chan WW, Chiou E, Obstein KL, et al. The efficacy of proton pump inhibitors for the treatment of asthma in adults: a meta-analysis. *Arch Intern Med*. 2011;171:620–9. <https://doi.org/10.1001/archinternmed.2011.116>.
- Chang MH, Hsu HY, Hsu HC, et al. The significance of spontaneous hepatitis B e antigen seroconversion in childhood: with special emphasis on the clearance of hepatitis B e antigen before 3 years of age. *Hepatology*. 1995;22:1387–92.
- Chang M-H, Chen TH-H, Hsu H-M, et al. Prevention of hepatocellular carcinoma by universal vaccination against hepatitis B virus: the effect and problems. *Clin Cancer Res*. 2005;11:7953–7. <https://doi.org/10.1158/1078-0432.CCR-05-1095>.
- Charlton MR, Burns JM, Pedersen RA, et al. Frequency and outcomes of liver transplantation for nonalcoholic steatohepatitis in the United States. *Gastroenterology*. 2011;141:1249–53. <https://doi.org/10.1053/j.gastro.2011.06.061>.
- Chen C-L, Fan S-T, Lee S-G, et al. Living-donor liver transplantation: 12 years of experience in Asia. *Transplantation*. 2003;75:S6–11. <https://doi.org/10.1097/01.TP.0000046533.93621.C7>.

- Choudhury J, Sanyal AJ. Clinical aspects of fatty liver disease. *Semin Liver Dis.* 2004;24:349–62. <https://doi.org/10.1055/s-2004-860864>.
- Christian JB, Arondekar B, Buysman EK, et al. Determining triglyceride reductions needed for clinical impact in severe hypertriglyceridemia. *Am J Med.* 2014;127:36–44.e1. <https://doi.org/10.1016/j.amjmed.2013.09.018>.
- Clarke P, Robinson MJ. Thickening milk feeds may cause necrotising enterocolitis. *Arch Dis Child Fetal Neonatal Ed.* 2004;89:F280.
- Cochran JB, Losek JD. Acute liver failure in children. *Pediatr Emerg Care.* 2007;23:129–35. <https://doi.org/10.1097/PEC.0b013e3180308f4b>.
- Contreras EM, Gupta SK. Steroids in pediatric eosinophilic esophagitis. *Gastroenterol Clin N Am.* 2014;43:345–56. <https://doi.org/10.1016/j.gtc.2014.02.008>.
- Corte Della C, Mosca A, Vania A, et al. Pediatric liver diseases: current challenges and future perspectives. *Expert Rev Gastroenterol Hepatol.* 2016;10:255–65. <https://doi.org/10.1586/17474124.2016.1129274>.
- D'Albuquerque LAC, Gonzalez AM, Wahle RC, et al. Liver transplantation for subacute hepatocellular failure due to massive steatohepatitis after bariatric surgery. *Liver Transpl.* 2008;14:881–5. <https://doi.org/10.1002/lt.21472>.
- D'Alessandro A, Esposito D, Pesce M, et al. Eosinophilic esophagitis: from pathophysiology to treatment. *World J Gastrointest Pathophysiol.* 2015;6:150–8. <https://doi.org/10.4291/wjgp.v6.i4.150>.
- Dani C, Pratesi S, Raimondi F, et al. Italian guidelines for the management and treatment of neonatal cholestasis. *Ital J Pediatr.* 2015;41:69. <https://doi.org/10.1186/s13052-015-0178-7>.
- de Meij TGT, Budding AE, Grasman ME, et al. Composition and diversity of the duodenal mucosa-associated microbiome in children with untreated coeliac disease. *Scand J Gastroenterol.* 2013;48:530–6. <https://doi.org/10.3109/00365521.2013.775666>.
- de Onís M, Monteiro C, Akre J, Glugston G. The worldwide magnitude of protein-energy malnutrition: an overview from the WHO global database on child growth. *Bull World Health Organ.* 1993;71:703–12.
- Dellon ES, Gonsalves N, Hirano I, et al. ACG clinical guideline: evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). *Am J Gastroenterol.* 2013;108:679–92-quiz 693.
- Dellon ES, Speck O, Woodward K, et al. Distribution and variability of esophageal eosinophilia in patients undergoing upper endoscopy. *Mod Pathol.* 2015;28:383–90. <https://doi.org/10.1038/modpathol.2014.110>.
- Denniston MM, Jiles RB, Drobeniuc J, et al. Chronic hepatitis C virus infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. *Ann Intern Med.* 2014;160:293–300. <https://doi.org/10.7326/M13-1133>.
- Dent J, El-Serag HB, Wallander M-A, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut.* 2005;54:710–7. <https://doi.org/10.1136/gut.2004.051821>.
- Desai TK, Stecevic V, Chang C-H, et al. Association of eosinophilic inflammation with esophageal food impaction in adults. *Gastrointest Endosc.* 2005;61:795–801.
- Drews RE, Weinberger SE. Thrombocytopenic disorders in critically ill patients. *Am J Respir Crit Care Med.* 2000;162:347–51. <https://doi.org/10.1164/ajrccm.162.2.ncc3-00>.
- Drossman DA, Hasler WL. Rome IV-functional GI disorders: disorders of gut-brain interaction. *Gastroenterology.* 2016;150:1257–61. <https://doi.org/10.1053/j.gastro.2016.03.035>.
- Enestvedt BK, Tofani C, Lee DY, et al. Endoscopic retrograde cholangiopancreatography in the pediatric population is safe and efficacious. *J Pediatr Gastroenterol Nutr.* 2013;57:649–54. <https://doi.org/10.1097/MPG.0b013e31829e0bb6>.
- Farrell GC, Larter CZ. Nonalcoholic fatty liver disease: from steatosis to cirrhosis. *Hepatology.* 2006;43:S99–S112. <https://doi.org/10.1002/hep.20973>.
- Fawaz R, Baumann U, Ekong U, et al. Guideline for the evaluation of cholestatic jaundice in infants: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr.* 2016;1 <https://doi.org/10.1097/MPG.0000000000001334>.
- Ferenci P, Lockwood A, Mullen K, et al. Hepatic encephalopathy—definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. *Hepatology.* 2002;35:716–21. <https://doi.org/10.1053/jhep.2002.31250>.
- Fish D, Kugathasan S. Inflammatory bowel disease. *Adolesc Med Clin.* 2004;15:67–90ix. <https://doi.org/10.1016/S1547336803000135>.
- Franciosi JP, Fiorino K, Ruchelli E, et al. Changing indications for upper endoscopy in children during a 20-year period. *J Pediatr Gastroenterol Nutr.* 2010;51:443–7. <https://doi.org/10.1097/MPG.0b013e3181d67bee>.
- Friedt M, Welsch S. An update on pediatric endoscopy. *Eur J Med Res.* 2013;18:24. <https://doi.org/10.1186/2047-783X-18-24>.
- Furuta GT, Katzka DA. Eosinophilic esophagitis. *N Engl J Med.* 2015;373:1640–8. <https://doi.org/10.1056/NEJMra1502863>.
- Giannini EG, Testa R, Savarino V. Liver enzyme alteration: a guide for clinicians. *CMAJ.* 2005;172:367–79. <https://doi.org/10.1503/cmaj.1040752>.
- Giefer MJ, Kozarek RA. Technical outcomes and complications of pediatric ERCP. *Surg Endosc.* 2015;29:3543–50. <https://doi.org/10.1007/s00464-015-4105-1>.
- Gieruszczak-Białek D, Konarska Z, Skórka A, et al. No effect of proton pump inhibitors on crying and irritability in infants: systematic review of randomized controlled trials. *J Pediatr.* 2015;166:767–70.e3. <https://doi.org/10.1016/j.jpeds.2014.11.030>.

- Gremse DA. GERD in the pediatric patient: management considerations. *MedGenMed*. 2004;6:13.
- Grigoleit HG, Grigoleit P. Gastrointestinal clinical pharmacology of peppermint oil. *Phytomedicine*. 2005;12:607–11. <https://doi.org/10.1016/j.phymed.2004.10.006>.
- Gupta SK, Vitanza JM, Collins MH. Efficacy and safety of oral budesonide suspension in pediatric patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2015;13:66–76.e3. <https://doi.org/10.1016/j.cgh.2014.05.021>.
- Gutierrez-Achury J, Coutinho de Almeida R, Wijmenga C. Shared genetics in coeliac disease and other immune-mediated diseases. *J Intern Med*. 2011;269:591–603. <https://doi.org/10.1111/j.1365-2796.2011.02375.x>.
- Halmos EP, Power VA, Shepherd SJ, et al. A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. *Gastroenterology*. 2014;146:67–75.e5. <https://doi.org/10.1053/j.gastro.2013.09.046>.
- Halvorson L, Halsey K, Darwin P, Goldberg E. The safety and efficacy of therapeutic ERCP in the pediatric population performed by adult gastroenterologists. *Dig Dis Sci*. 2013;58:3611–9. <https://doi.org/10.1007/s10620-013-2857-9>.
- Hansen K, Horslen S. Metabolic liver disease in children. *Liver Transpl*. 2008;14:713–33. <https://doi.org/10.1002/lt.21520>.
- Hassall E. Endoscopy in children with GERD: “the way we were” and the way we should be. *Am J Gastroenterol*. 2002;97:1583–6. <https://doi.org/10.1111/j.1572-0241.2002.05853.x>.
- Hassall E, Kerr W, El-Serag HB. Characteristics of children receiving proton pump inhibitors continuously for up to 11 years duration. *J Pediatr*. 2007;150:262–267.e1. <https://doi.org/10.1016/j.jpeds.2006.08.078>.
- Henderson P, Casey A, Lawrence SJ, et al. The diagnostic accuracy of fecal calprotectin during the investigation of suspected pediatric inflammatory bowel disease. *Am J Gastroenterol*. 2012;107:941–9. <https://doi.org/10.1038/ajg.2012.33>.
- Heuschkel R, Salvestrini C, Beattie RM, et al. Guidelines for the management of growth failure in childhood inflammatory bowel disease. *Inflamm Bowel Dis*. 2008;14:839–49. <https://doi.org/10.1002/ibd.20378>.
- Hill ID, Fasano A, Guandalini S, et al. NASPGHAN clinical report on the diagnosis and treatment of gluten-related disorders. *J Pediatr Gastroenterol Nutr*. 2016;63:156–65. <https://doi.org/10.1097/MPG.0000000000001216>.
- Hirsch W, Beck R, Behrmann C, et al. Reliability of cranial CT versus intracerebral pressure measurement for the evaluation of generalised cerebral oedema in children. *Pediatr Radiol*. 2000;30:439–43. <https://doi.org/10.1007/s002470000255>.
- Hoerning A, Raub S, Dechêne A, et al. Diversity of disorders causing neonatal cholestasis - the experience of a tertiary pediatric center in Germany. *Front Pediatr*. 2014;2:65. <https://doi.org/10.3389/fped.2014.00065>.
- Holmberg SD, Spradling PR, Moorman AC, Denniston MM. Hepatitis C in the United States. *N Engl J Med*. 2013;368:1859–61. <https://doi.org/10.1056/NEJMp1302973>.
- Holterman A-XL, Holterman M, Browne A, et al. Patterns of surgical weight loss and resolution of metabolic abnormalities in superobese bariatric adolescents. *J Pediatr Surg*. 2012;47:1633–9. <https://doi.org/10.1016/j.jpedsurg.2012.02.002>.
- Holterman A-XL, Guzman G, Fantuzzi G, et al. Nonalcoholic fatty liver disease in severely obese adolescent and adult patients. *Obesity (Silver Spring)*. 2013;21:591–7. <https://doi.org/10.1002/oby.20174>.
- Husain SZ, Morinville V, Pohl J, et al. Toxic-metabolic risk factors in pediatric pancreatitis: recommendations for diagnosis, management, and future research. *J Pediatr Gastroenterol Nutr*. 2016;62:609–17. <https://doi.org/10.1097/MPG.0000000000001035>.
- Husby S, Koletzko S, Korponay-Szabó IR, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. *J Pediatr Gastroenterol Nutr*. 2012;54:136–60.
- Hyams J, Crandall W, Kugathasan S, et al. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. *Gastroenterology*. 2007;132:863–73-quiz 1165–6. <https://doi.org/10.1053/j.gastro.2006.12.003>.
- Hyams JS, Di Lorenzo C, Saps M, et al. Functional disorders: children and adolescents. *Gastroenterology*. 2016;150:1456–1468.e2. <https://doi.org/10.1053/j.gastro.2016.02.015>.
- Iacono G, Bonventre S, Scalici C, et al. Food intolerance and chronic constipation: manometry and histology study. *Eur J Gastroenterol Hepatol*. 2006;18:143–50.
- Iovino P, Tremolaterra F, Boccia G, et al. Irritable bowel syndrome in childhood: visceral hypersensitivity and psychosocial aspects. *Neurogastroenterol Motil*. 2009;21:940–e74. <https://doi.org/10.1111/j.1365-2982.2009.01303.x>.
- Jensen ET, Kappelman MD, Kim HP, et al. Early life exposures as risk factors for pediatric eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr*. 2013;57:67–71. <https://doi.org/10.1097/MPG.0b013e318290d15a>.
- Jensen ET, Hoffman K, Shaheen NJ, et al. Esophageal eosinophilia is increased in rural areas with low population density: results from a national pathology database. *Am J Gastroenterol*. 2014;109:668–75. <https://doi.org/10.1038/ajg.2014.47>.
- Jeppesen PB, Mortensen PB. The influence of a preserved colon on the absorption of medium chain fat in patients with small bowel resection. *Gut*. 1998;43:478–83.
- Kandula L, Lowe ME. Etiology and outcome of acute pancreatitis in infants and toddlers. *J Pediatr*. 2008;152:106–10.e1. <https://doi.org/10.1016/j.jpeds.2007.05.050>.
- Kavitt RT, Penson DF, Vaezi MF. Eosinophilic esophagitis: dilate or medicate? A cost analysis model of the choice of initial therapy. *Dis Esophagus*. 2014;27:418–23. <https://doi.org/10.1111/j.1442-2050.2012.01409.x>.

- Kelly DA, Davenport M. Current management of biliary atresia. *Arch Dis Child*. 2007;92:1132–5. <https://doi.org/10.1136/adc.2006.101451>.
- Kelly DA, Stanton A. Jaundice in babies: implications for community screening for biliary atresia. *BMJ*. 1995;310:1172–3.
- Kemmer N, Neff GW, Franco E, et al. Nonalcoholic fatty liver disease epidemic and its implications for liver transplantation. *Transplantation*. 2013;96:860–2. <https://doi.org/10.1097/01.TP.0000436723.59879.01>.
- Khanna R, MacDonald JK, Levesque BG. Peppermint oil for the treatment of irritable bowel syndrome: a systematic review and meta-analysis. *J Clin Gastroenterol*. 2014;48:505–12. <https://doi.org/10.1097/MCG.0b013e3182a88357>.
- Kieft-de Jong JC, Escher JC, Arends LR, et al. Infant nutritional factors and functional constipation in childhood: the generation R study. *Am J Gastroenterol*. 2010;105:940–5. <https://doi.org/10.1038/ajg.2010.96>.
- Kierkus J, Oracz G, Korczowski B, et al. Comparative safety and efficacy of proton pump inhibitors in paediatric gastroesophageal reflux disease. *Drug Saf*. 2014;37:309–16. <https://doi.org/10.1007/s40264-014-0154-y>.
- Kiljander T, Junghard O, Beckman O, Lind T. Effect of esomeprazole 40 mg once or twice daily on asthma: a randomized, placebo-controlled study. *Am J Respir Crit Care Med*. 2010;181:1042–8. <https://doi.org/10.1164/rccm.200910-1537OC>.
- Kiljander T, Rantanen T, Kellokumpu I, et al. Comparison of the effects of esomeprazole and fundoplication on airway responsiveness in patients with gastroesophageal reflux disease. *Clin Respir J*. 2013;7:281–7. <https://doi.org/10.1111/crj.12005>.
- Kirschner BS. Safety of azathioprine and 6-mercaptopurine in pediatric patients with inflammatory bowel disease. *Gastroenterology*. 1998;115:813–21.
- Kitamoto T, Kitamoto A, Yoneda M, et al. Genome-wide scan revealed that polymorphisms in the PNPLA3, SAMM50, and PARVB genes are associated with development and progression of nonalcoholic fatty liver disease in Japan. *Hum Genet*. 2013;132:783–92. <https://doi.org/10.1007/s00439-013-1294-3>.
- Kotlyar DS, Osterman MT, Diamond RH, et al. A systematic review of factors that contribute to hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2011;9:36–41.e1. <https://doi.org/10.1016/j.cgh.2010.09.016>.
- Krasko A, Deshpande K, Bonvino S. Liver failure, transplantation, and critical care. *Crit Care Clin*. 2003;19:155–83.
- Kugathasan S, Judd RH, Hoffmann RG, et al. Epidemiologic and clinical characteristics of children with newly diagnosed inflammatory bowel disease in Wisconsin: a statewide population-based study. *J Pediatr*. 2003;143:525–31.
- Kumar S, Ooi CY, Werlin S, et al. Risk factors associated with pediatric acute recurrent and chronic pancreatitis: lessons from INSPPIRE. *JAMA Pediatr*. 2016; <https://doi.org/10.1001/jamapediatrics.2015.4955>.
- Kurtovic J, Riordan SM, Williams R. Fulminant hepatic failure. *Curr Treat Options Gastroenterol*. 2005;8:503–18.
- Lakatos P-L. Recent trends in the epidemiology of inflammatory bowel diseases: up or down? *World J Gastroenterol*. 2006;12:6102–8. <https://doi.org/10.3748/wjg.v12.i38.6102>.
- Lashner BA. Epidemiology of inflammatory bowel disease. *Gastroenterol Clin N Am*. 1995;24:467–74.
- Lee C, Gong Y, Brok J, et al. Hepatitis B immunisation for newborn infants of hepatitis B surface antigen-positive mothers. *Cochrane Database Syst Rev*. 2006:CD004790. <https://doi.org/10.1002/14651858.CD004790.pub2>.
- Lee J, Shuker M, Brown-Whitehorn T, et al. Oral viscous budesonide can be successfully delivered through a variety of vehicles to treat eosinophilic esophagitis in children. *J Allergy Clin Immunol Pract*. 2016; <https://doi.org/10.1016/j.jaip.2016.02.005>.
- Lewis JR, Mohanty SR. Nonalcoholic fatty liver disease: a review and update. *Dig Dis Sci*. 2010;55:560–78. <https://doi.org/10.1007/s10620-009-1081-0>.
- Lightdale JR, Gremse DA, Section on Gastroenterology, Hepatology, and Nutrition (2013) Gastroesophageal reflux: management guidance for the pediatrician. *Pediatrics* 131:e1684–e1695. <https://doi.org/10.1542/peds.2013-0421>.
- Littner MR, Leung FW, Ballard ED, et al. Effects of 24 weeks of lansoprazole therapy on asthma symptoms, exacerbations, quality of life, and pulmonary function in adult asthmatic patients with acid reflux symptoms. *Chest*. 2005;128:1128–35. <https://doi.org/10.1378/chest.128.3.1128>.
- Ludvigsson JF, Leffler DA, Bai JC, et al. The Oslo definitions for coeliac disease and related terms. London: BMJ Publishing Group Ltd and British Society of Gastroenterology; 2013. p. 43–52.
- Mack DR, Langton C, Markowitz J, et al. Laboratory values for children with newly diagnosed inflammatory bowel disease. *Pediatrics*. 2007;119:1113–9. <https://doi.org/10.1542/peds.2006-1865>.
- Mack CL, Gonzalez-Peralta RP, Gupta N, et al. NASPGHAN practice guidelines: diagnosis and management of hepatitis C infection in infants, children, and adolescents. *J Pediatr Gastroenterol Nutr*. 2012;54:838–55.
- Mahajan R, Liu SJ, Klevens RM, Holmberg SD. Indications for testing among reported cases of HCV infection from enhanced hepatitis surveillance sites in the United States, 2004–2010. *Am J Public Health*. 2013;103:1445–9. <https://doi.org/10.2105/AJPH.2013.301211>.
- Markowitz J, Grancher K, Kohn N, et al. A multicenter trial of 6-mercaptopurine and prednisone in children with newly diagnosed Crohn's disease. *Gastroenterology*. 2000;119:895–902.
- Markowitz JE, Spergel JM, Ruchelli E, Liacouras CA. Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents.

- Am J Gastroenterol. 2003;98:777–82. <https://doi.org/10.1111/j.1572-0241.2003.07390.x>.
- Martin AJ, Pratt N, Kennedy JD, et al. Natural history and familial relationships of infant spilling to 9 years of age. *Pediatrics*. 2002;109:1061–7.
- Matsui A, Ishikawa T. Identification of infants with biliary atresia in Japan. *Lancet*. 1994;343:925.
- McGill MR, Sharpe MR, Williams CD, et al. The mechanism underlying acetaminophen-induced hepatotoxicity in humans and mice involves mitochondrial damage and nuclear DNA fragmentation. *J Clin Invest*. 2012;122:1574–83. <https://doi.org/10.1172/JCI59755>.
- McMahon BJ, Alward WL, Hall DB, et al. Acute hepatitis B virus infection: relation of age to the clinical expression of disease and subsequent development of the carrier state. *J Infect Dis*. 1985;151:599–603.
- Mehta NM, Corkins MR, Lyman B, et al. Defining pediatric malnutrition: a paradigm shift toward etiology-related definitions. *JPEN J Parenter Enteral Nutr*. 2013;37:460–81. <https://doi.org/10.1177/0148607113479972>.
- Menard-Katcher C, Swerdlow MP, Mehta P, et al. Contribution of esophagram to the evaluation of complicated pediatric eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr*. 2015;61:541–6. <https://doi.org/10.1097/MPG.0000000000000849>.
- Milla PJ, Atherton DA, Leonard JV, et al. Disordered intestinal function in glycogen storage disease. *J Inher Metab Dis*. 1978;1:155–7.
- Mofrad P, Contos MJ, Haque M, et al. Clinical and histologic spectrum of nonalcoholic fatty liver disease associated with normal ALT values. *Hepatology*. 2003;37:1286–92. <https://doi.org/10.1053/jhep.2003.50229>.
- Molina-Infante J, Katzka DA, Dellon ES. Proton pump inhibitor-responsive esophageal eosinophilia: a historical perspective on a novel and evolving entity. *Rev Esp Enferm Dig*. 2015;107:29–36.
- Molleston JP, White F, Teckman J, Fitzgerald JF. Obese children with steatohepatitis can develop cirrhosis in childhood. *Am J Gastroenterol*. 2002;97:2460–2. <https://doi.org/10.1111/j.1572-0241.2002.06003.x>.
- Molleston JP, Schwimmer JB, Yates KP, et al. Histological abnormalities in children with nonalcoholic fatty liver disease and normal or mildly elevated alanine aminotransferase levels. *J Pediatr*. 2014;164:707–713.e3. <https://doi.org/10.1016/j.jpeds.2013.10.071>.
- Morinville VD, Barmada MM, Lowe ME. Increasing incidence of acute pancreatitis at an American pediatric tertiary care center: is greater awareness among physicians responsible? *Pancreas*. 2010;39:5–8. <https://doi.org/10.1097/MPA.0b013e3181baac47>.
- Mottin CC, Moretto M, Padoin AV, et al. The role of ultrasound in the diagnosis of hepatic steatosis in morbidly obese patients. *Obes Surg*. 2004;14:635–7. <https://doi.org/10.1381/096089204323093408>.
- Mukkada VA, Furuta GT. Management of refractory eosinophilic esophagitis. *Dig Dis*. 2014;32:134–8. <https://doi.org/10.1159/000357296>.
- Narkewicz MR, Dell'Olio D, Karpen SJ, et al. Pattern of diagnostic evaluation for the causes of pediatric acute liver failure: an opportunity for quality improvement. *J Pediatr*. 2009;155:801–806.e1. <https://doi.org/10.1016/j.jpeds.2009.06.005>.
- Nascimbeni F, Pais R, Bellentani S, et al. From NAFLD in clinical practice to answers from guidelines. *J Hepatol*. 2013;59:859–71. <https://doi.org/10.1016/j.jhep.2013.05.044>.
- National Center for Health Statistics (US). Health, United States, 2011: with special feature on socioeconomic status and Health. Hyattsville, MD: National Center for Health Statistics (US); 2012.
- Nelson SP, Chen EH, Syniar GM, Christoffel KK. Prevalence of symptoms of gastroesophageal reflux during childhood: a pediatric practice-based survey. Pediatric Practice Research Group. *Arch Pediatr Adolesc Med*. 2000;154:150–4.
- Newton KP, Singer SA. Celiac disease in children and adolescents: special considerations. *Semin Immunopathol*. 2012;34:479–96. <https://doi.org/10.1007/s00281-012-0313-0>.
- Nio M, Ohi R, Miyano T, et al. Five- and 10-year survival rates after surgery for biliary atresia: a report from the Japanese Biliary Atresia Registry. *J Pediatr Surg*. 2003;38:997–1000.
- Nitsche C, Maertin S, Scheiber J, et al. Drug-induced pancreatitis. *Curr Gastroenterol Rep*. 2012;14:131–8. <https://doi.org/10.1007/s11894-012-0245-9>.
- Nobili V, Vajro P, Dezsofi A, et al. Indications and limitations of bariatric intervention in severely obese children and adolescents with and without nonalcoholic steatohepatitis: ESPGHAN Hepatology Committee position statement. *J Pediatr Gastroenterol Nutr*. 2015;60:550–61. <https://doi.org/10.1097/MPG.0000000000000715>.
- Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011–2012. *JAMA*. 2014;311:806–14. <https://doi.org/10.1001/jama.2014.732>.
- O'Keefe SJD, Buchman AL, Fishbein TM, et al. Short bowel syndrome and intestinal failure: consensus definitions and overview. *Clin Gastroenterol Hepatol*. 2006;4(1):6–10.
- Oliva-Hemker M, Fiocchi C. Etiopathogenesis of inflammatory bowel disease: the importance of the pediatric perspective. *Inflamm Bowel Dis*. 2002;8:112–28.
- Ong JP, Aggarwal A, Krieger D, et al. Correlation between ammonia levels and the severity of hepatic encephalopathy. *Am J Med*. 2003;114:188–93.
- Paarlahti P, Kurppa K, Ukkola A, et al. Predictors of persistent symptoms and reduced quality of life in treated coeliac disease patients: a large cross-sectional study. *BMC Gastroenterol*. 2013;13:75. <https://doi.org/10.1186/1471-230X-13-75>.
- Park JH. Role of colonoscopy in the diagnosis and treatment of pediatric lower gastrointestinal disorders. *Korean J Pediatr*. 2010;53:824–9. <https://doi.org/10.3345/kjp.2010.53.9.824>.
- Park AJ, Latif SU, Ahmad MU, et al. A comparison of presentation and management trends in acute pancreatitis between infants/toddlers and older children. *J*

- Pediatr Gastroenterol Nutr.* 2010;51:167–70. <https://doi.org/10.1097/MPG.0b013e3181cea545>.
- Patton HM, Lavine JE, Van Natta ML, et al. Clinical correlates of histopathology in pediatric nonalcoholic steatohepatitis. *Gastroenterology.* 2008;135:1961–1971. e2. <https://doi.org/10.1053/j.gastro.2008.08.050>.
- Pediatric Gastroenterology Chapter of Indian Academy of Pediatrics, Bhatia V, Bavdekar A, et al. Management of acute liver failure in infants and children: consensus statement of the pediatric gastroenterology chapter, Indian academy of pediatrics. *Indian Pediatr.* 2013;50:477–82.
- Pelletier DL, Frongillo EA, Habicht JP. Epidemiologic evidence for a potentiating effect of malnutrition on child mortality. *Am J Public Health.* 1993;83:1130–3.
- Pelletier DL, Frongillo EA, Schroeder DG, Habicht JP. The effects of malnutrition on child mortality in developing countries. *Bull World Health Organ.* 1995;73:443–8.
- Perminow G, Frigessi A, Rydning A, et al. Incidence and clinical presentation of IBD in children: comparison between prospective and retrospective data in a selected Norwegian population. *Scand J Gastroenterol.* 2006;41:1433–9. <https://doi.org/10.1080/00365520600789891>.
- Peters NJ, Mahajan JK, Bawa M, et al. Esophageal perforations due to foreign body impaction in children. *J Pediatr Surg.* 2015;50:1260–3. <https://doi.org/10.1016/j.jpedsurg.2015.01.015>.
- Peterson KA, Boynton KK. Which patients with eosinophilic esophagitis (EoE) should receive elemental diets versus other therapies? *Curr Gastroenterol Rep.* 2014;16:364. <https://doi.org/10.1007/s11894-013-0364-y>.
- Pittler MH, Ernst E. Peppermint oil for irritable bowel syndrome: a critical review and metaanalysis. *Am J Gastroenterol.* 1998;93:1131–5. <https://doi.org/10.1111/j.1572-0241.1998.00343.x>.
- Pohl JF, Uc A. Paediatric pancreatitis. *Curr Opin Gastroenterol.* 2015;31:380–6. <https://doi.org/10.1097/MOG.0000000000000197>.
- Polson J, Lee WM, American Association for the Study of Liver Disease. AASLD position paper: the management of acute liver failure. *Hepatology.* 2005;41:1179–97.
- WHO Publication. Hepatitis B vaccines: WHO position paper—recommendations. *Vaccine.* 2010;28:589–90. <https://doi.org/10.1016/j.vaccine.2009.10.110>.
- Rahman T, Hodgson H. Clinical management of acute hepatic failure. *Intensive Care Med.* 2001;27:467–76.
- Rahman I, Patel P, Boger P, et al. Therapeutic upper gastrointestinal tract endoscopy in paediatric gastroenterology. *World J Gastrointest Endosc.* 2015;7:169–82. <https://doi.org/10.4253/wjge.v7.i3.169>.
- Rampertab SD, Pooran N, Brar P, et al. Trends in the presentation of celiac disease. *Am J Med.* 2006;119:355. e9–14. <https://doi.org/10.1016/j.amjmed.2005.08.044>.
- Raphael BP, Duggan C. Prevention and treatment of intestinal failure-associated liver disease in children. *Semin Liver Dis.* 2012;32:341–7. <https://doi.org/10.1055/s-0032-1329903>.
- Ravi K, Talley NJ, Smyrk TC, et al. Low grade esophageal eosinophilia in adults: an unrecognized part of the spectrum of eosinophilic esophagitis? *Dig Dis Sci.* 2011;56:1981–6. <https://doi.org/10.1007/s10620-011-1594-1>.
- Rodríguez-Sánchez J, Gómez Torrijos E, López Viedma B, et al. Efficacy of IgE-targeted vs empiric six-food elimination diets for adult eosinophilic oesophagitis. *Allergy.* 2014;69:936–42. <https://doi.org/10.1111/all.12420>.
- Rosenthal P, Blanckaert N, Kabra PM, Thaler MM. Formation of bilirubin conjugates in human newborns. *Pediatr Res.* 1986;20:947–50. <https://doi.org/10.1203/00006450-198610000-00010>.
- Rudolph CD, Mazur LJ, Liptak GS, et al. Guidelines for evaluation and treatment of gastroesophageal reflux in infants and children: recommendations of the North American Society for Pediatric Gastroenterology and Nutrition. *J Pediatr Gastroenterol Nutr.* 2001;32(Suppl 2):S1–31.
- Ruemmele FM, Sauvat F, Colomb V, et al. Seventeen years after successful small bowel transplantation: long term graft acceptance without immune tolerance. *Gut.* 2006;55:903–4. <https://doi.org/10.1136/gut.2006.093989>.
- Saadeh S, Younossi ZM, Remer EM, et al. The utility of radiological imaging in nonalcoholic fatty liver disease. *Gastroenterology.* 2002;123:745–50.
- Saito T, Terui K, Mitsunaga T, et al. Role of pediatric endoscopic retrograde cholangiopancreatography in an era stressing less-invasive imaging modalities. *J Pediatr Gastroenterol Nutr.* 2014;59:204–9. <https://doi.org/10.1097/MPG.0000000000000399>.
- Sandborn WJ, Van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology.* 2012;142:257–65.e1–3. <https://doi.org/10.1053/j.gastro.2011.10.032>.
- Saps M, Pensabene L, Turco R, et al. Rotavirus gastroenteritis: precursor of functional gastrointestinal disorders? *J Pediatr Gastroenterol Nutr.* 2009;49:580–3. <https://doi.org/10.1097/MPG.0b013e31819bcbd2>.
- Sauer CG, Middleton JP, McCracken C, et al. Magnetic resonance enterography healing and magnetic resonance enterography remission predicts improved outcome in pediatric Crohn disease. *J Pediatr Gastroenterol Nutr.* 2016;62:378–83. <https://doi.org/10.1097/MPG.0000000000000976>.
- Schwimmer JB, Deutsch R, Rauch JB, et al. Obesity, insulin resistance, and other clinicopathological correlates of pediatric nonalcoholic fatty liver disease. *J Pediatr.* 2003;143:500–5. [https://doi.org/10.1067/S0022-3476\(03\)00325-1](https://doi.org/10.1067/S0022-3476(03)00325-1).
- Schwimmer JB, Behling C, Newbury R, et al. Histopathology of pediatric nonalcoholic fatty liver disease. *Hepatology.* 2005;42:641–9. <https://doi.org/10.1002/hep.20842>.
- Schwimmer JB, Deutsch R, Kahen T, et al. Prevalence of fatty liver in children and adolescents. *Pediatrics.* 2006;118:1388–93. <https://doi.org/10.1542/peds.2006-1212>.

- Schwimmer JB, Newton KP, Awai HI, et al. Paediatric gastroenterology evaluation of overweight and obese children referred from primary care for suspected non-alcoholic fatty liver disease. *Aliment Pharmacol Ther.* 2013;38:1267–77. <https://doi.org/10.1111/apt.12518>.
- Schwimmer JB, Middleton MS, Behling C, et al. Magnetic resonance imaging and liver histology as biomarkers of hepatic steatosis in children with nonalcoholic fatty liver disease. *Hepatology.* 2015;61:1887–95. <https://doi.org/10.1002/hep.27666>.
- Shanmugam NP, Dhawan A. Selection criteria for liver transplantation in paediatric acute liver failure: the saga continues. *Pediatr Transplant.* 2011;15:5–6. <https://doi.org/10.1111/j.1399-3046.2010.01457.x>.
- Sheikh S, Stephen T, Howell L, Eid N. Gastroesophageal reflux in infants with wheezing. *Pediatr Pulmonol.* 1999;28:181–6.
- Shi Z, Yang Y, Wang H, et al. Breastfeeding of newborns by mothers carrying hepatitis B virus: a meta-analysis and systematic review. *Arch Pediatr Adolesc Med.* 2011;165:837–46. <https://doi.org/10.1001/archpediatrics.2011.72>.
- Singer AL, Olthoff KM, Kim H, et al. Role of plasmapheresis in the management of acute hepatic failure in children. *Ann Surg.* 2001;234:418–24.
- Singh S, Allen AM, Wang Z, et al. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. *Clin Gastroenterol Hepatol.* 2015;13:643–54.e1–9-quiz e39–40. <https://doi.org/10.1016/j.cgh.2014.04.014>.
- Slae M, Persad R, Leung AJ-T, et al. Role of environmental factors in the development of pediatric eosinophilic esophagitis. *Dig Dis Sci.* 2015;60:3364–72. <https://doi.org/10.1007/s10620-015-3740-7>.
- Smits MJ, van Wijk MP, Langendam MW, et al. Association between gastroesophageal reflux and pathologic apneas in infants: a systematic review. *Neurogastroenterol Motil.* 2014;26:1527–38. <https://doi.org/10.1111/nmo.12405>.
- Sokal EM, Paganelli M, Wirth S, et al. Management of chronic hepatitis B in childhood: ESPGHAN clinical practice guidelines: consensus of an expert panel on behalf of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition. *J Hepatol.* 2013;59:814–29.
- Squires RH. Acute liver failure in children. *Semin Liver Dis.* 2008;28:153–66. <https://doi.org/10.1055/s-2008-1073115>.
- Squires RH, Shneider BL, Bucuvalas J, et al. Acute liver failure in children: the first 348 patients in the pediatric acute liver failure study group. *J Pediatr.* 2006;148:652–8. <https://doi.org/10.1016/j.jpeds.2005.12.051>.
- Squires RH, Duggan C, Teitelbaum DH, et al. Natural history of pediatric intestinal failure: initial report from the Pediatric Intestinal Failure Consortium. *J Pediatr.* 2012;161:723–8.e2. <https://doi.org/10.1016/j.jpeds.2012.03.062>.
- Størdal K, White RA, Eggesbø M. Early feeding and risk of celiac disease in a prospective birth cohort. *Pediatrics.* 2013;132:e1202–9. <https://doi.org/10.1542/peds.2013-1752>.
- Straumann A, Bussmann C, Zuber M, et al. Eosinophilic esophagitis: analysis of food impaction and perforation in 251 adolescent and adult patients. *Clin Gastroenterol Hepatol.* 2008;6:598–600. <https://doi.org/10.1016/j.cgh.2008.02.003>.
- Stravitz RT, Kramer AH, Davern T, et al. Intensive care of patients with acute liver failure: recommendations of the U.S. Acute Liver Failure Study Group. *Crit Care Med.* 2007;35:2498–508.
- Suchy FJ. Neonatal cholestasis. *Pediatr Rev.* 2004;25:388–96.
- Suchy FJ, Burdelski M, Tomar BS, Sokol RJ. Cholestatic liver disease: working group report of the first world congress of pediatric gastroenterology, hepatology, and nutrition. *J Pediatr Gastroenterol Nutr.* 2002;35(Suppl 2):S89–97.
- Szabo FK, Fei L, Cruz LA, Abu-El-Haija M. Early enteral nutrition and aggressive fluid resuscitation are associated with improved clinical outcomes in acute pancreatitis. *J Pediatr.* 2015;167:397–402.e1. <https://doi.org/10.1016/j.jpeds.2015.05.030>.
- Tabbers MM, DiLorenzo C, Berger MY, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. *J Pediatr Gastroenterol Nutr.* 2014;58:258–74. <https://doi.org/10.1097/MPG.0000000000000266>.
- Tassopoulos NC, Papaevangelou GJ, Sjogren MH, et al. Natural history of acute hepatitis B surface antigen-positive hepatitis in Greek adults. *Gastroenterology.* 1987;92:1844–50.
- Taylor SA, Whittington PF. Neonatal acute liver failure. *Liver Transpl.* 2016;22:677–85. <https://doi.org/10.1002/lt.24433>.
- Temiz A. Efficiency of upper gastrointestinal endoscopy in pediatric surgical practice. *World J Clin Pediatr.* 2015;4:113–9. <https://doi.org/10.5409/wjcp.v4.i4.113>.
- Thompson JS, Weseman R, Rochling FA, Mercer DF. Current management of the short bowel syndrome. *Surg Clin North Am.* 2011;91:493–510. <https://doi.org/10.1016/j.suc.2011.02.006>.
- Thomson M, Belsha D. Endoscopic management of acute gastrointestinal bleeding in children: time for a radical rethink. *J Pediatr Surg.* 2016;51:206–10. <https://doi.org/10.1016/j.jpedsurg.2015.10.064>.
- Tilney HS, Constantinides V, Ioannides AS, et al. Pouch-anal anastomosis vs straight ileoanal anastomosis in pediatric patients: a meta-analysis. *J Pediatr Surg.* 2006;41:1799–808. <https://doi.org/10.1016/j.jpedsurg.2006.06.005>.
- Tran TH. Advances in pediatric celiac disease. *Curr Opin Pediatr.* 2014;26:585–9. <https://doi.org/10.1097/MOP.0000000000000128>.
- Trauner M, Meier PJ, Boyer JL. Molecular pathogenesis of cholestasis. *N Engl J Med.* 1998;339:1217–27. <https://doi.org/10.1056/NEJM199810223391707>.

- Trauner M, Fickert P, Halilbasic E, Moustafa T. Lessons from the toxic bile concept for the pathogenesis and treatment of cholestatic liver diseases. *Wien Med Wochenschr.* 2008;158:542–8. <https://doi.org/10.1007/s10354-008-0592-1>.
- Trivedi CD, Pitchumoni CS. Drug-induced pancreatitis: an update. *J Clin Gastroenterol.* 2005;39:709–16.
- Troendle DM, Abraham O, Huang R, Barth BA. Factors associated with post-ERCP pancreatitis and the effect of pancreatic duct stenting in a pediatric population. *Gastrointest Endosc.* 2015;81:1408–16. <https://doi.org/10.1016/j.gie.2014.11.022>.
- Turner D, Travis SPL, Griffiths AM, et al. Consensus for managing acute severe ulcerative colitis in children: a systematic review and joint statement from ECCO, ESPGHAN, and the Porto IBD Working Group of ESPGHAN. London: Nature Publishing Group; 2011. p. 574–88.
- Vajro P, Lenta S, Socha P, et al. Diagnosis of nonalcoholic fatty liver disease in children and adolescents: position paper of the ESPGHAN Hepatology Committee. *J Pediatr Gastroenterol Nutr.* 2012;54:700–13. <https://doi.org/10.1097/MPG.0b013e318252a13f>.
- Vandenplas Y, Rudolph CD, Di Lorenzo C, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr.* 2009;49:498–547.
- Vaquero J, Fontana RJ, Larson AM, et al. Complications and use of intracranial pressure monitoring in patients with acute liver failure and severe encephalopathy. *Liver Transpl.* 2005;11:1581–9. <https://doi.org/10.1002/lt.20625>.
- Venigalla S, Gourley GR. Neonatal cholestasis. *Semin Perinatol.* 2004;28:348–55.
- Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther.* 2011;34:274–85. <https://doi.org/10.1111/j.1365-2036.2011.04724.x>.
- Vos MB. NASPGHAN clinical practice guideline for the diagnosis and treatment of nonalcoholic fatty liver disease in children. *J Pediatr Gastroenterol Nutr.* 2016;64(2):319–34.
- Wade J, Rolando N, Philpott-Howard J, Wendon J. Timing and aetiology of bacterial infections in a liver intensive care unit. *J Hosp Infect.* 2003;53:144–6.
- Wang Y, Parker CE, Feagan BG, MacDonald JK (2016) Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* CD000544. <https://doi.org/10.1002/14651858.CD000544.pub4>.
- Welsh JA, Karpen S, Vos MB. Increasing prevalence of nonalcoholic fatty liver disease among United States adolescents, 1988–1994 to 2007–2010. *J Pediatr.* 2013;162:496–500.e1. <https://doi.org/10.1016/j.jpeds.2012.08.043>.
- Weng H-L, Cai X, Yuan X, et al. Two sides of one coin: massive hepatic necrosis and progenitor cell-mediated regeneration in acute liver failure. *Front Physiol.* 2015;6:178. <https://doi.org/10.3389/fphys.2015.00178>.
- Werlin SL, Kugathasan S, Frautschy BC. Pancreatitis in children. *J Pediatr Gastroenterol Nutr.* 2003;37:591–5.
- Whittington PF. Gestational alloimmune liver disease and neonatal hemochromatosis. *Semin Liver Dis.* 2012;32:325–32. <https://doi.org/10.1055/s-0032-1329901>.
- Whittington PF, Hibbard JU. High-dose immunoglobulin during pregnancy for recurrent neonatal haemochromatosis. *Lancet.* 2004;364:1690–8. [https://doi.org/10.1016/S0140-6736\(04\)17356-X](https://doi.org/10.1016/S0140-6736(04)17356-X).
- Yang C-FJ, Duro D, Zurakowski D, et al. High prevalence of multiple micronutrient deficiencies in children with intestinal failure: a longitudinal study. *J Pediatr.* 2011;159:39–44.e1. <https://doi.org/10.1016/j.jpeds.2010.12.049>.
- Yıldırım AE, Altun R, Ocal S, et al. The safety and efficacy of ERCP in the pediatric population with standard scopes: does size really matter? *Spring.* 2016;5:128. <https://doi.org/10.1186/s40064-016-1749-9>.
- Yoneda M, Mawatari H, Fujita K, et al. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with nonalcoholic fatty liver disease (NAFLD). *Dig Liver Dis.* 2008;40:371–8. <https://doi.org/10.1016/j.dld.2007.10.019>.
- Younossi ZM, Stepanova M, Afendy M, et al. Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008. *Clin Gastroenterol Hepatol.* 2011;9:524–530.e1-quiz e60. <https://doi.org/10.1016/j.cgh.2011.03.020>.
- Zevit N, Shamir R. Wireless capsule endoscopy of the small intestine in children. *J Pediatr Gastroenterol Nutr.* 2015;60:696–701. <https://doi.org/10.1097/MPG.0000000000000782>.
- Zhang Y, Li L, Guo C, et al. Effects of probiotic type, dose and treatment duration on irritable bowel syndrome diagnosed by Rome III criteria: a meta-analysis. *BMC Gastroenterol.* 2016;16:62. <https://doi.org/10.1186/s12876-016-0470-z>.
- Zholudev A, Zurakowski D, Young W, et al. Serologic testing with ANCA, ASCA, and anti-OmpC in children and young adults with Crohn's disease and ulcerative colitis: diagnostic value and correlation with disease phenotype. *Am J Gastroenterol.* 2004;99:2235–41. <https://doi.org/10.1111/j.1572-0241.2004.40369.x>.
- Zsoldos F, Pármiczky A, Moszbacher D, et al. Pain in the early phase of pediatric pancreatitis (PINEAPPLE trial): pre-study protocol of a multinational prospective clinical trial. *Digestion.* 2016;93:121–6. <https://doi.org/10.1159/000441352>.



Ziad Solh, Anthony K.C. Chan, and Mihir D. Bhatt

Introduction

Blood is composed of multiple cellular and non-cellular components, each deserving of special consideration for a full understanding of human blood physiology and disease. In this chapter, we discuss the current understanding of blood physiology and recent advances in the treatment of disorders in red cells, platelets, white cells, and plasma components. The field of pediatric hematology has witnessed significant advances in the past decade. Novel therapeutic options for blood disorders such as sickle cell disease and immune thrombocytopenia are being investigated and implemented. Cutting edge therapies such as gene therapy for hemophilia herald a new dawn of therapies and potential cure.

Iron-deficiency Anemia

Anemia is defined as a hemoglobin concentration, hematocrit, or red blood cell number below two standard deviations from the age-specific mean

(Table 11.1). It is the most common hematologic abnormality encountered by pediatricians. Anemia can be classified based on mean corpuscular volume into microcytic, normocytic, and macrocytic anemias (Janus and Moerschel 2010). It can further be classified based on pathophysiology into anemia resulting from decreased production in the bone marrow, increased red cell destruction, and blood loss. In this chapter, we focus on the most common type of anemia: iron-deficiency anemia. It is a microcytic anemia related to decreased production of hemoglobin due to reduced availability of iron - an essential component of the hemoglobin structure (Jimenez et al. 2015).

Diagnosis of Iron Deficiency

Iron deficiency is diagnosed based on clinical suspicion leading to laboratory evaluation with iron studies. Clinical symptoms in children may include mood changes, neurocognitive/developmental delay, growth retardation, epithelial changes, and pica. Hemoglobin value may be used as a screening test, but because the hemo-

Z. Solh, M.D., M.Sc., F.R.C.P.C., (✉)
Department of Pathology and Molecular Medicine,
McMaster University,
Room 3N27, 1280 Main Street West, Hamilton, ON,
Canada, L8S 4K1

Medical Services and Innovation, Canadian Blood
Services, Hamilton, ON, Canada
e-mail: ziad.solh@medportal.ca

A.K.C. Chan, F.R.C.P.C., F.R.C.Path
M.D. Bhatt, B.H.Sc., M.D., F.R.C.P.C.
Division of Hematology/Oncology, Department of
Pediatrics, McMaster University,
Room 3N27, 1280 Main Street West, Hamilton, ON,
Canada, L8S 4K1
e-mail: akchan@mcmaster.ca; bhattm2@mcmaster.ca

Table 11.1 Normal ranges of red blood cell laboratory indices by age

| Age | Mean Hb [−2SD] (g/L) | Mean hct [−2SD] (proportion of 1.0) | MCV [−2SD] (fL) |
|------------------------|-------------------------|--|-----------------------|
| Birth | 165 [135] | 0.51 [0.42] | 108 [98] |
| 1–3 days | 185 [145] | 0.56 [0.45] | 108 [95] |
| 1 month | 140 [100] | 0.43 [0.31] | 104 [85] |
| 2 months | 115 [90] | 0.35 [0.28] | 96 [77] |
| 3–6 months | 115 [95] | 0.35 [0.29] | 91 [74] |
| 6 months to 2 years | 120 [105] | 0.36 [0.33] | 78 [70] |
| 2–6 years | 125 [115] | 0.37 [0.34] | 81 [75] |
| 6–12 years | 135 [115] | 0.40 [0.35] | 86 [77] |
| 12–18 years | | | |
| Females | 140 [120] | 0.41 [0.36] | 90 [78] |
| Males | 145 [130] | 0.43 [0.37] | 88 [78] |

Adapted from Richardson (2007)

Hb hemoglobin, hct hematocrit, MCV mean corpuscular volume

globin declines only in the later stages of iron deficiency, this test may miss the earlier stages of iron deficiency.

Complete iron studies are more reliable and include: hemoglobin, blood smear, reticulocyte count, ferritin, and transferrin saturation (TS). TS is the most useful test to evaluate iron deficiency. Although total iron is low and total iron binding capacity (TIBC) is high in iron deficiency, these two tests are not accurate or useful in isolation; instead, they are best used together to calculate TS. Most laboratories calculate and report the TS so that the clinical team does not have to do this. In a normal individual, 20–40% of transferrin sites are used to transport iron. In an iron deficient patient, less than 20% are used, which is reflected in a TS < 20%. In the absence of inflammatory conditions that result in an elevated ferritin, a ferritin value <30 ng/mL supports the diagnosis of iron deficiency (McDonagh et al. 2015).

It is important to note that the differential diagnosis of microcytic anemia includes thalassemia. Because thalassemia patients are not immune to iron deficiency, a thorough iron work up is necessary to exclude iron deficiency (or treat it) before a diagnosis of hemoglobinopathy can be excluded because low iron may

result in false negative hemoglobin electrophoresis results.

Development of Iron Deficiency in Children

At birth, newborns experience an increase in oxygen availability which leads to the downregulation of erythropoietin and a subsequent gradual decline in hemoglobin. The physiologic hemoglobin nadir in term infants (90–110 g/L) occurs at 8–12 weeks of life. When oxygen delivery no longer meets metabolic needs, erythropoietin is upregulated again leading to a physiologic hemoglobin recovery.

In preterm infants, the hemoglobin nadir is more profound (70–90 g/L), and it occurs earlier at 3–6 weeks of life. This anemia of prematurity ensues from a variety of reasons. Most preterm infants do not get the benefit of the maternal transfer of iron which occurs in the third trimester, resulting in lower hemoglobin at birth. Iatrogenic causes from frequent blood draws also contribute to the hemoglobin drop. A poor erythropoietin response in preterm infants is also postulated to exacerbate and prolong anemia.

In toddlers, the most common cause of iron deficiency anemia is nutritional and marked by excessive cow's milk consumption beyond an average of 500 mL a day. The reasons cow's milk leads to iron deficiency are threefold: (1) milk is filling and causes slow gastric emptying, which in turn leads to decreased appetite for other iron-rich foods; (2) calcium found in milk inhibits iron absorption; and (3) cow's milk protein may cause an allergy with microscopic or gross gastrointestinal bleeding.

Post-pubertal females are at an increased risk of iron deficiency due to menstrual blood loss. Referral to a gynecologist should be considered for hormonal or non-hormonal options to control chronic menstrual bleeding.

Treatment of Iron Deficiency Anemia

The treatment of iron deficiency anemia requires a combination of dietary changes and iron supple-

mentation (Siu 2015). Dietary changes may include the reduction of milk consumption and increasing the intake of iron-rich foods. Iron from animal sources is better absorbed by the human gut than plant-based iron. Dietary iron is also better absorbed in the presence of vitamin C (i.e. in combination with foods rich in ascorbic acid).

Iron supplementation may be in the form of oral or intravenous iron. Oral iron is available in a variety of affordable formulations and is recommended at a dose of 6 mg/kg/day of elemental iron for 1 month; once the iron indices have been corrected this is followed by 3 mg/kg/day for 2 months of maintenance. If oral iron is poorly tolerated, intravenous iron may be better tolerated and lead to more rapid replacement of iron stores. Intravenous iron may also be used in patients who fail oral iron therapy due to iron refractory iron deficiency anemia (IRIDA) which is a disorder of iron metabolism due to the *TMPRSS6* gene mutation leading to the upregulation of hepcidin and decreased absorption of iron from the duodenum (De Falco et al. 2013).

Hydroxyurea in Sickle Cell Disease

Sickle cell disease (SCD) is a group of qualitative hemoglobin (Hb) disorders which can be caused by a number of hemoglobin variants: Hb SS, SC, S-beta thalassemia, SO Arab, SD, and other rare S hemoglobins. Hb S polymerizes in the deoxygenated state leading to crescent-shaped red cells that are poorly deformable when passing through capillary microcirculation. This leads to chronic hemolysis, vascular occlusion, and end-organ damage (Solh et al. 2016).

Significant advances in SCD therapy have taken place over the past decade. Most notable is the role of hydroxyurea, which was initially introduced as a chemotherapeutic drug for the treatment of leukemia and myeloproliferative disease, but gained recognition in SCD clinical practice as an agent that increases Hb F levels. Hb F overexpression leads to a relative decrease in Hb S levels and improved red cell deformability. The BABY HUG study is a randomized

controlled trial which included infants aged 9–18 months with Hb SS or S β^0 thalassaemia (Wang et al. 2011). Hydroxyurea was given as a health maintenance drug to 96 study group subjects at a dose of 20 mg/kg/day for 2 years, and a placebo was given to 97 subjects in the control group. The results of the trial showed that hydroxyurea decreased the frequency of pain crises and dactylitis significantly. There was also a trend suggestive of decreased acute chest syndrome, hospitalisation and transfusion. Hydroxyurea also increased the level of Hb (improved anemia), Hb F and decreased white blood cell (WBC) count (leukocytosis is involved in the pathophysiology of SCD morbidities). Mild-moderate neutropenia was the only toxicity noted.

Unfortunately, a major challenge in SCD clinical practice is overcoming a parent's reluctance to consent to treating their child with a drug that is historically associated with cancer treatment. In such cases, it is paramount to devote time to counselling the parents about the history of hydroxyurea, its pathophysiology, its significant benefits, and the limited side effect profile. This is coupled with reassuring a parent that hydroxyurea maintenance therapy would not occur without close monitoring of bloodwork and clinical status at follow-up visits.

Prior to starting hydroxyurea, the following baseline tests should be ordered: complete blood count (CBC), reticulocyte count, Hb F level, renal function, and liver function. The pediatric starting dose is 20 mg/kg unless creatinine clearance is low. After ensuring adherence to daily therapy for 2–4 weeks, a CBC may be done to confirm the expected decrease in WBC and platelet count and a rise in mean corpuscular volume (MCV). If these indices are unchanged from baseline, verify the dose calculation, and review adherence with the patient. The hydroxyurea dose can be adjusted based on CBC and reticulocyte count (every 2–4 weeks) until the maximum tolerated dose is reached. If the patient develops one or more abnormal hematological index (e.g., neutropenia, thrombocytopenia, Hb < 50 g/L, or reticulocytopenia, the hydroxyurea can be held until recovery, then

resumed at a reduced dose. When a tolerated dose is reached, less frequent monitoring is appropriate (e.g., every 3 months). Pregnancy planning is an important counselling point due to the known teratogenicity of hydroxyurea (Platt 2008; Canadian Haemoglobinopathy Association 2014).

Iron Chelation in Thalassemia

The thalassemias are a group of quantitative hemoglobinopathies caused by insufficiencies in globin chain synthesis. This leads to hypochromic microcytic anemia and an imbalance in globin chains leading to unstable globin tetramer deposition within red cells, impaired erythropoiesis and hemolysis (Kelly 2012).

The two major thalassemia syndromes are alpha-thalassemia (disorder in α -chain) and beta-thalassemia (disorder in β -chain), which affect the synthesis of the most prevalent adult hemoglobin (Hb A: $\alpha_2\beta_2$). Four genes control α -chain synthesis while two control β -chain synthesis. The severity of thalassemia syndromes varies based on the genetic mutation and the number of globin genes affected (Kelly 2012). The genetics, pathophysiology and investigation of thalassemia syndromes are beyond the scope of this section which will focus on chelation therapy.

A therapeutic cornerstone for severe thalassemia (e.g. β -thalassemia major) is regular life-long red cell transfusion to suppress dyserythropoiesis. Transfusions are usually administered every 2–5 weeks, to maintain a pre-transfusion Hb value above 90–105 g/L. However, without iron chelation, patients may only be expected to survive until 10–25 years of age succumbing to cardiac iron overload. With iron chelation as the other cornerstone of therapy, patient survival may be extended to over 40 years of age (Modell et al. 2000). The third cornerstone of therapy is multidisciplinary care, which highlights the prevention of multi-organ deterioration and the management of medical and psychosocial aspects of thalassemia (Guidelines for the Management of Transfusion Dependent Thalassaemia, 3rd Edition 2014).

Desferrioxamine (Desferal[®] or deferoxamine; DFO) is a hexadentate chelator which is licensed for children over the age of 2 years. It requires slow subcutaneous infusion for 8–12 h daily or at least five nights a week. Subcutaneous infusion can be costly, cumbersome and time-consuming for patients. It has a very short half-life whereby it only chelates iron during infusion, and it is excreted via the colon and kidney. To increase the availability of chelatable iron in the gut, vitamin C can be started (after several weeks of deferoxamine infusion) at a dose no more than 2–3 mg/kg/day and taken just before the deferoxamine infusions (Guidelines for the Management of Transfusion Dependent Thalassaemia, 3rd Edition 2014). Due to its side effect profile (auditory, visual, and renal disturbances), deferoxamine is only recommended for use if the serum ferritin is above 1000 $\mu\text{g/L}$ or after the first 10–20 transfusions at a dose of 20–40 mg/kg/day for children (50–60 mg/kg/day for adults).

Deferiprone (Ferriprox[®], Kelfer[®], GPO-L-ONE[®]; DFP) is a bidentate chelator which is administered orally as a liquid or a tablet, which improves compliance (95%) compared to subcutaneous deferoxamine (72%) (Olivieri and Brittenham 1997). There is insufficient safety data for licensing in children 2–6 years of age, but it is used in children >6 years if deferoxamine is not tolerated or ineffective (Guidelines for the Management of Transfusion Dependent Thalassaemia, 3rd Edition 2014). Side effects include agranulocytosis, nausea, liver dysfunction, and arthropathy. The recommended dose is 75 mg/kg/day three times a day. Vitamin C co-therapy with deferiprone is of unclear benefit and therefore not recommended. Deferiprone may be used in combination with deferoxamine to treat severe cardiac iron overload (Galanello et al. 2010).

Deferasirox (Exjade[®], Asunra[®]; DFX) is an oral once daily tridentate iron chelator. It is dispersed (not dissolved) in water or juice and recommended to be taken before a meal. Its long half-life and daily dosing make it an attractive option for patients. Studies have shown that the dose can be adjusted between 20 and 40 mg/kg/

day depending on the degree of iron overload (Guidelines for the Management of Transfusion Dependent Thalassaemia, 3rd Edition 2014; Porter et al. 2013). It is licensed in most countries as first line therapy in children over 2 years of age, similarly to deferoxamine. Side effects include gastrointestinal upset, renal impairment and proteinuria, and hepatic dysfunction.

Transfusion Medicine Controversies: Transfusion Triggers and Age of Blood

Transfusion medicine specialists have recently confronted two important controversies which affect both the clinical care and the blood banking needs of transfused patients. The first controversy is that of red blood cell transfusion thresholds with the second being the optimal storage age of red cells as they relate to patient outcomes. The neonatal and pediatric populations have received special attention during the resolution of these controversies.

Red Cell Transfusion Triggers

Since the TRICC trial was published in 1999, it has been accepted that critically ill adults (except those with myocardial infarction and unstable angina) do not have a 30-day survival benefit from liberal transfusions (keeping Hb > 100 g/L) compared to a restrictive strategy (keeping Hb > 70 g/L). In fact, a restrictive strategy was shown to result in less in-hospital mortality in this adult population (Hebert et al. 1999). Similar neonatal and pediatric data were not available until several years later when the PINT and TRIPICU trials were published in 2006 and 2007, respectively. PINT showed that maintaining a higher Hb threshold in extremely low birth weight neonates did not confer any mortality or morbidity advantage (Kirpalani et al. 2006). The Hb threshold took into account physiological changes in Hb values with post-natal age i.e. the tested thresholds decreased with age. Ventilatory support also raised the tested threshold to a more

liberal transfusion strategy. The TRIPICU trial was done in stable critically ill children (Lacroix et al. 2007). The results showed that a restrictive Hb threshold (70 g/L) was as safe as a liberal one (95 g/L). The results were not applicable to unstable pediatric patients.

In general, no universal transfusion “trigger” exists. Instead, the decision to transfuse varies depending on the individual clinical scenario taking into account both the overall clinical picture and the Hb value. Higher thresholds can be considered if there is symptomatic anemia or cardio-respiratory compromise. It is important to restrict iatrogenic blood loss due to blood sampling, especially in the neonate, to minimize transfusion needs.

Age of Blood

During storage, red blood cells undergo structural and biochemical changes which have been hypothesized to result in clinical effects post-transfusion. The hypothesis has been the basis of several randomized trials exploring the effect of storage age on patient outcomes. The ABLE trial (in critically ill adults) and the RECSS trial (in cardiac surgery patients over 12 years of age) both showed no difference in outcomes between fresh and older blood (Lacroix et al. 2015; Steiner et al. 2015). Subsequently, the INFORM trial—a much larger and pragmatic trial including a general adult population—was performed showing no difference in mortality (Heddle et al. 2016). The ARIPI trial focussed on premature neonates and found no difference in the composite outcome of death and neonatal morbidities when fresh (mean of 5 days) and standard/older blood (mean 14 days) were used (Fergusson et al. 2012). This evidence points to the general safety of storing and using red blood cells up to their time of expiration in these patient populations. The Age of Blood in Children in Pediatric Intensive Care Units (ABC PICU) trial is ongoing (NCT01977547).

Other aspects of the blood supply being investigated are the recently found association between blood donor characteristics and recipi-

ent mortality. A study of adult red cell transfusion recipients found a higher mortality rate when the donors were female; mortality rate was also inversely related to donor age (Chasse et al. 2016). This hypothesis has yet to be tested prospectively and in pediatric recipients of transfusion.

Although transfusion is an important life-saving therapy, there is a possibility that its overuse may be associated with transfusion-transmitted non-infectious harm to patients. This is difficult to ascertain because transfusions are usually given to individuals with underlying disease who have higher morbidity and mortality rates (i.e. transfusion is a confounding factor). For example, the neonatal entity of transfusion associated necrotizing enterocolitis (TA-NEC) remains problematic due to the underlying neonatal anemia which has also been associated with NEC (Patel et al. 2016). As a result, the controversy of transfusion-transmitted harm may remain unresolved for some time.

Management of Immune Thrombocytopenia

Before discussing the treatment of immune thrombocytopenia (ITP) in children, it is important to describe the latest standardized terminology which was agreed upon in 2009 by the International Working Group of ITP experts (Rodeghiero et al. 2009). The group published a standardization document outlining their recommendations: the term “idiopathic thrombocytopenic purpura” is considered inaccurate, and “immune thrombocytopenia” is preferred; ITP is primary if there is no inciting cause, and secondary if there is an underlying autoimmune or other medical disorder. This new terminology emphasizes the immune-mediated pathophysiology of ITP, the absence of purpura in the majority of cases, and the importance of ruling out an underlying cause.

In addition, a platelet count below $100 \times 10^9 \text{ L}^{-1}$ (instead of $150 \times 10^9 \text{ L}^{-1}$) was established as the new threshold for diagnosis owing to the observation that a platelet count

between 100 and $150 \times 10^9 \text{ L}^{-1}$ is common in some populations with a low probability of developing severe thrombocytopenia. ITP is now classified as newly diagnosed (within 3 months of diagnosis), persistent (3–12 months from diagnosis), and chronic (>12 months from diagnosis).

First-line management of ITP in non-bleeding children is observation of symptoms with reassessment of platelet count. If a rapid (24–48 h) increase in platelet count is desired to prevent the low (<3%) risk of hemorrhage (including intracranial hemorrhage), prophylaxis can be offered with intravenous immunoglobulin (IVIg) (0.8–1 g/kg/day for 1–2 days), or anti-D for Rh-positive non-splenectomized patients (50–75 $\mu\text{g}/\text{kg}$ for 1 dose) (Neunert 2013; Cooper 2014). Anti-D is not recommended for children with low hemoglobin due to bleeding or autoimmune hemolysis. A short course of high-dose steroids (for example prednisone 4 mg/kg/day for 4 days) is also an option for first-line prophylaxis bearing in mind that the onset of platelet response is not immediate and can occur 1 week later (Blanchette and Carcao 2000). Platelet transfusion is generally not useful in ITP but may have a role in the actively bleeding patient while awaiting the effects of other treatments (Cooper 2014).

Splenectomy is the only known long lasting treatment for chronic immune thrombocytopenia, but it has to be weighed against the risk of sepsis. Rituximab offers the benefit of a relatively long lasting response (6–12 months) but complete remission is rare. There is currently not enough evidence to support the use of tranexamic acid, recombinant factor (F) VIIa, or immunosuppressive agents like azathioprine or mycophenolate mofetil (these agents have been used off-label).

Thrombopoietin (TPO) receptor agonists are novel agents that are licensed for use in adult and with very recent published data in children with persistent ITP. **Romiplostim** (AMG 53, Nplate; Amgen, Thousand Oaks, CA) is a subcutaneously administered recombinant protein. A phase 3 placebo-controlled double-blinded study ran-

domized 42 children to romiplostim and 20 children to placebo. A platelet response to a count over $50 \times 10^9 \text{ L}^{-1}$ was achieved in 22 (52%) patients in the study group and 2 (10%) in the placebo group; $p = 0.002$, odds ratio 9.1 [95% CI: 1.9–43.2] (Tarantino et al. 2016). **Eltrombopag** (SB-497115; GSK, Brentford, UK) is a small molecule TPO receptor agonist agent dosed once a day orally. The PETIT trial randomized 45 children to receive eltrombopag, and 22 children to the placebo group. A platelet response to a count over $50 \times 10^9 \text{ L}^{-1}$ was achieved in 28 (62%) study group patients and 7 (32%) placebo patients; $p = 0.011$, odds ratio 4.31 [95% CI: 1.39–13.34] (Bussel et al. 2015).

Evans Syndrome

Evans syndrome is characterized by ITP, autoimmune hemolytic anemia (AIHA) and/or autoimmune neutropenia. Some children may present with isolated cytopenia, commonly ITP or AIHA, and then develop additional cytopenias months or even years later. Of the children diagnosed with pediatric AIHA, up to one-third may have Evans syndrome (Aladjidi et al. 2011; Vaglio et al. 2007).

The underlying immune defect in Evans syndrome has not been identified yet despite many suggested immunoregulatory abnormalities. There is evidence of auto-antibody formation against antigens on the blood cells without obvious cross reactivity (Pegels et al. 1982). The patients with Evans syndrome are more likely to develop systemic autoimmunity. Many patients presenting with Evans syndrome have autoimmune lymphoproliferative syndrome (ALPS) as the underlying cause of their immune dysregulation, while some may have common variable immunodeficiency (CVID) or other immunodeficiencies (Teachey et al. 2005). It is thus important to check for ALPS in all patients with two cytopenias. In a study by Seif et al. (2010), almost half of 45 patients with Evans syndrome were eventually diagnosed with ALPS.

Evans syndrome is much more difficult to treat compared to ITP, AIHA or autoimmune neutropenia alone. It is frequently chronic, relapsing and refractory. Many patients do not respond fully to steroid therapy and require multiple agents. A study showed that almost two-thirds of patients with Evans syndrome required multiple agents compared with only one-third of patients with isolated AIHA (Aladjidi et al. 2011). Most commonly used treatments are steroids and IVIG. IVIG is used more commonly in patients with ITP.

Other treatment options include rituximab, mycophenolate mofetil and sirolimus. Rituximab is an effective second-line treatment for patients with Evans syndrome. In a retrospective study by Bader-Meunier et al. (2007), rituximab therapy was administered in combination with prednisone (14 patients) or other immunosuppressive drugs (three patients) in 17 patients. Thirteen of the 17 patients (76%) experienced partial or complete remission in cytopenias. Three patients relapsed at a median follow-up of 2.4 years. In the ten long-term responders, they were able to discontinue completely or taper steroid therapy to less than 50% of initial dosing.

Splenectomy is another mode of second-line treatment that has been shown to reverse cytopenias in patients with Evans syndrome. However, the response rate is lower than for patients with isolated ITP or AIHA (Chou and Schreiber 2015). In patients who respond initially, relapse is not uncommon. Splenectomy is generally reserved for patients who fail all medical treatments.

Diagnosis and Management of DIC

Disseminated intravascular coagulation (DIC) is a syndrome of systemic activation of blood coagulation, characterized by intravascular thrombin-induced fibrin generation which leads to thrombosis of small and medium-sized vessels, and organ dysfunction. Platelet and coagulation factor consumption also leads to a bleeding diathesis.

The causes of DIC vary from infection and cancer, to trauma and liver disease among other etiologies (Wada et al. 2013). In neonates, sepsis from Group B *streptococcus* and perinatal stress (asphyxia, respiratory distress syndrome, meconium aspiration) are the most common causes of DIC, whereas in older children bacterial sepsis and injury (trauma, burn, drowning) are the top causes followed by malignancy, toxins (snake bites, recreational drugs), liver disease and immunological reactions such as acute hemolytic transfusion reactions and transplant rejection (Rajagopal et al. 2017).

These etiologies have in common the ability to release tissue factor from endothelial cells and mononuclear cells. Tissue factor activates the extrinsic coagulation pathway by forming a complex with coagulation FVII, which then leads to thrombin generation and clot formation. Thrombin also activates the intrinsic and common pathways, which propagates further coagulation. Consumptive coagulopathy ensues which leads to the thrombo-hemorrhagic syndrome of DIC. Fibrin degradation products and D-dimers may form due to the action of plasmin on fibrin.

The diagnosis of DIC is challenging due to the differences in presentation and laboratory abnormalities present in each case. To simplify the diagnostic approach, several scoring systems have been developed in adult patients by guidelines

committees including: the British Committee for Standards in Haematology (BCSH), the Japanese Society of Thrombosis and Hemostasis (JSTH), the Italian Society for Thrombosis and Hemostasis (SISST), and the International Society on Thrombosis and Hemostasis (ISTH). For pediatric patients, there is controversy regarding the applicability of these scoring systems due to age-related differences in laboratory values and due to the low sensitivity of some coagulation tests in diagnosing early DIC in pediatrics (Soundar et al. 2013; Rajagopal et al. 2017). See Table 11.2 regarding pediatric considerations in the investigation of DIC.

The ISTH DIC scoring system uses four steps: (1) Risk assessment based on underlying disorder associated with DIC; (2) Obtaining global coagulation tests (platelet count, prothrombin time [PT], fibrinogen, fibrin-related marker such as D-dimer or fibrinogen degradation product); (3) Evaluating or scoring each laboratory value; (4) Calculating a total score (≥ 5 is compatible with overt DIC). Other scoring systems (Soundar et al. 2013) have found that serial laboratory tests which show a trend are significantly more sensitive in detecting pediatric DIC (though this approach is less specific for DIC).

The management of DIC in pediatrics is primarily aimed at treating the underlying condition (infection, malignancy) and replacing

Table 11.2 Pediatric considerations for DIC laboratory testing

| Laboratory test | Age considerations | Sampling and analysis considerations |
|---|--|---|
| Low platelet count | | – Platelet clumping due to difficult venous access |
| Prolonged prothrombin time (PT), activated partial thromboplastin time (aPTT) | – Vary with age – Neonatal polycythemia leads to excess citrate in tube | – Heparin contamination from central lines – Insufficient sampling leads to excess citrate in tube |
| Prolonged international normalized ratio (INR) | – Vary with age – INR control values use adult plasma, so pediatric results appear abnormal | – Laboratory should develop locally derived ranges using local reagents and analysers |
| Low fibrinogen | – Congenital hypofibrinogenemia must be considered | – Acute-phase reactant – The functional Clauss fibrinogen assay is more accurate in DIC |
| Elevated D-dimer | – No reference range available in pediatrics | – |

deficient coagulation factor using plasma protein products. Equally essential management strategies are the serial monitoring of laboratory values and the regulation of excess thrombin using heparin. Continuous infusion of unfractionated heparin is the preferable pediatric option, in the non-bleeding patient, due to its short half-life and its reversibility with protamine sulfate. Platelet transfusion should be reserved for the bleeding patient or those undergoing invasive procedures with a platelet count below $50 \times 10^9 \text{ L}^{-1}$. Plasma transfusion is only indicated in bleeding patients whose PT or activated partial thromboplastin time (aPTT) are over 1.5 times the upper age-based limit. Cryoprecipitate may be used in bleeding patients if the fibrinogen is below $<1.5 \text{ g/L}$. Fibrinogen concentrates are not currently licensed for DIC management; they are only licensed for congenital afibrinogenemia and congenital hypofibrinogenemia. The use of antithrombin and recombinant activated protein C (rAPC) are not widely accepted in pediatrics due to the lack of sufficient evidence. Due to the risk of thrombosis, recombinant FVIIa and antifibrinolytics are not recommended (Rajagopal et al. 2017).

Developments in Hemophilia Treatment

Hemophilia is a bleeding disorder caused by deficiency of FVIII (Hemophilia A) or FIX (Hemophilia B). The management of children with hemophilia requires a multi-disciplinary team and multi-dimensional approach. It includes provision of replacement therapy with coagulation factors that the patients are missing. The factor treatment is provided during acute bleeding and for prophylaxis. There are two major classes of factor replacement therapies, namely plasma-derived and recombinant products. Plasma-derived products are extracted and purified from human plasma, while recombinant factors are produced from cell lines (human or animal) which are engineered to express large amounts of factor. This section will address the development and use of longer-acting FVIII and

FIX products as well as employment of gene therapy in the treatment of hemophilia.

Over the last decade, longer acting factor replacement products have been engineered to allow for longer dosing intervals. Long-acting FVIII and FIX products are available and approved for older children and adults in Canada. Some of the ways that FVIII half-life has been increased include pegylation, fusion to immunoglobulin Fc domain and reconstitution with pegylated liposomes. FIX half-life has been extended by pegylation, fusion to Fc domain and fusion to albumin. With adequate control of bleeding episodes and less frequent infusions, it is expected that the extended half-life factors would lead to an improvement in quality of life in children and caregivers. A preliminary analysis of Haem-A-QoL, a quality of life measurement tool, has shown numerical improvements in total scores from baseline for adult hemophilia patients taking Eloctate and Alprolix. Final analyses are pending.

Long-Acting FVIII Products

FVIII-Fc Fusion

Eloctate[®] is a recombinant product, rFVIII_hFc, made of FVIII fused with a human immunoglobulin Fc domain (Dumont et al. 2012). The Fc domain binds the neonatal Fc receptor and protects the factor from degradation. The half-life is extended 1.5–2 times in studies. The pilot study as well as the dosing study were published in 2012 and 2014, respectively (Powell et al. 2012; Mahlangu et al. 2014). The pilot study, consisting of 16 patients, and dosing study, consisting of 165 patients, showed that rFVIII_hFc was well tolerated and patients did not develop inhibitors to the fusion protein during 28 days of observation and 50 exposure days, respectively. The half-life of rFVIII_hFc in the pilot study was 18.8 h compared to 11 h for rFVIII and the trough levels with twice weekly dosing were 1–3 units/dL. There is wide variation in the pharmacokinetics of FVIII among different individuals. Eloctate[®] was approved by the US FDA in June of 2014 for patients with hemophilia A.

FVIII with Pegylated Liposomes

One strategy used to prolong FVIII half-life was reconstitution with pegylated liposomes. It seemed effective in preclinical studies, wherein it not only prolonged the half-life FVIII, but also reduced bleeding complications (Baru et al. 2005). However, in randomized controlled trials in humans, the pharmacokinetic profile was comparable to native FVIII. Hence, this strategy was not further pursued. Then, it was thought that reconstitution with liposomal carriers may do the trick. There is a molecule wherein plasma-derived FVIII is reconstituted with a liposomal diluent immediately prior to infusion, which is under study (Spira et al. 2012).

Long-Acting FIX Products

FIX-Fc Fusion

Alprolix[®] is a recombinant molecule, rFIXFc, made of FVIII fused with a human immunoglobulin Fc domain. The Fc domain causes the protein to be recycled to the circulation through its binding to the neonatal Fc receptor, which extends the half-life 3–5 times. The half-life of the rFIXFc is measured at 54–90 h, compared with 18 h for unmodified FIX products (Peters et al. 2010). Powell et al. (2013) published the first observational study of rFIXFc, where its efficacy was examined in prevention of bleeding using prophylactic as well as on-demand dosing. The annual bleeding rates were 3, 1.4, and 17.7 with once-weekly dose-adjusted prophylaxis, interval-adjusted prophylaxis, and on-demand dosing, respectively. There were no inhibitors, thromboembolic events, or anaphylactic reactions in two other open label studies of 138 patients (Shapiro et al. 2012). Alprolix[®] was approved by the US Food and Drug Administration (FDA) in 2014 for prophylaxis and treatment (<http://www.alprolix.com/pdfs/PrescribingInformation.pdf> [Accessed on April 01, 2014]).

FIX-Albumin Fusion

Idelvion[®] is a recombinant FIX product which is produced by fused human FIX and human albumin genes. The protein circulates as a fused protein

until the link is cleaved during FIX activation. The half-life of Idelvion[®] this product is 102 h (Santagostino et al. 2016). In addition to increased half-life, Idelvion[®] also has the potential for higher trough levels. Idelvion[®] was approved by the US FDA in 2016 for prophylaxis or treatment of bleeding.

Pegylated FIX

N9-GP[®] is a pegylated long-acting FIX product. The PEG moiety is removed during the proteolytic activation of FIX in the coagulation cascade. The half-life of N9-GP[®] was measured at 93 h in the initial study (Negrier et al. 2011). Collins et al. (2014) published the first N9-GP trial in humans, in which they had 74 patients with hemophilia B who were treated with prophylaxis or on-demand treatment. The annual bleeding rates were 1.04, 2.93, and 15.58 with 40 IU/kg weekly, 10 IU/kg weekly, and on-demand dosing, respectively. Forty-five percent of patients receiving prophylaxis had no bleeding, while 17% of patients receiving 10 IU/kg had no bleeding. No inhibitors developed and there were no other safety concerns during the trial.

Gene Therapy

Gene therapy is a curative option for patients with hemophilia as it has the potential to replace the deficient factor. With gene therapy, achieving fully normal factor levels is not the aim. It is sufficient to convert severe hemophilia patients (<1% factor level) to moderate (1–5%) or mild factor levels (>5%) to improve their clinical phenotype.

There are two important technologies being explored: (1) Injection of FVIII or FIX encoding vectors into the recipient, and (2) *Ex vivo* gene therapy in which cells from the intended recipients are explanted and genetically modified to secrete the factor.

There have been two studies in Hemophilia A. In the study by Roth et al. (2001), dermal fibroblasts from six patients were explanted, transfected with a plasmid for FVIII and then

injected into the omentum. The FVIII activity increased in 4/6 patients, with decreased in bleeding and factor requirement. No serious side effects were reported. Powell et al. (2003) used a retroviral vector for expression of a B-domain-deleted human FVIII. Out of 13 patients treated, FVIII requirement decreased in five patients. No major adverse events were reported.

There have been multiple studies examining the utility of gene therapy in Hemophilia B patients. These studies have all evaluated adeno-viral gene transduction of FIX constructs.

Nathwani et al. (2011, 2014) treated ten patients with intravenous infusion of adeno-associated virus serotype 8 (AAV8) vector expressing a codon-optimized FIX. These patients experienced a dose dependent increase in FIX levels. A follow-up study showed that the increase in FIX level was persistent over a median of 3.2 years. The annual bleeding rates in these patient groups decreased from 16% to 2%. Four out of seven patients were able to discontinue prophylaxis. In terms of side effects, temporary asymptomatic elevations in transaminases were reported. There were no other major adverse events.

Gene therapy is promising, but challenging. There are many unresolved issues including T cell response to viral insertion vector, factor

delivery, neutralizing antibody response cost and safety (Scott and Lozier 2012).

Oral Anticoagulants in Children

The mainstay of anticoagulation therapy in neonates and children with thrombosis comprises of unfractionated heparin, low molecular weight heparin and warfarin. Warfarin is the only oral anticoagulant approved for use in children; however, its therapeutic effect is significantly influenced by changes in diet and medications (Ansell et al. 2008). Secondly, it requires rigorous monitoring with international normalized ratio (INR) to ensure appropriate therapeutic effect. Given these reasons, it is not very practical to use warfarin in children for shorter treatment durations of 3–6 months.

New oral anticoagulants such as FXa inhibitors (rivaroxaban, apixaban, and edoxaban) and direct thrombin inhibitors (argatroban, dabigatran, and bivalirudin), have been tested and approved for use in adults. However, there is limited data for use in children. Many of these agents are in the clinical trial phase in pediatric patients (Table 11.3). In the meantime, it is not recommended to use these agents outside of clinical studies.

Table 11.3 Drug and research study information for oral anticoagulant use in pediatrics

| Anticoagulant | General information | Published studies | Ongoing studies |
|---------------|---|---|--|
| Rivaroxaban | Direct Xa inhibitor, once daily dosing | PK/PD studies in children ages 6 months to 18 years comparing dose equivalent to adult 20 mg dose | PK/PD study in <6 months children; phase II and III studies in all children >6 months |
| Apixaban | Direct Xa inhibitor, twice daily dosing | None | Phase I PK/PD study in all children; phase III study in 1–18 years (phase III open only once phase I completed in each age cohort) |
| Edoxaban | Direct Xa inhibitor, once daily dosing, useful for patients with renal impairment | None | Phase I PK/PD study in 0–18 years |
| Dabigatran | Direct thrombin inhibitor, twice daily dosing | Phase II study in adolescents | Phase II and III studies in different cohorts for prophylaxis and treatment |

From von Vajna et al. 2016

PK pharmacokinetics, PD pharmacodynamics

The new oral anticoagulants, including apixaban, dabigatran, rivaroxaban, have been studied and approved in adults for thromboprophylaxis after hip and knee arthroplasty, treatment of venous thromboembolism and stroke prevention in atrial fibrillation. They are currently being evaluated in children in international studies. Pediatric studies are required before usage because of uncertainties about dosing, effectiveness and safety related to differences in children compared to adults. Children are different from adults for many reasons, including developmental hemostasis, pharmacokinetics/pharmacodynamics, renal function, and hepatic function.

Autoimmune Lymphoproliferative Syndrome (ALPS)

ALPS is caused by dysregulation of the immune system, specifically due to an inability to regulate lymphocyte apoptosis (Rao and Oliveira 2011). Such deregulation leads most commonly to lymphoproliferative disease and less often autoimmune disease. Manifestations of lymphoproliferative disease, such as lymphadenopathy, hepatomegaly, splenomegaly, occur most commonly in children with a median age of onset being 2.7–3 years (Neven et al. 2011; Price et al. 2014). Autoimmune disease is more common in adult onset ALPS. The exact incidence and prevalence of ALPS are unknown. There is a proven male predominance, with male to female ratio being 2.2 in the French cohort and 1.6 in NIH cohort (Neven et al. 2011; Price et al. 2014).

The majority of patients with ALPS (approximately 67%) have a confirmed genetic defect, with majority having a germline mutation in the

FAS gene (classified as ALPS-FAS, MIM #601859) (Madkaikar et al. 2011). ALPS-FAS is inherited in an autosomal dominant manner. In rare cases, ALPS is caused by mutations in the genes encoding Fas ligand (ALPS-FASLG) or caspase 10 (ALPS-CASP10) (Magerus-Chatinet et al. 2013; Zhu et al. 2006). The Fas/Fas ligand (FasL) pathway is implicated in the defective lymphocyte apoptosis, leading to expansion of antigen-specific lymphocyte populations.

The diagnostic criteria for ALPS has been revised multiple times, with the most recent being published in 2010 (Table 11.4) (Oliveira et al. 2010). The main laboratory abnormalities include the expansion of CD4 and CD8 negative T cells (or double-negative T [DNT] cells) in blood and tissue, elevated interleukin-10 (IL-10) in blood, elevated vitamin B₁₂, and defective Fas-mediated apoptosis *in vitro*. A definitive diagnosis of ALPS is based upon the presence of both required criteria and one primary accessory criterion. A probable diagnosis is based upon the presence of both required criteria plus one secondary accessory criterion. Important differential diagnoses include lymphoma, immunodeficiency disorders, and autoimmune disorders.

The management of ALPS should focus on three domains: management of clinical manifestations, preventing complications and curative therapy. The treatment of lymphoproliferation and autoimmune disease, the two main manifestations, is based mostly on clinical experience and observational studies. Immunosuppressants such as steroids, sirolimus, tacrolimus, cyclosporine, and mycophenolate mofetil have been used with some success. The benefits, however, need to be weighed with side effects (Blesing 2003;

Table 11.4 Diagnostic criteria for ALPS

| Required | Primary accessory | Secondary accessory |
|---|--|--|
| <ul style="list-style-type: none"> – Chronic (>6 months) nonmalignant, noninfectious lymphadenopathy, splenomegaly, or both – Elevated CD4–/CD8– T cells with normal or elevated lymphocyte counts | <ul style="list-style-type: none"> – Defective lymphocyte apoptosis (assay repeated at least once) – Somatic or germline pathogenic mutations in FAS, FASLG, or CASP10 | <ul style="list-style-type: none"> – Positive family history – Elevated plasma levels of soluble Fas ligand (FasL), interleukin-10 (IL-10), vitamin B₁₂, or interleukin-18 (IL-18) – Autoimmune cytopenias with elevated (polyclonal) immunoglobulin G (IgG) levels – Typical immunohistologic findings as determined by an experienced hematopathologist (see ‘Laboratory findings’ above) |

Rao et al. 2005; Teachey et al. 2010). Due to side effects and return of symptoms post-discontinuation, immunosuppression is reserved for severe and life-threatening complications (Blesing 2003). Patients with autoimmune manifestations (such as autoimmune cytopenias) have a harder time discontinuing immunosuppression than those with only lymphoproliferation. Of note, IVIG monotherapy has been successful in some patients to manage cytopenias (Blesing 2003). The most frequent complication of ALPS and its therapies is infection. Prophylactic antimicrobials to prevent opportunistic, fungal and viral infections are warranted in some cases. Patients with signs or symptoms of infection should be worked up and treated aggressively.

The only curative therapy for ALPS is hematopoietic stem cell transplantation (HSCT), and it is generally done with reduced-intensity conditioning regimens to minimize morbidity and mortality (Sleight et al. 1998). It is offered after careful discussion of risks versus chance of success in each patient. Some transplant indications include development of lymphoma, severe recurrent infections, severe refractory autoimmune cytopenias, or severe disease type at diagnosis.

Acquired Aplastic Anemia in Children

Aplastic anemia is a disorder of abnormal bone marrow function, which leads to pancytopenia. Inherited and acquired causes of aplastic anemia are listed in Table 11.5. Acquired aplastic anemia is most common, and within acquired 70–80% of children have idiopathic aplastic anemia and no identifiable risk factor (Guinan 2009). The incidence of aplastic anemia in children is estimated to be 2 per million, with an equal incidence in boys and girls.

The pathophysiology of aplastic anemia is thought to be loss of pluripotent hematopoietic stem cells due to injury from autoimmunity or external toxins (Young et al. 2010). Some possible theories behind immune-mediated attack of hematopoietic stem cells include aberrant

Table 11.5 Inherited and acquired causes of aplastic anemia

| | |
|-----------|--|
| Inherited | Fanconi anemia |
| | Dyskeratosis congenita |
| | Schwachman Diamond syndrome |
| | Congenital amegakaryocytic thrombocytopenia |
| | Diamond Blackfan anemia |
| | Reticular dysgenesis |
| | GATA-2 syndromes |
| Acquired | Viruses: Hepatitis, Parvo, EBV, CMV, VZV, HSV, HIV |
| | Drugs/chemicals: chemo, benzenes, chloramphenicol, anti-epileptics, anti-inflammatory, sulfonamides, quinine, anti-histamines, lindane |
| | Radiation |
| | Paroxysmal nocturnal hematuria |
| | Immune: eosinophilic fasciitis, systemic lupus erythematosus, graft versus host disease |
| | Myelodysplasia |
| | Pregnancy |

CMV cytomegalovirus, *EBV* Epstein-Barr virus, *HIV* human immunodeficiency virus, *HSV* herpes simplex virus, *VZV* varicella zoster virus

immune response, oligoclonal T-cell expansion, and cytotoxic T-cell mediated suppression of hematopoietic progenitors. In acquired aplastic anemia, there is absence of abnormal infiltrates and normal reticulin.

Aplastic anemia patients usually present with signs and symptoms from cytopenias: bruising and bleeding secondary to thrombocytopenia; fatigue and pallor due to anemia; and fever, infection and ulcerations because of neutropenia. Complete blood count will help to identify cytopenias, but the definitive diagnosis of aplastic anemia is made by bone marrow aspiration and biopsy. Some features on bone marrow examination include decreased cellularity, marrow invasion by fat and stroma cells, and reduced but morphologically normal hematopoietic cells.

Aplastic anemia is classified as moderate, severe or very severe. Moderate aplastic anemia is defined by decreased bone marrow cellularity (<50%), depressed two out of three cell lines (anemia with absolute reticulocyte counts [ARC]

<60,000 μL^{-1} , absolute neutrophil count [ANC] <1500 μL^{-1} , platelet counts <100,000 μL^{-1}), and not meeting criteria for severe aplastic anemia (SAA). SAA is defined as <25% bone marrow cellularity or 25–50% bone marrow cellularity with <30% hematopoietic cells and severe depression of two out of three cells lines defined by ARC <40,000 μL^{-1} , ANC <500 μL^{-1} , platelets <20,000 μL^{-1} . Very severe aplastic anemia is defined by the same criteria as SAA, but having an ANC <200 μL^{-1} (Hartung et al. 2013).

The management of aplastic anemia consists of two potential therapies: (1) immunosuppressive therapy (IST) or HSCT (Davies and Guinan 2007; Young et al. 2006). For those children who have a matched sibling donor, the preferred option for treatment is HSCT. For the rest of children, IST is the preferred treatment modality. IST regimens consist of combination of antithymocyte globulin ATG, cyclosporine, steroids and sometimes growth factors (Davies and Guinan 2007). The response rate for IST is around 70–75% at 3–6 months, but the long-term event free survival is 40–50% at 10 years. HSCT on the other hand has a much better long-term event free survival up to 90%, however there are important side effects such as graft versus host disease, infertility, and secondary malignancy that need to be considered. HSCT is offered to patients without matched sibling donors at relapse post-IST.

Along with curative therapy, it is extremely important to provide adequate supportive care for aplastic anemia patients. Supportive includes prompt and aggressive management of infections as well as transfusion support for cytopenias.

Neutropenia

Neutropenia in children is divided into four categories based on severity: (1) mild (1000 to 1500 μL^{-1}), (2) moderate (500–1000 μL^{-1}), (3) severe (200–500 μL^{-1}), and (4) very severe (below 200 μL^{-1}). The severity of the neutropenia correlates with susceptibility to severe bacterial infection, and the duration of the neutropenia compounds this risk.

Factors That Affect the Neutrophil Count

Normal values for absolute neutrophil count are age-dependent. At birth, neutrophils can constitute up to 70% of white blood cells (minimum 6000 μL^{-1}), and at 1 week to 1 month of age they range from 30% to 45% (minimum 1000 μL^{-1}) rising again at 6–8 years of age to over 50% (minimum 1500 μL^{-1}). Adult levels can approach 60% (Segel and Halterman 2008).

Normal neutrophil values are also race-dependent. At least 3–5% of children of African descent have a neutrophil count below 1500 μL^{-1} without any underlying pathology.

The neutrophil count may be affected by medications. Steroid medications demarginate neutrophils from the vascular wall raising the neutrophil count. Hormonal therapy with granulocyte colony stimulating factor drives stem cells to produce neutrophils.

Signs and Symptoms of a Neutropenic Child

The clinical manifestations of neutropenia include: oral ulceration, gingival inflammation, otitis media, cellulitis, pustules, adenitis, pneumonia, perianal infection, ischio-rectal fossa abscess, and sepsis. Implicated organisms commonly include *Staphylococcus aureus* from the patient's own skin flora, and gram negative organisms from the gastrointestinal flora (Walkovich and Boxer 2013).

Management of a Neutropenic Patient

The evaluation of a child with neutropenia should not only include screening questions for the above manifestations, but also a detailed family history and physical examination to rule out congenital anomalies, which can indicate an inherited cause. Acquired neutropenia is more common than the inherited form. It can be induced by infection (viral or bacterial), drugs,

sequestration/hypersplenism, autoimmune disease, neonatal-maternal alloimmunity, and severe nutritional deficiencies in vitamin B₁₂ or folate (Segel and Halterman 2008).

If an inherited cause is suspected, referral to a hematologist and genetic counsellor is recommended for further investigations and management. Marrow failure syndromes require bone marrow biopsy and genetic investigations to rule out Fanconi Anemia, Dyskeratosis Congenita, Schwachman-Diamond Syndrome, Kostmann Syndrome, and Blackfan-Diamond Syndrome. Cure for these conditions lies in stem cell transplantation. However, due to chromosomal fragility, Fanconi Anemia patients may not tolerate standard transplant chemotherapeutic conditioning regimens, so a reduced intensity regimen is considered. Cyclic neutropenia may result in severe neutropenic manifestations every 18–21 days, and can be prevented with G-CSF injections preceding and during these periods of neutropenia.

Prolonged neutropenia may be treated with granulocyte transfusion at specialized centres; however, the efficacy of granulocyte transfusions in various clinical settings has not been proven. Granulocyte transfusions are logistically and technically difficult, requiring close collaboration between blood suppliers and hospitals (Price et al. 2015).

Conclusion

In conclusion, an enhanced understanding of neonatal and pediatric blood physiology is allowing clinicians to better apply therapies previously employed in adults. Special considerations in the pediatric and neonatal populations are important to optimize outcomes by distinguishing the investigation and management needs of pediatric patients from those of adult patients. For these reasons, the pediatric and neonatal populations are being given special attention in international trials whose findings are highly anticipated. With appropriate knowledge translation efforts, strong evidence can be accepted into clinical practice to improve patient outcomes.

References

- Aladjidi N, Leverger G, Leblanc T, Picat MQ, Michel G, Bertrand Y, et al. New insights into childhood autoimmune hemolytic anemia: a French national observational study of 265 children. *Haematologica*. 2011;96(5):655–63.
- Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians evidence-based clinical practice guidelines (8th edn). *Chest*. 2008;133(6 Suppl):160S–98S.
- Bader-Meunier B, Aladjidi N, Bellmann F, Monpoux F, Nelken B, Robert A, et al. Rituximab therapy for childhood Evans syndrome. *Haematologica*. 2007;92(12):1691–4.
- Baru M, Carmel-Goren L, Barenholz Y, Dayan I, Ostropelets S, Slepoy I, et al. Factor VIII efficient and specific non-covalent binding to PEGylated liposomes enables prolongation of its circulation time and haemostatic efficacy. *Thromb Haemost*. 2005;93(6):1061–8.
- Blanchette V, Carcao M. Approach to the investigation and management of immune thrombocytopenic purpura in children. *Semin Hematol*. 2000;37(3):299–314.
- Bleesing JJ. Autoimmune lymphoproliferative syndrome (ALPS). *Curr Pharm Des*. 2003;9(3):265–78.
- Bussel JB, de Miguel PG, Despotovic JM, Grainger JD, Sevilla J, Blanchette VS, et al. Eltrombopag for the treatment of children with persistent and chronic immune thrombocytopenia (PETIT): a randomised, multicentre, placebo-controlled study. *Lancet Haematol*. 2015;2(8):e315–25.
- Canadian Haemoglobinopathy Association. Consensus statement on the care of patients with sickle cell disease in Canada. Ottawa, ON: Canadian Haemoglobinopathy Association; 2014.
- Chasse M, Timmouth A, English SW, Acker JP, Wilson K, Knoll G, et al. Association of blood donor age and sex with recipient survival after red blood cell transfusion. *JAMA Intern Med*. 2016;176(9):1307–14.
- Chou ST, Schreiber AD. Autoimmune Hemolytic Anemia. In: Orkin SH, Fisher DE, Look T, Lux SE, Ginsburg D, Nathan DG, editors. *Nathan and Oski's hematology and oncology of infancy and childhood*. 8th ed. Philadelphia, PA: WB Saunders; 2015. p. 411.
- Collins PW, Young G, Knobe K, Karim FA, Angchaisuksiri P, Banner C, et al. Recombinant long-acting glycoPEGylated factor IX in hemophilia B: a multinational randomized phase 3 trial. *Blood*. 2014;124(26):3880–6.
- Cooper N. A review of the management of childhood immune thrombocytopenia: how can we provide an evidence-based approach? *Br J Haematol*. 2014;165(6):756–67.
- Davies JK, Guinan EC. An update on the management of severe idiopathic aplastic anaemia in children. *Br J Haematol*. 2007;136(4):549–64.
- De Falco L, Sanchez M, Silvestri L, Kannengiesser C, Muckenthaler MU, Iolascon A, et al. Iron refrac-

- tory iron deficiency anemia. *Haematologica*. 2013;98(6):845–53.
- Dumont JA, Liu T, Low SC, Zhang X, Kamphaus G, Sakorafas P, et al. Prolonged activity of a recombinant factor VIII-Fc fusion protein in hemophilia A mice and dogs. *Blood*. 2012;119(13):3024–30.
- Fergusson DA, Hebert P, Hogan DL, LeBel L, Rouvinez-Bouali N, Smyth JA, et al. Effect of fresh red blood cell transfusions on clinical outcomes in premature, very low-birth-weight infants: the ARIPI randomized trial. *JAMA*. 2012;308(14):1443–51.
- Galanello R, Agus A, Campus S, Danjou F, Giardina PJ, Grady RW. Combined iron chelation therapy. *Ann N Y Acad Sci*. 2010;1202:79–86.
- Guinan EC. Acquired aplastic anemia in childhood. *Hematol Oncol Clin North Am*. 2009;23(2):171–91.
- Hartung HD, Olson TS, Bessler M. Acquired aplastic anemia in children. *Pediatr Clin N Am*. 2013;60(6):1311–36.
- Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med*. 1999;340(6):409–17.
- Heddle NM, Cook RJ, Arnold DM, Liu Y, Barty R, Crowther MA, et al. Effect of short-term vs. long-term blood storage on mortality after transfusion. *N Engl J Med*. 2016;375(20):1937–45.
- Janus J, Moerschel SK. Evaluation of anemia in children. *Am Fam Physician*. 2010;81(12):1462–71.
- Jimenez K, Kulnigg-Dabsch S, Gasche C. Management of iron deficiency anemia. *Gastroenterol Hepatol (NY)*. 2015;11(4):241–50.
- Kelly N. Thalassemia. *Pediatr Rev*. 2012;33(9):434–5.
- Kirpalani H, Whyte RK, Andersen C, Asztalos EV, Heddle N, Blajchman MA, et al. The premature infants in need of transfusion (PINT) study: a randomized, controlled trial of a restrictive (low) versus liberal (high) transfusion threshold for extremely low birth weight infants. *J Pediatr*. 2006;149(3):301–7.
- Lacroix J, Hebert PC, Hutchison JS, Hume HA, Tucci M, Ducruet T, et al. Transfusion strategies for patients in pediatric intensive care units. *N Engl J Med*. 2007;356(16):1609–19.
- Lacroix J, Hebert PC, Fergusson DA, Tinmouth A, Cook DJ, Marshall JC, et al. Age of transfused blood in critically ill adults. *N Engl J Med*. 2015;372(15):1410–8.
- Madkaikar M, Mhatre S, Gupta M, Ghosh K. Advances in autoimmune lymphoproliferative syndromes. *Eur J Haematol*. 2011;87(1):1–9.
- Magerus-Chatinet A, Stolzenberg MC, Lanzarotti N, Neven B, Daussy C, Picard C, et al. Autoimmune lymphoproliferative syndrome caused by a homozygous null FAS ligand (FASLG) mutation. *J Allergy Clin Immunol*. 2013;131(2):486–90.
- Mahlangu J, Powell JS, Ragni MV, Chowdary P, Josephson NC, Pabinger I, et al. Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. *Blood*. 2014;123(3):317–25.
- McDonagh MS, Blazina I, Dana T, Cantor A, Bougatsos C. Screening and routine supplementation for iron deficiency anemia: a systematic review. *Pediatrics*. 2015;135(4):723–33.
- Modell B, Khan M, Darlison M. Survival in beta-thalassaemia major in the UK: data from the UK Thalassaemia Register. *Lancet*. 2000;355(9220):2051–2.
- Nathwani AC, Tuddenham EG, Rangarajan S, Rosales C, McIntosh J, Linch DC, et al. Adenovirus-associated virus vector-mediated gene transfer in hemophilia B. *N Engl J Med*. 2011;365(25):2357–65.
- Nathwani AC, Reiss UM, Tuddenham EG, Rosales C, Chowdary P, McIntosh J, et al. Long-term safety and efficacy of factor IX gene therapy in hemophilia B. *N Engl J Med*. 2014;371(21):1994–2004.
- Negrier C, Knobe K, Tiede A, Giangrande P, Moss J. Enhanced pharmacokinetic properties of a glycoPEGylated recombinant factor IX: a first human dose trial in patients with hemophilia B. *Blood*. 2011;118(10):2695–701.
- Neunert CE. Current management of immune thrombocytopenia. *Hematology Am Soc Hematol Educ Program*. 2013;2013:276–82.
- Neven B, Magerus-Chatinet A, Florquin B, Gobert D, Lambotte O, De SL, et al. A survey of 90 patients with autoimmune lymphoproliferative syndrome related to TNFRSF6 mutation. *Blood*. 2011;118(18):4798–807.
- Oliveira JB, Blessing JJ, Dianzani U, Fleisher TA, Jaffe ES, Lenardo MJ, et al. Revised diagnostic criteria and classification for the autoimmune lymphoproliferative syndrome (ALPS): report from the 2009 NIH International Workshop. *Blood*. 2010;116(14):e35–40.
- Olivieri N, Brittenham G. Final results of the randomised trial of deferiprone and deferoxamine. *Blood*. 1997;90:264a.
- Thalassaemia International Federation. Guidelines for the management of transfusion dependent thalassaemia (TDT). 3rd ed. Nicosia: Thalassaemia International Federation; 2014.

Reference Type: Abstract

- Patel RM, Knezevic A, Shenvi N, Hinkes M, Keene S, Roback JD, et al. Association of red blood cell transfusion, anemia, and necrotizing enterocolitis in very low-birth-weight infants. *JAMA*. 2016;315(9):889–97.
- Pegels JG, Helmerhorst FM, van Leeuwen EF, Dalen P, Engelfriet CP, von dem Borne AE. The Evans syndrome: characterization of the responsible autoantibodies. *Br J Haematol*. 1982;51(3):445–50.
- Peters RT, Low SC, Kamphaus GD, Dumont JA, Amari JV, Lu Q, et al. Prolonged activity of factor IX as a monomeric Fc fusion protein. *Blood*. 2010;115(10):2057–64.
- Platt OS. Hydroxyurea for the treatment of sickle cell anemia. *N Engl J Med*. 2008;358(13):1362–9.
- Porter JB, Elalfy MS, Taher AT, Aydinok Y, Chan LL, Lee SH, et al. Efficacy and safety of deferasirox at low and high iron burdens: results from the EPIC

- magnetic resonance imaging substudy. *Ann Hematol*. 2013;92(2):211–9.
- Powell JS, Ragni MV, White GC, Lusher JM, Hillman-Wiseman C, Moon TE, et al. Phase I trial of FVIII gene transfer for severe hemophilia A using a retroviral construct administered by peripheral intravenous infusion. *Blood*. 2003;102(6):2038–45.
- Powell JS, Josephson NC, Quon D, Ragni MV, Cheng G, Li E, et al. Safety and prolonged activity of recombinant factor VIII Fc fusion protein in hemophilia A patients. *Blood*. 2012;119(13):3031–7.
- Powell JS, Pasi KJ, Ragni MV, Ozelo MC, Valentino LA, Mahlangu JN, et al. Phase 3 study of recombinant factor IX Fc fusion protein in hemophilia B. *N Engl J Med*. 2013;369(24):2313–23.
- Price S, Shaw PA, Seitz A, Joshi G, Davis J, Niemela JE, et al. Natural history of autoimmune lymphoproliferative syndrome associated with FAS gene mutations. *Blood*. 2014;123(13):1989–99.
- Price TH, Boeckh M, Harrison RW, McCullough J, Ness PM, Strauss RG, et al. Efficacy of transfusion with granulocytes from G-CSF/dexamethasone-treated donors in neutropenic patients with infection. *Blood*. 2015;126(18):2153–61.
- Rajagopal R, Thachil J, Monagle P. Disseminated intravascular coagulation in paediatrics. *Arch Dis Child*. 2017;102(2):187–93.
- Rao VK, Oliveira JB. How I treat autoimmune lymphoproliferative syndrome. *Blood*. 2011;118(22):5741–51.
- Rao VK, Dugan F, Dale JK, Davis J, Tretler J, Hurley JK, et al. Use of mycophenolate mofetil for chronic, refractory immune cytopenias in children with autoimmune lymphoproliferative syndrome. *Br J Haematol*. 2005;129(4):534–8.
- Richardson M. Microcytic anemia. *Pediatr Rev*. 2007;28(1):5–14.
- Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood*. 2009;113(11):2386–93.
- Roth DA, Tawa NE Jr, O'Brien JM, Treco DA, Selden RF. Nonviral transfer of the gene encoding coagulation factor VIII in patients with severe hemophilia A. *N Engl J Med*. 2001;344(23):1735–42.
- Santagostino E, Martinowitz U, Lissitchkov T, Pan-Petes B, Hanabusa H, Oldenburg J, et al. Long-acting recombinant coagulation factor IX albumin fusion protein (rIX-FP) in hemophilia B: results of a phase 3 trial. *Blood*. 2016;127(14):1761–9.
- Scott DW, Lozier JN. Gene therapy for haemophilia: prospects and challenges to prevent or reverse inhibitor formation. *Br J Haematol*. 2012;156(3):295–302.
- Segel GB, Halterman JS. Neutropenia in pediatric practice. *Pediatr Rev*. 2008;29(1):12–23.
- Seif AE, Manno CS, Sheen C, Grupp SA, Teachey DT. Identifying autoimmune lymphoproliferative syndrome in children with Evans syndrome: a multi-institutional study. *Blood*. 2010;115(11):2142–5.
- Shapiro AD, Ragni MV, Valentino LA, Key NS, Josephson NC, Powell JS, et al. Recombinant factor IX-Fc fusion protein (rFIXFc) demonstrates safety and prolonged activity in a phase 1/2a study in hemophilia B patients. *Blood*. 2012;119(3):666–72.
- Siu AL. Screening for iron deficiency anemia in young children: USPSTF recommendation statement. *Pediatrics*. 2015;136(4):746–52.
- Sleight BJ, Prasad VS, DeLaat C, Steele P, Ballard E, Arceci RJ, et al. Correction of autoimmune lymphoproliferative syndrome by bone marrow transplantation. *Bone Marrow Transplant*. 1998;22(4):375–80.
- Solh Z, Taccone MS, Marin S, Athale U, Breakey VR. Neurological PREsentations in sickle cell patients are not always stroke: a review of posterior reversible encephalopathy syndrome in sickle cell disease. *Pediatr Blood Cancer*. 2016;63(6):983–9.
- Soundar EP, Jariwala P, Nguyen TC, Eldin KW, Teruya J. Evaluation of the International Society on Thrombosis and Haemostasis and institutional diagnostic criteria of disseminated intravascular coagulation in pediatric patients. *Am J Clin Pathol*. 2013;139(6):812–6.
- Spira J, Plyushch O, Andreeva T, Zorenko V, Zozulya N, Velichkoi I, et al. Safety and efficacy of a long-acting liposomal formulation of plasma-derived factor VIII in haemophilia A patients. *Br J Haematol*. 2012;158(1):149–52.
- Steiner ME, Ness PM, Assmann SF, Triulzi DJ, Sloan SR, Delaney M, et al. Effects of red-cell storage duration on patients undergoing cardiac surgery. *N Engl J Med*. 2015;372(15):1419–29.
- Tarantino MD, Bussel JB, Blanchette VS, Despotovic J, Bennett C, Raj A, et al. Romiplostim in children with immune thrombocytopenia: a phase 3, randomised, double-blind, placebo-controlled study. *Lancet*. 2016;388(10039):45–54.
- Teachey DT, Manno CS, Axsom KM, Andrews T, Choi JK, Greenbaum BH, et al. Unmasking Evans syndrome: T-cell phenotype and apoptotic response reveal autoimmune lymphoproliferative syndrome (ALPS). *Blood*. 2005;105(6):2443–8.
- Teachey DT, Seif AE, Grupp SA. Advances in the management and understanding of autoimmune lymphoproliferative syndrome (ALPS). *Br J Haematol*. 2010;148(2):205–16.
- Vaglio S, Arista MC, Perrone MP, Tomei G, Testi AM, Coluzzi S, et al. Autoimmune hemolytic anemia in childhood: serologic features in 100 cases. *Transfusion*. 2007;47(1):50–4.
- von Vajna E, Alam R, So TY. Current clinical trials on the use of direct oral anticoagulants in the pediatric population. *Cardiol Ther*. 2016;5(1):19–41.
- Wada H, Thachil J, Di NM, Mathew P, Kurosawa S, Gando S, et al. Guidance for diagnosis and treatment of DIC from harmonization of the recommendations from three guidelines. *J Thromb Haemost*. 2013;11(4):761–7.
- Walkovich K, Boxer LA. How to approach neutropenia in childhood. *Pediatr Rev*. 2013;34(4):173–84.

- Wang WC, Ware RE, Miller ST, Iyer RV, Casella JF, Minniti CP, et al. Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG). *Lancet*. 2011;377(9778):1663–72.
- Young NS, Calado RT, Scheinberg P. Current concepts in the pathophysiology and treatment of aplastic anemia. *Blood*. 2006;108(8):2509–19.
- Young NS, Bacigalupo A, Marsh JC. Aplastic anemia: pathophysiology and treatment. *Biol Blood Marrow Transplant*. 2010;16(1 Suppl):S119–25.
- Zhu S, Hsu AP, Vacek MM, Zheng L, Schaffer AA, Dale JK, et al. Genetic alterations in caspase-10 may be causative or protective in autoimmune lymphoproliferative syndrome. *Hum Genet*. 2006;119(3):284–94.



Update in Pediatric Hospital Medicine

12

Elizabeth J.N. Davis and Ricardo Quinonez

Acute Viral Bronchiolitis

Introduction

Bronchiolitis is the most common cause of hospitalization for infants less than 12 months of age with the disease causing approximately 100,000 annual hospitalizations in the United States (Ralston et al. 2014; Friedman et al. 2014; Hasegawa et al. 2013). A significant amount of literature on this subject has been published since the first 2006 iteration of the American Academy of Pediatrics (AAP) Clinical Practice Guideline (American Academy of Pediatrics Subcommittee on Diagnosis and Management of Bronchiolitis 2006). Both the AAP and the Canadian Paediatric

Society (CPS) published updated recommendations on the diagnosis, management, and prevention of bronchiolitis in November of 2014 (Ralston et al. 2014; Friedman et al. 2014). As a reflection of most of the literature that surrounds the management of this challenging entity, the new guidelines contain a majority of action statements that recommend against the use of tests and therapies. Table 12.1 summarizes the major updates between the AAP 2006 and 2014 iterations.

Background

Viral lower respiratory tract pathogens are the cause of bronchiolitis in infants and children less than 2 years old. The disorder is self-limiting and is characterized by edema, acute inflammation, and necrosis of the epithelial cells lining the small airways combined with increased mucous production. The clinical patient manifestations typically include cough and rhinitis at the start of the illness that often progresses to a variable degree of respiratory distress with accessory muscle use, tachypnea, wheezing, rales, nasal flaring, and/or hypoxia. Those with a mild manifestation of symptoms can often be managed as an outpatient, but many still require hospitalization for supportive care of moderate to severe disease (Ralston et al. 2014; Friedman et al. 2014; Agency for Healthcare Research and Quality 2003). The decision to admit a patient

E.J.N. Davis, M.D., F.A.A.P. (✉)
Division of Pediatric Hospital Medicine,
Department of Pediatrics,
Baylor College of Medicine,
Houston, TX, USA

The Children's Hospital of San Antonio,
San Antonio, TX, USA
e-mail: Elizabeth.Davis2@bcm.edu;
Elizabeth.davis2@christushealth.org

R. Quinonez, M.D.
Division of Pediatric Hospital Medicine,
Department of Pediatrics,
Baylor College of Medicine,
Houston, TX, USA

Texas Children's Hospital, Houston, TX, USA
e-mail: Quinonez@bcm.edu

Table 12.1 Key changes in recommendations for the management of acute viral bronchiolitis in 2014 (Ralston et al. 2014; American Academy of Pediatrics Subcommittee on Diagnosis and Management of Bronchiolitis 2006)

| | |
|----------------------------|--|
| Bronchodilators | <ul style="list-style-type: none"> • Do not administer bronchodilators (albuterol, salbutamol, epinephrine) • Monitored trial no longer recommended |
| Hypertonic saline | <ul style="list-style-type: none"> • Not mentioned in 2006 guideline • Do not give in outpatient or emergency department settings • Option to give in hospitalized patients |
| Oxygen | <ul style="list-style-type: none"> • No need to give if oxygen saturation is >90% • No need to use continuous pulse oximetry |
| Corticosteroids | <ul style="list-style-type: none"> • Do not administer (upgraded from do not give routinely) |
| Hydration | <ul style="list-style-type: none"> • Administer nasogastric or intravenous fluids if unable to take fluids orally |
| Palivizumab | <ul style="list-style-type: none"> • Do not give to otherwise healthy infants with gestational age ≥ 29 weeks, 0 days |
| Second-hand smoke exposure | <ul style="list-style-type: none"> • Inquire about second-hand smoke exposure • Counsel about risks of exposure |

should be based on clinical judgment with assessment of the respiratory status, ability to maintain hydration, risk of severe disease progression, and the family's ability to care for the patient at home (Friedman et al. 2014).

Respiratory syncytial virus (RSV) is the most common etiology of bronchiolitis (Agency for Healthcare Research and Quality 2003; Miller et al. 2013; Mullins et al. 2003). Other viruses that cause the same clinical manifestations include human rhinovirus, influenza, coronavirus, human metapneumovirus, and parainfluenza virus (Miller et al. 2013). December through March is typically the time with the highest incidence of RSV, but regional variations demonstrate high RSV prevalence as early as August and as late as May (Mullins et al. 2003; Centers for Disease Control and Prevention 2013). Also, some of the other viruses are present in other months meaning bronchiolitis can be seen year

round (Agency for Healthcare Research and Quality 2003).

Diagnosis

The diagnosis of bronchiolitis should be made clinically with history and physical exam. The provider should use the clinical assessment to distinguish between viral bronchiolitis and other disorders, characterize the severity of illness, and identify risk factors for severe disease. Both guidelines recommend against routine use of chest x-rays, viral testing, or other lab testing as these studies do not correlate with disease severity or clinical outcomes, provide no value to the patient, and may lead to unnecessary antibiotics or hospitalizations (Ralston et al. 2014; Friedman et al. 2014; Mansbach et al. 2012; Swingler et al. 1998; Schuh et al. 2007).

Management

The mainstay of treatment in bronchiolitis is supportive care with nasal suctioning and supplemental oxygen if needed. Providers should not give antibiotics to patients with viral bronchiolitis unless there is a concomitant bacterial infection, and they should not give corticosteroids or use chest physiotherapy (Ralston et al. 2014; Friedman et al. 2014).

Bronchodilators

Several studies, including many meta-analyses and systematic reviews on the use of bronchodilators in bronchiolitis, have shown a lack of effect on need for hospitalization, disease resolution, or length of stay (LOS), and the effect they may have on clinical symptom scores is transient (Ralston et al. 2014; Friedman et al. 2014; Kellner et al. 1996; Flores and Horwitz 1997; Zorc and Hall 2010; Wainwright 2010; Gadomski and Scribani 2014). As such, a major change to the treatment recommendations in the AAP guideline and also included in the CPS guideline is the recommendation against the use of bronchodilators (albuterol or salbutamol) for bronchiolitis,

even as a trial (Ralston et al. 2014; Friedman et al. 2014).

Both guidelines also recommend against the use of nebulized epinephrine in hospitalized patients with bronchiolitis due to multiple studies and reviews showing lack of effect on LOS or other outcomes such as change in respiratory rate, respiratory effort, or time on oxygen (Hartling et al. 2003, Hartling et al. 2011a, b; Wainwright et al. 2003; Skjerven et al. 2013). One large multicenter study also found that using it on a fixed schedule prolonged LOS (Skjerven et al. 2013). The use of epinephrine in the emergency department or outpatient setting, however, remains controversial. One large, multicenter, randomized, double-blind, placebo-controlled trial with 800 infants compared hospitalization rates over 7 days between four study groups: nebulized epinephrine plus oral dexamethasone, nebulized epinephrine plus oral placebo, nebulized placebo plus oral dexamethasone, and nebulized placebo plus oral placebo (Plint et al. 2009). They found that the group receiving epinephrine combined with dexamethasone was less likely to be hospitalized by day 7 than the double placebo group. However, when they adjusted for multiple comparisons, this difference was no longer statistically significant. A Cochrane review (Hartling et al. 2011a) also found that rates of hospital admissions were reduced on the day of the first emergency department visit but not overall (by day 7). While the CPS guideline suggests that providers may trial a dose of nebulized epinephrine with careful monitoring of clinical response, the AAP guideline cautions against its use since home use is not routine, and the transient effect seen during observation does not affect the overall course of the illness (Ralston et al. 2014; Friedman et al. 2014).

Hypertonic Saline

New for the AAP 2014 management guideline and also included in the CPS guideline are recommendations on the use of hypertonic saline (HTS). HTS should not be administered to patients in the outpatient or emergency department settings as it has no effect on hospitalization rates (Ralston et al. 2014; Friedman et al. 2014;

Zhang et al. 2008). Both guidelines suggest that HTS may be used on hospitalized patients due to some available literature showing a reduction in length of stay (LOS) (Zhang et al. 2008, 2015; Badgett et al. 2015). The published literature, however, had inconsistent findings on this potential effect, and the reduction in LOS only involved patient populations with an average LOS of >3 days (the average LOS in the US is 2.4 days) (Ralston et al. 2014; Friedman et al. 2014; Brooks et al. 2016).

Since the publications of the guidelines, newer evidence suggests that the original reported benefits of HTS may have been overstated. First, the results of two US randomized controlled trials failed to show any effect of HTS as it relates to length of stay. Second, in June of 2016, Brooks et al. (2016) published a reanalysis of the studies included in two prior meta-analyses. Among the 18 RCTs reporting LOS as an outcome, they found two main sources of excessive heterogeneity. First, there was an outlier study population with significantly different discharge criteria and substantially longer than expected LOS. Second, they found baseline differences between the treatment arms in the day of illness at enrollment resulting in a systematic bias favoring the treatment arm in most of the small positive studies (those presenting later in illness were more likely to be allocated to the HTS group). Once the authors controlled for these factors to resolve the heterogeneity, HTS no longer had any effect on LOS.

Suctioning

Nasal suctioning has long been a common therapeutic intervention to clear the increased mucous produced in bronchiolitis and temporarily reduce increased work of breathing. Despite the obvious reasons for use as a supportive measure, very little data exists on the role of suctioning in the management of patients with bronchiolitis. A retrospective cohort study published in 2013 (Mussman et al. 2013) assessed the relationships between frequency and type of suctioning with LOS. The authors hypothesized that repeated nasopharyngeal suctioning (“deep” suction), compared to noninvasive nasal suctioning, would

lead to worse outcomes due to local trauma and that frequent noninvasive suctioning would improve outcomes. Infants 2–12 months of age were included with 740 infants in the device type cohort (deep vs noninvasive suctioning) and 695 infants in the suctioning lapse cohort. They excluded patients who were intubated, with a tracheostomy, admitted to the PICU, or who had a LOS less than 12 h and included only index admissions. The percentage of deep suctioning exposures in the first 24 h of admission were calculated and categorized into four ranges, and the data was analyzed using a multivariable model adjusted for inverse weighting of propensity to receive deep suctioning. For the suctioning lapse group, the number of sequential suctioning events separated by more than 4 h was counted for the first 24 h of admission. They found a statistically significant association of increased length of stay for the group that had deep suctioning in the first 24 h and for those with lapses greater than 4 h (mean difference 0.6 days and 1 day, respectively). While further studies are needed, this study suggests that aggressive nasopharyngeal (“deep”) suctioning may prolong LOS, and patients benefit from frequent less aggressive nasal suctioning. These findings complement a prior study from 2011 on predictors of LOS in bronchiolitis that also found a significant association between nasopharyngeal suctioning early in the hospitalization and increased LOS (Weisgerber et al. 2011).

Feeding and Hydration

Infants with poor feeding or difficulty feeding safely due to level of respiratory distress may receive either nasogastric (NG) or intravenous fluids (Ralston et al. 2014; Friedman et al. 2014). The inclusion of NG fluids is new to the AAP guideline recommendations, and hydration via this route appears to be safe for both older and young infants (Oakley et al. 2013, 2016). A multicenter, open, randomized trial (Oakley et al. 2013) comparing NG and IV fluid therapy in infants 2–12 months of age with bronchiolitis found no significant difference in length of stay, escalation of care, need for ventilator support, or adverse events between the

groups. There was no difference in parent satisfaction scores between the groups, but the NG route had a higher success rate of insertion and fewer required attempts of insertion than the IV route (Oakley et al. 2013). More recently, a descriptive, retrospective cohort study examined the use of NG fluids in infants <2 months of age with bronchiolitis and found no difference in the rate of adverse events between the NG and IV groups, no aspiration events, and no difference in LOS (Oakley et al. 2016).

Oxygen

Over the past two decades, the hospitalization rate of children with bronchiolitis has significantly increased while the mortality rate has remained constant. One of the implicated contributors to this rise in hospitalizations is the increased use of pulse-oximetry during this time (Schroeder et al. 2004). Oxygen saturation does not correlate with and is not a proxy for respiratory distress (Wang et al. 1992), and yet it has been shown to be a main factor in the decision to admit and lengthening of LOS (Ralston et al. 2014; Schroeder et al. 2004; Cunningham and McMurray 2012). Physiologically, when the oxygen saturation is 90%, it takes much higher elevations in the arterial pressure of oxygen to cause further increases in the saturation versus when the saturation is <90%, and increasing saturations above the 90% threshold has no clear clinical benefit (Ralston et al. 2014; Anaesthesia UK 2005). Also, studies on healthy infants show that transient hypoxemia occurs commonly without apparent harm (Hunt et al. 1999), and the intermittent hypoxemia that asthmatic children experience does not cause intellectual impairment or behavioral problems (Rivetveld and Colland 1999; Bender et al. 1987). Based on this data, both guidelines give the recommendation that providers may choose not to use oxygen in patients with oxyhemoglobin saturations equal to or higher than 90% (Ralston et al. 2014; Friedman et al. 2014) or use continuous pulse-oximetry in infants and children with bronchiolitis (Ralston et al. 2014). More data has since been published that further supports this recommendation (Cunningham et al. 2015; McCulloh et al. 2015).

Cunningham et al. (2015) performed a multicenter, randomized, controlled, double-blind equivalence study to see if the $\geq 90\%$ target for infants with bronchiolitis was equivalent to the $\geq 94\%$ target for illness resolution. To accomplish this, they randomly assigned one group of infants (307) to be connected to a modified oximeter that would display a measured value of 90% as 94%. Another group of infants (308) were placed on a standard oximeter that displayed the accurate measured values. Each group only received oxygen if the displayed value was $< 94\%$, as was the standard practice. They found that the $\geq 90\%$ oxygen saturation target to be equally safe and effective as the $\geq 94\%$ target with no difference between the groups in adverse events or escalation of care. The modified group also had a significantly shorter LOS and time on oxygen but fewer readmissions and no increase in post-discharge parental anxiety. In a multicenter, randomized, superiority trial, McCulloh et al. (2015) studied the effect of intermittent versus continuous pulse-oximetry use on LOS in nonhypoxemic bronchiolitis patients. While they found similar LOS in both groups, the intermittent group did not have more escalations of care or require more diagnostic or therapeutic interventions suggesting that providers can routinely consider using intermittent pulse-oximetry monitoring on patients with bronchiolitis who are clinically improving.

Prevention

Exposure to tobacco smoke increases both the severity of the illness and the risk for hospitalization. Providers should screen every patient with bronchiolitis for tobacco smoke exposure, counsel the caregivers about the risks associated with it, and provide recommendations and resources for smoking cessation to these families. Providers should also recommend and encourage exclusive breastfeeding for at least 6 months to reduce the incidence and severity of bronchiolitis. Shared decision-making between provider and caregiver can happen if the provider educates about the evidence-based diagnosis, treatment, prevention,

and expected course of the illness (Ralston et al. 2014).

Urinary Tract Infections With and Without Bacteremia

Summary of Updated Guideline

Urinary tract infections (UTIs) are the most common serious bacterial infection (SBI) in young children (Roberts et al. 2011; Roman et al. 2015), and the diagnosis and treatment of infants and young children with febrile UTIs has seen major changes over the past few years. The AAP published an updated clinical practice guideline in 2011 for the diagnosis and management of an initial febrile UTI in the 2–24 month ages (Roberts et al. 2011). One of the most important changes included requiring both the evidence of infection in the urinalysis (pyuria and/or bacteriuria) and the presence of at least 50,000 colony-forming units (CFUs) per ml in the urine culture of a specimen obtained by catheterization or suprapubic aspiration to positively diagnose a UTI. The guideline now recommends against the routine use of a voiding cystourethrogram (VCUG) after the initial febrile UTI. They advise instead to screen with a renal and bladder ultrasound (RBUS). A VCUG is then only advised if the RBUS shows hydronephrosis, scarring, or other signs of high-grade vesicoureteral reflux or obstructive uropathy, or for recurrent febrile UTIs (Roberts et al. 2011).

Diagnosing a UTI in Young Infants

The updated guideline included the requirement of evidence of pyuria in the UA to diagnose a UTI to distinguish a true UTI from asymptomatic bacteriuria since the presence of pyuria indicates the presence of the inflammatory response of a true infection (Roberts et al. 2011; Roberts 2015). However, concerns over the sensitivity of the UA in young infants continued since the guideline did not include infants < 2 months of age and since the sensitivity of a UA in children has been

reported as 75–85% (Schroeder et al. 2015). The question, however, is whether a negative UA with a positive urine culture represents a false-negative UA or a false-positive urine culture (asymptomatic bacteriuria) in febrile infants. To assess the diagnostic accuracy of the UA in generally healthy febrile infants <3 months of age, Schroeder et al. (2015) used a population of infants with a bacteremic UTI (defined as the same organism in the urine and blood with $\geq 50,000$ CFUs per ml in the urine culture) from a multicenter database to represent those with true infection (245 infants). To calculate UA specificity, they used a sample of febrile infants <3 months of age who had a negative urine culture in their workup for a serious bacterial infection (115 infants). Leukocyte esterase had a sensitivity of 97.6% (95% CI 92.5–99.2%) and a specificity of 93.9% (95% CI 87.9–97.5%). Pyuria (>3 white blood cells/high-power field) had a sensitivity of 96% (95% CI 92.5–98.1%) and a specificity of 91.3% (95% CI 84.6–95.6%). The results did not differ significantly between infants ≤ 30 days old and infants >30 days old. This study highlights the UA as a highly sensitive test in diagnosing a UTI. While the authors acknowledge that the results could be due to spectrum bias, they discuss the literature that supports a lack of difference between non-bacteremic and bacteremic UTIs (discussed below) (Roman et al. 2015; Schroeder et al. 2016). The discrepancy between these results showing the high sensitivity of UA and the prior lower sensitivities reported is more likely due to the urine culture being a faulty gold standard that was used in prior studies with many of the positive urine cultures representing asymptomatic bacteriuria (Schroeder et al. 2015; Roberts 2015).

Prophylactic Antibiotics in Children with Vesicoureteral Reflux

Whether to give prophylactic antibiotics to infants and young children with vesicoureteral reflux (VUR) remains a source of debate. The results of the Randomized Intervention for Children with Vesicoureteral Reflux

(RIVUR) trial (Hoberman et al. 2014) showed that prophylactic antibiotics (trimethoprim-sulfamethoxazole) reduced the risk of recurrent UTI in children with VUR by 50% and was particularly effective in those whose initial UTI was febrile and in those with baseline bowel or bladder dysfunction. When comparing the effect based on severity of VUR, though, prophylaxis was more effective in those with grades I–II reflux vs the higher risk grades III–IV. Also, they did not find a difference in the occurrence of renal scarring between the study and placebo groups, and the study group had a 3.3 times higher rate of resistant organisms causing the recurrent infections (Hoberman et al. 2014).

The question about the effect of prophylactic antibiotics on the occurrence of renal scarring could not truly be answered by this study given that it was underpowered to detect this outcome. While the RIVUR trial shows the effectiveness of prophylactic antibiotics in preventing recurrent UTIs in children with VUR, others have questioned the efficiency of this management approach (Afshar 2014; Cara-Fuentes et al. 2015). Based on the number needed to treat, one would have to treat eight children for 2 years with prophylactic antibiotics to prevent one UTI (Afshar 2014). Others have highlighted the fact that it takes 2 years to see a significant difference in the rate of UTIs, that the difference was only seen in patients younger than 2 years old with grades I–II VUR vs grades III–IV, and that the resolution of VUR seen in many of the patients may have contributed to the effects (Cara-Fuentes et al. 2015).

The decision of whether to use prophylactic antibiotics continues to be multifactorial. Providers should consider factors such as morbidity related to UTIs, costs, side effects, the potential for resistant organisms, the number needed to treat, the likelihood of compliance, and parent preference with shared decision-making. It is also worth highlighting that the natural history of VUR is self-resolution in almost all but the worse cases (Roberts et al. 2011). Looking instead at subgroups of patients who may be the most likely to benefit, such as those with bowel and bladder dys-

function, may be the wiser choice in the ongoing debate of UTI prophylaxis (Afshar 2014).

Bacteremic UTIs

A significant amount of evidence supports the conclusion that oral and parenteral antibiotics are equally efficacious in infants and young children with febrile UTIs (Roberts et al. 2011; Hoberman et al. 1999; Strohmeier et al. 2014). These patients do not routinely require hospitalization for parenteral antibiotics unless the patient is ill-appearing or cannot tolerate oral intake well enough to maintain hydration (Roberts et al. 2011). How to manage patients with a bacteremic UTI (same organism in urine and blood) and when to obtain a blood culture in patients with a UTI pose challenges that the current guidelines do not address. However, current evidence demonstrates that despite variability in management, there is little difference in clinical outcome (Roman et al. 2015; Schroeder et al. 2016). Multiple studies have demonstrated that bacteremic UTIs occur infrequently with the prevalence decreasing with increasing age, and patients with and without bacteremia lack easily identifiable clinical differences (Hoberman et al. 1999; Honkinen et al. 2000; Schnadower et al. 2010; Newman et al. 2002). In 2015, Roman et al. (2015) published a retrospective, cross-sectional, double cohort study from a large institution that confirmed these findings. In addition, the study demonstrated the decline in number of blood cultures obtained in infants with UTIs between 1998 and 2012 (study period), the different treatment courses, and yet equal 30-day outcomes in infants <1 year of age with UTIs with and without bacteremia. Despite the considerable variation in management of bacteremic infants, (parenteral antibiotics ranged from 0 to >14 days), the clinical outcomes were excellent with no infant having a recurrent UTI within 30 days, requiring ICU transfer or other escalation of care, having a positive CSF culture in those tested, or having a positive repeat blood culture (Roman et al. 2015). Despite these findings, this study and other literature has found that detection of bacteremia leads

to longer hospitalizations with parenteral therapy (Honkinen et al. 2000; Magin et al. 2007; Averbuch 2014; Brady et al. 2010).

Expanding on this, Schroeder et al. (2016) conducted a multicenter, retrospective cohort study to assess the predictors of parenteral antibiotic duration and the association between this treatment duration and relapses within 30 days in infants <3 months of age with a bacteremic UTI. They included 251 infants with a bacteremic UTI from 20 hospitals in 11 healthcare institutions across the United States, excluding those with major comorbidities or indwelling urinary or central venous catheters at the time of cultures and those initially managed in the ICU. They again found significant variability in the duration of parenteral antibiotics with the most prevalence at 3, 7, 10, and 14 days but without impact on outcome. None had a relapsed bacteremic UTI, and none deteriorated during treatment. Only six had a relapsed non-bacteremic UTI with the same organism (2.4%, 95% CI 0.8–5.1%), but these were associated with an abnormal VCUG, and there was no difference in duration of parenteral antibiotics in those with and without relapsed non-bacteremic UTI. Institutional practices accounted for some of the variability in duration, and they found five independent predictors of duration that only partially accounted for variability. Older age, female gender, and year of blood culture were associated with a slightly shorter course while a positive repeat blood culture during acute treatment and a non-*E. coli* organism lengthened treatment, although only 13.5% of infants had the latter factors. Rather than clinical response to therapy guiding the duration of parenteral antibiotics, the tendency toward certain numbers of days (3, 7, 10, 14 days) suggests that providers instead pick a fixed number of treatment days (Schroeder et al. 2016).

These large, retrospective studies provide the largest sets of data that demonstrate bacteremic UTIs may be no different than non-bacteremic UTIs. They question the need for blood cultures in infants with a UTI and show lack of apparent benefit of prolonged hospitalizations and parenteral antibiotics for infants with a bacteremic UTI who have recovered clinically, especially in the face of

more obvious risks of hospitalization (Roman et al. 2015; Schroeder et al. 2016).

Bacteremia in Young Infants

Changing Epidemiology

While fever without a localizing source in young infants continues to be a common problem and presents a clinical dilemma, the changing epidemiology of serious bacterial infections (SBI) in this age group has largely been understudied with few changes in the choice of empiric antibiotic therapy (Biondi et al. 2013; Mischler et al. 2015). Not only has vaccine development largely reduced the incidence of bacteremia and meningitis, but also the change in epidemiology over the past two decades is largely the result of changes in screening and treatment for group B *Streptococcus* (GBS) prior to delivery and more rigorous food safety guidelines (Mischler et al. 2015). Many studies characterizing the epidemiology of bacteremia during this era were limited by small sample sizes and geographic isolation (Biondi et al. 2013; Mischler et al. 2015). In 2013, Biondi et al. (2013) published the first large, geographically diverse study to identify the causes of bacteremia in otherwise healthy febrile infants ≤ 90 days old outside of the intensive care unit (ICU). They performed a retrospective review of positive blood cultures of this patient population admitted to general inpatient units across six hospital systems across the United States. They found that in the 181 patients with pathogenic blood cultures, *E. coli* was the most prevalent organism, GBS was the second most prevalent, and they found no *Listeria monocytogenes* (Biondi et al. 2013). Similarly, in the follow-up study published in 2015 (Mischler et al. 2015) with a larger, more nationally representative sample (392 samples from 17 sites across the country), they again demonstrated that *E. coli* was the most prevalent, followed by GBS with no cases of *Listeria monocytogenes*. Both studies also discussed the rates of concurrent UTI and meningitis for each pathogen and contribute to

the discussion about the changing types and causes of SBI in young infants (Biondi et al. 2013; Mischler et al. 2015). These studies demonstrate that current empiric antibiotic strategies for treating young infants at risk for SBI may be outdated as the epidemiology of bacterial pathogens changes over time.

Time to Blood Culture Positivity

Another changing trend in the inpatient evaluation of otherwise healthy febrile infants ≤ 90 days of age is the length of the observation period. The standard to observe these infants for 48–72 h was set during a time when blood cultures were manually assessed at infrequent intervals (Biondi et al. 2014). Now that most laboratories use continuous, automated monitoring systems, the time to detection of bacterial growth is significantly shorter. In a large, multicenter, retrospective study, 91%, 96%, and 99% of the pathogenic blood cultures in this patient population turned positive by 24, 36, and 48 h, respectively (Biondi et al. 2014). These findings combined with the overall low rate of bacteremia in this age group suggest that a 24 h observation period is adequate to detect most clinically significant bacteremia. The impact of this is noteworthy given the possibility of significant decreases in length of stay for this common reason for hospitalization in infants. Safely reducing the observation time of many infants in this patient population can reduce the risks, costs and complications associated with hospitalization (Biondi et al. 2014).

Brief Resolved Unexplained Event (BRUE)

Introduction

An apparent life-threatening event (ALTE) is defined as “an episode that is frightening to the observer and that is characterized by some combination of apnea (central or occasionally obstructive), color change (usually cyanotic or

pallid but occasionally erythematous or plethoric), marked change in muscle tone (usually marked limpness), choking, or gagging. In some cases the observer fears that the infant has died.” (National Institutes of Health 1987) This definition comes from a consensus development conference held in 1986 by the National Institutes of Health with the purpose of addressing the relationship between sudden infant death syndrome (SIDS) and apnea and the safety and effectiveness of home monitoring (National Institutes of Health 1987). Young patients are often hospitalized for observation after having an ALTE largely because of the uncertainty providers and parents feel in knowing if the patient is at risk for a repeat event or if there is a serious underlying condition that precipitated such an event. Much of this uncertainty comes from the lack of specificity in the definition of an ALTE and the lack of consensus on how to manage a well-appearing patient who had an unexplained ALTE (Tieder et al. 2013, 2016).

In May 2016, the American Academy of Pediatrics published the first clinical practice guideline for the evaluation of infants who have had an apparent life threatening event (Tieder et al. 2016). The guideline achieves three primary objectives: to give the recommendation to replace the term “apparent life threatening event (ALTE)” with the more specifically-defined “brief resolved unexplained event (BRUE)”, to stratify infants into low or high risk (based on the likelihood of a serious underlying condition), and to provide evidence-based management recommendations of lower-risk infants. By providing recommendations for evaluation and management of lower-risk infants, the guideline intends to reduce unnecessary and costly interventions, promote patient- and family-centered care, and improve patient outcomes. It also provides support for its implementation and identifies areas of needed research. The guideline avoids providing recommendations for higher-risk infants because there is insufficient evidence or there are clinical practice guidelines available for the specific

conditions that high risk infants may have (Tieder et al. 2016).

Definition

A BRUE is defined as an event occurring in an infant less than 1 year of age that the observer describes as sudden, brief, resolved, and including ≥ 1 of the following: cyanosis or pallor; absent, decreased, or irregular breathing; marked change in tone, meaning hyper- or hypotonia; and an altered level of responsiveness (see Table 12.2 for full list of inclusion and exclusion criteria). The term BRUE should be used as the diagnosis only when there is no explanation for the event after obtaining an appropriate history and physical exam. For instance, if fever, nasal congestion, and increased work of breathing are present, then the event may be explained by a temporary airway obstruction from a viral infection. Alternatively, an event with choking after feeding and spitting up may indicate gastroesophageal reflux (GER) or another gastrointestinal cause. The BRUE definition provides some specificity that the original ALTE definition lacked, allowing it to be more applicable to clinical care and research. With specific criteria, the provider can focus on the infants who have an unexplained reason for the event and clearly assess risk as well as remove those who have features consistent with normal infant physiology or a self-limited condition. Also, the diagnosis is based on the objective characterization of features that the clinician makes rather than the caregiver’s perception that the event was life-threatening, as the prior definition suggested. A more precise diagnosis, made after a thorough history and physical, may prevent unnecessary testing and hospitalizations by removing the uncertainty and perceived risk of a recurrent event that compels such testing and observation in the first place. The guideline provides an extensive list of historical and physical exam features providers should consider in the evaluation of a potential BRUE (Tieder et al. 2016).

Table 12.2 BRUE definition and factors for inclusion and exclusion (Tieder et al. 2016)

| | Includes | Excludes |
|---|--|--|
| Brief | Duration <1 min; typically 20–30s | Duration ≥1 min |
| Resolved | Patient returned to baseline state of health after the event Normal vital signs Normal appearance | At the time of evaluation: <ul style="list-style-type: none"> • Fever or recent fever • Apnea, bradypnea, tachypnea, Bradycardia or tachycardia • Hypertension, hypotension, or hemodynamic instability • Mental status changes, somnolence, lethargy • Hyper- or hypotonia • Vomiting • Petechiae, bruising, or other signs of trauma • Abnormal growth parameters • Stridor, stertor, wheezing • Repeat event(s) |
| Unexplained | Not explained by an identifiable medical condition | <ul style="list-style-type: none"> • Event consistent with nasal congestion, GER, swallow dysfunction, etc. • History or PE concerning for child abuse, congenital airway abnormality, etc. |
| <i>Event characterization</i> | | |
| Cyanosis or pallor | Central cyanosis: blue or purple coloration of face, gums, trunk Central pallor: pale coloration of face or trunk | <ul style="list-style-type: none"> • Perioral cyanosis or acrocyanosis • Rubor |
| Absent, decreased, or irregular breathing | Central apnea, obstructive apnea, or mixed obstructive apnea | <ul style="list-style-type: none"> • Periodic Breathing of the newborn • Breath-holding spell |
| Marked change in tone (hyper- or hypotonia) | Hypertonia Hypotonia | <ul style="list-style-type: none"> • Hypertonia associated with crying, gagging, or choking due to problems feeding or GER • Tone changes associated with breath-holding spell • Nystagmus or tonic eye deviation • Tonic-clonic seizure activity • Infantile spasms |
| Altered responsiveness | Loss of consciousness, mental status change, lethargy, somnolence, postictal phase | <ul style="list-style-type: none"> • Loss of consciousness with breath-holding spell |

Adapted from: Tieder JS, et al. Brief Resolved Unexplained Events (Formerly Apparent Life-Threatening Events) and Evaluation of Lower-Risk Infants. *Pediatrics*. 2016;137 (2003):e20160590

Risk Assessment and Management

Based on an extensive review of the ALTE literature, the new BRUE guideline identifies the subset of patients who are unlikely to have a recurrent event or an undiagnosed serious condition. These patients are at lower risk of adverse outcomes and can likely be managed safely without extensive diagnostic evaluation or hospitalization (Tieder et al. 2016).

The following criteria encompass lower risk:

- Age >60 days
- Gestational age ≥32 weeks and postconceptional age ≥45 weeks
- First BRUE ever and not occurring in clusters
- Duration of event <1 min
- No CPR required by a trained medical provider

Table 12.3 Choosing wisely pediatric hospital medicine recommendations

| |
|---|
| Don't order chest radiographs in patients with asthma or bronchiolitis |
| Don't use bronchodilators in children with bronchiolitis |
| Don't use systemic corticosteroids in children with lower respiratory tract infections |
| Don't treat gastroesophageal reflux in infants with acid suppression therapy |
| Don't use continuous pulse oximetry routinely in children with acute respiratory illness unless they are on supplemental oxygen |

- No concerning historical features (see Table 12.2 in guideline)
- No concerning physical exam findings (see Table 12.3 in guideline)

After identifying that the patient had a BRUE and falls into the lower risk category, the provider can then follow the key action statements regarding recommended management that are categorized based on the strength of the recommendation (Tieder et al. 2016).

Providers **should**:

- Educate caregivers about BRUEs and engage in shared-decision-making to guide evaluation, disposition, and follow-up
- Offer resources for CPR training to caregiver

Providers **may**:

- Obtain pertussis testing and a 12-lead ECG
- Briefly monitor patients with continuous pulse-ox and serial observations

Providers **should not**:

- Obtain a WBC count, blood culture, CSF analysis or culture, serum sodium, potassium, chloride, blood urea nitrogen, creatinine, calcium, ammonia, blood gases, urine organic acids, plasma amino acids or acylcarnitine, chest radiograph, echocardiogram, EEG, studies for GER, or lab evaluation for anemia

- Initiate home cardio-respiratory monitoring
- Prescribe acid suppression therapy or anti-epileptic medications

Providers **need not**

- Obtain viral respiratory testing, urinalysis, blood glucose, serum bicarbonate, serum lactic acid, or neuroimaging
- Admit the patient to the hospital solely for cardiorespiratory monitoring

This new guideline, while limited in its scope, offers an initial pathway for standardizing management of this common inpatient entity. The guideline does, however, have significant limitations. The most important of these is that the authors decided to limit recommendations to children over 2 months of age. A significant number of children who present to the hospital with a BRUE are less than 2 months. Thus, this guideline may not apply to a significant number of the patients where standardization is most needed. Future research should address management and diagnosis in younger infants (under 2 months of age), who currently fall into the high risk group.

Osteomyelitis

Introduction

Osteomyelitis is a bacterial infection that accounts for 1% of all pediatric hospitalizations. It generally requires hospitalization for the initial diagnosis and management, and it often involves a prolonged course of antibiotics to prevent chronic infection and other complications (Zaoutis et al. 2009). After resolution of acute symptoms of fever, pain, and disability, most children complete 4–6 weeks of antibiotic therapy at home. Until recently, the recommended route of administration has been through central venous catheters, usually a peripherally inserted central catheter (PICC) (Keren et al. 2015). However, published case series have demon-

strated excellent outcomes in patients who were treated with a short course of parenteral antibiotics and transitioned early to oral antibiotics to complete therapy (Peltola et al. 1997; Le Saux et al. 2002; Jagodzinski et al. 2009; Kolyvas et al. 1980; Arnold et al. 2012). Benefits of early transition to oral antibiotic therapy include lower costs and complications. While PICCs are effective at delivering antibiotics, they are often associated with a high rate of infectious, thrombotic, and mechanical complications (Ruebner et al. 2006; Bourgeois et al. 2011).

Oral Versus Intravenous Antibiotic Therapy

While there are no large prospective randomized controlled trials (RCT) comparing oral and intravenous (IV) routes of antibiotic therapy, there are two large retrospective cohort studies comparing early transition to oral versus IV antibiotics in children with osteomyelitis (Zaoutis et al. 2009; Keren et al. 2015). The second of these studies was designed in a way to mimic an RCT (Keren et al. 2015). Both studies used data from the Pediatric Health Information System (PHIS database), which contains administrative and billing data from over 45 freestanding children's hospitals associated with the Children's Hospital Association. Data from this system includes information on demographics, diagnosis, medications, procedures, and repeat hospitalizations.

Zaoutis et al. (Zaoutis et al. 2009) published the first of these large studies in 2009 looking at the degree of variation across hospitals in the use of early transition to oral antibiotics and whether there is an association between this therapy and treatment failure. The primary outcome of treatment failure was defined as rehospitalization within 6 months due to acute or chronic osteomyelitis, a potential complication of acute osteomyelitis, or a musculoskeletal surgical procedure. Secondary outcomes were rehospitalization within 6 months due to a catheter-related complication, an antibiotic-related adverse drug reaction, or any other reason. The authors obtained

data on 1969 children 2 months to 17 years with acute osteomyelitis meeting inclusion criteria from 29 freestanding children's hospitals. Of these, 1021 had a central venous catheter (CVC) for prolonged IV antibiotics while 948 did not and were transitioned to oral antibiotics prior to discharge. There were no significant differences between the groups in terms of demographics, site of infection, LOS, surgical intervention, infecting organism, disease severity, or in-hospital antibiotic therapy. They found no difference in treatment failure between the groups (5% [54 of 1021] in the IV group, 4% [38 of 948] in the oral group). The authors also demonstrated significant variation across hospitals in the proportion of children who had a CVC for prolonged antibiotics ranging from 10% to 95%. Data from their secondary outcomes showed that children in the prolonged IV therapy group were more likely to have treatment-related complications (e.g. catheter related complications, antibiotic related complications), had a significantly higher readmission rate for antimicrobial complications, and had a significantly higher overall 6-month rehospitalization rate for any reason. The authors concluded that the two methods of treatment are equally effective, that early transition to oral therapy is associated with fewer complications, and that the results of the study should encourage hospitals to develop clinical practice guidelines and protocols for early transition to oral antibiotics and thus reduce practice variation (Zaoutis et al. 2009).

While promising, the above study had significant limitations that may have partly contributed to the lack of widespread reduction in PICC use in favor of the oral treatment route among most hospitals. These limitations included its retrospective nature and lack of validation of the osteomyelitis diagnosis and treatment choice, adjustment for severity of illness, and information about reasons for readmissions and revisits. In 2015, Keren et al. (2015) published a subsequent study seeking to again compare the effectiveness and complication rates of the two treatment modalities (early transition to oral antibiotics vs prolonged IV antibiotics) while addressing some of Zaoutis et al.'s limitations.

Treatment failure was again the primary outcome, which was defined as a revisit to the ED or rehospitalization for a change in the antibiotic or length of treatment, a switch from the oral to PICC route, a pathologic bone fracture, or a surgical procedure related to the infection (i.e. abscess drainage, debridement, bone biopsy, etc.). Secondary outcomes included a return ED visit or rehospitalization for antibiotic- or PICC-related complications or a composite of these with treatment failure. This study also utilized administrative data from the PHIS database, but they supplemented it with additional clinical information from detailed, manual chart review, thus validating treatment allocation, outcomes, and covariates. This study also used within- and across-hospital full matching based on propensity scores to account for confounders at the hospital and patient levels. While still not as robust at avoiding confounders as a randomized trial, propensity based matching mimics an RCT by most closely comparing similar patients in both arms of the study. In addition, this study improves on the prior study by including children hospitalized between 2009–2012 when methicillin-resistant *S aureus* (MRSA) was more prevalent (Keren et al. 2015).

Their results were nearly identical to Zaoutis et al. There were 1005 children in the oral antibiotic group and 1055 children in the PICC antibiotic group across 36 hospitals. Treatment failure rates were similar in the oral group (5% [50 of 1005]) and PICC group (6% [63 of 1055]), including those in the matched analyses. In the stratified analyses, they did find that the risk for treatment failure was increased in children older than 5 years in the PICC group. However, having MRSA as the causative organism did not impact the outcome of treatment failure based on treatment route. For the secondary outcomes, 15% (158 of 1055) in the PICC group had a PICC-related complication. As such, the PICC group had a significantly higher risk of needing a return ED visit or hospitalization for an adverse event in any matched analysis. The across-hospital variation in the use of the PICC route to give antibiotics on discharge was again broad and ranged from 0% to

100%. The authors concluded that discharging otherwise healthy patients with osteomyelitis to complete antibiotic therapy via an invasive PICC offers no advantage over the less invasive oral antibiotic option, and the latter confers fewer risks and complications (Keren et al. 2015).

When to Transition to Oral Antibiotics

With the above studies as well as previously published case series demonstrating the safety and efficacy of transitioning from parenteral to oral antibiotic therapy in the treatment of acute osteomyelitis, others have studied the best way to determine the timing of this transition. In one such study (Arnold et al. 2012), authors conducted an 8-year single-center retrospective study where it was standard practice to transition from parenteral antibiotics to oral antibiotics when the patient had clinical improvement and a C-reactive protein (CRP) level $<2-3$ mg/dL. Of the 194 patients reviewed, only one had a treatment failure, and this was due to a retained infected bone fragment in the joint space. This study only included patients with culture-positive infection, but it did include MRSA infections (Arnold et al. 2012).

Another single-center study (Chou and Arjandas 2016) evaluated patients in the author's institution who were transitioned from parenteral antibiotics to oral antibiotics once the CRP level had declined by $\geq 50\%$, as per their protocol. They included both culture-positive and culture-negative infections. They found that using a decline in the CRP level by $\geq 50\%$ over a 4 day period combined with clinical improvement was a safe way to determine the timing of transition in therapy (Chou and Arjandas 2016).

Using clinical improvement combined with a declining CRP level (whether by $\geq 50\%$ or to near normal levels of $<2-3$ mg/dL) is a useful way in determining when it is safe to transition from parenteral to oral antibiotic therapy and may help to shorten the length of stay and standardize practice.

High Value Care

Introduction

Pediatric hospitalists have been at the forefront of high value care in pediatrics. This is reflected by publications in the field in the last few years. While this issue has received much attention in adult medicine, few publications in pediatrics have addressed this issue. Particularly, the issue of overuse in pediatrics has received very few pages in journals. Overuse has been defined as “the provision of health care when the risk of harm exceeds its potential benefit, when the benefits are negligible, or when fully informed patients would forego care.” It includes overtreatment and overdiagnosis (Morgan et al. 2016). A recent publication in *Pediatrics*, led by pediatric hospitalists, reviewed a year’s worth of publications dealing with the issue of overuse in pediatrics (Coon et al. 2017).

Choosing Wisely

The American Board of Internal Medicine Foundation (ABIM-F) has developed the Choosing Wisely® campaign (www.choosing-wisely.org). Through this campaign ABIM-F has encouraged medical societies to develop a list of five items within their scope of practice, “Things Providers and Patients Should Question.” In 2013 The Society of Hospital Medicine published the first pediatric list. The methodology and evidence supporting this list was also later published in *The Journal of Hospital Medicine* (Quinonez et al. 2013). The list is heavily focused on respiratory illnesses, particularly bronchiolitis. This is not unexpected given the frequency of this diagnosis in the inpatient setting. The investigators encouraged hospital medicine practitioners to utilize this list as a guide to prioritize quality improvement projects. Indeed, the recommendation to limit pulse oximetry has led to at least one such project (Schondelmeyer et al. 2015), and this recommendation was later incorporated into the 2014 AAP bronchiolitis guidelines (Ralston et al. 2014) (Table 12.3).

Table 12.4 Possible overdiagnosed conditions in pediatrics

| |
|--|
| Neuroblastoma |
| Bacteremia |
| Medium-chain acyl-CoA dehydrogenase deficiency |
| Hyperbilirubinemia |
| Vesicoureteral reflux |
| Hypercholesterolemia |
| Food allergy |
| Gastroesophageal reflux |
| Hypoxemia in bronchiolitis |
| Urinary tract infection |
| Aspiration |
| Attention deficit hyperactivity disorder |
| Cholelithiasis |
| Skull fracture |
| Obstructive sleep apnea |

Overdiagnosis

In 2014, some of the same authors involved in the Choosing Wisely campaign published a comprehensive review of overdiagnosis in pediatrics (Coon et al. 2014). While overdiagnosis has been frequently observed in adult care, this first of its kind review explored conditions in pediatrics that may suffer from overdiagnosis.

Table 12.4 shows the list of conditions reviewed by the authors. The conditions range from ADHD to bacteremia. Since the publication of this review, further evidence has given support to possible overdiagnosis. One clear example is overdiagnosis of hypoxemia in bronchiolitis. Since the 1980’s the widespread use of portable pulse oximeters has seen a concomitant increase of up to 300% in admissions for bronchiolitis (Hasegawa et al. 2013). Several studies have demonstrated that pulse oximetry readings have a strong influence over a clinician’s decision to admit a patient to the hospital (Mower et al. 1995). Most convincingly, a recent Canadian randomized controlled trial showed that a difference of just 3% points, all within the normal range in oxygen saturations, influenced the decision to admit patients to the hospital in a significant way, despite having no other clinical differences (Schuh et al. 2014). This same group has also demonstrated that significant desaturations, even to the 70s, occur in patients managed in the

outpatient setting frequently and have little association to proximal outcomes such as revisits to care (Principi et al. 2016).

References

- Afshar K. Randomized intervention for children with vesicoureteral reflux (RIVUR) study: a new look at an old question? Commentary on antimicrobial prophylaxis for children with vesicoureteral reflux. *Urology*. 2014;84(5):991–2.
- Agency for Healthcare Research and Quality. Management of bronchiolitis in infants and children. Evidence report/technology assessment no. 69. AHRQ Publication No. 03-E014. Rockville, MD: Agency for Healthcare Research and Quality; 2003.
- American Academy of Pediatrics Subcommittee on Diagnosis and Management of Bronchiolitis. Diagnosis and management of bronchiolitis. *Pediatrics*. 2006; 118(4):1774–93.
- Anaesthesia UK. Oxygen dissociation curve. 2005. <http://www.frca.co.uk/article.aspx?articleid=100345>.
- Arnold JC, Canavino CR, Ross M, et al. Acute bacterial osteoarticular infections: eight-year analysis of C-reactive protein for oral step-down therapy. *Pediatrics*. 2012;130(4):e821–8.
- Averbuch D, Nir-Paz RI, Tenenbaum A, et al. Factors associated with bacteremia in young infants with urinary tract infection. *Pediatr Infect Dis J*. 2014;33:571–5.
- Badgett RG, Vindhya M, Stirnaman JT, et al. A living systematic review of nebulized hypertonic saline for acute bronchiolitis in infants. *JAMA Pediatr*. 2015;169(8):788–9.
- Bender BG, Belleau L, Fukuhara JT, et al. Psychomotor adaptation in children with severe chronic asthma. *Pediatrics*. 1987;79(5):723–7.
- Biondi E, Evans R, Mischler M, et al. Epidemiology of bacteremia in febrile infants in the United States. *Pediatrics*. 2013;132(6):990–6.
- Biondi E, Mischler M, Jerardi K, et al. Blood culture time to positivity in febrile infants with bacteremia. *JAMA Pediatr*. 2014;168(9):844–9.
- Bourgeois FC, Lamagna P, Chiang VW. Peripherally inserted central catheters. *Pediatr Emerg Care*. 2011;27(6):556–61.
- Brady PW, Conway PH, Goudie A. Length of intravenous antibiotic therapy and treatment failure in infants with urinary tract infections. *Pediatrics*. 2010;126:196–203.
- Brooks C, Harrison W, Ralston S. Association between hypertonic saline and hospital length of stay in acute viral bronchiolitis: a reanalysis of 2 meta-analyses. *JAMA Pediatr*. 2016;170(6):577–84.
- Cara-Fuentes G, Gupta N, Garin E. The RIVUR study: a review of its findings. *Pediatr Nephrol*. 2015;30:703–6.
- Centers for Disease Control and Prevention. Respiratory syncytial virus activity—United States, July 2011–January 2013. *MMWR Morb Mortal Wkly Rep*. 2013;62(8):141–4.
- Chou A, Arjandas M. The use of C-reactive protein as a guide for transitioning to oral antibiotics in pediatric osteoarticular infections. *J Pediatr Orthop*. 2016;36(2):173–7.
- Coon ER, Quinonez RA, Moyer VA, Schroeder AR. Overdiagnosis: how our compulsion for diagnosis may be harming children. *Pediatrics*. 2014;134(5):1013–23.
- Coon ER, Young PC, Quinonez RA, et al. Update on pediatric overuse. *Pediatrics*. 2017;139(2):e20162797.
- Cunningham S, McMurray A. Observational study of two oxygen saturation targets for discharge in bronchiolitis. *Arch Dis Child*. 2012;97(4):361–3.
- Cunningham S, Rodriguez A, Adams T, et al. Bronchiolitis of Infancy Discharge Study (BIDS) Group. Oxygen saturation targets in infants with bronchiolitis (BIDS): a double-blind, randomised, equivalence trial. *Lancet*. 2015;386:141–1048.
- Flores G, Horwitz RI. Efficacy of beta2-agonists in bronchiolitis: a reappraisal and meta-analysis. *Pediatrics*. 1997;100(2.1):233–9.
- Friedman JN, Rieder MJ, Walton JM. Canadian Paediatric Society Acute Care Committee, Drug Therapy and Hazardous Substances Committee. Bronchiolitis: recommendations for diagnosis, monitoring, and management of children one to 24 months of age. *Paediatr Child Health*. 2014;19(9):485–91.
- Gadomski AM, Scribani MB. Bronchodilators for bronchiolitis. *Cochrane Database Syst Rev*. 2014;6:CD001266.
- Hartling L, Wiebe N, Russell K, et al. A meta-analysis of randomized controlled trials evaluating the efficacy of epinephrine for the treatment of acute viral bronchiolitis. *Arch Pediatr Adolesc Med*. 2003;157(10):957–64.
- Hartling L, Bialy LM, Vandermeer B, et al. Epinephrine for bronchiolitis. *Cochrane Database Syst Rev*. 2011a;6:CD003123.
- Hartling L, Fernandes RM, Bialy L, et al. Steroids and bronchodilators for acute bronchiolitis in the first two years of life: systematic review and meta-analysis. *BMJ*. 2011b;342:d1714.
- Hasegawa K, Tsugawa Y, Brown DF, et al. Trends in bronchiolitis hospitalizations in the United States, 2000–2009. *Pediatrics*. 2013;132(1):28–36.
- Hoberman A, Wald ER, Hickey RW, et al. Oral versus initial intravenous therapy for urinary tract infections in young febrile children. *Pediatrics*. 1999;104(1):79–86.
- Hoberman A, Greenfield SP, Mattoo TK, et al. RIVUR Trial Investigators. Antimicrobial prophylaxis for children with vesicoureteral reflux. *N Engl J Med*. 2014;370(25):2367–76.
- Honkinen O, Jahnukainen T, Mertsola J, et al. Bacteremic urinary tract infection in children. *Pediatr Infect Dis J*. 2000;19(7):630–4.
- Hunt CE, Corwin MJ, Lister G, et al. Collaborative Home Infant Monitoring Evaluation (CHIME) Study Group. Longitudinal assessment of hemoglobin oxygen saturation in healthy infants during the first 6 months of age. *J Pediatr*. 1999;135(5):580–6.

- Jagodzinski NA, Kanwar R, Graham K, Bache CE. Prospective evaluation of a shortened regimen of treatment for acute osteomyelitis and septic arthritis in children. *J Pediatr Orthop*. 2009;29(5):518–25.
- Kellner JD, Ohlsson A, Gadamski AM, Wang EE. Efficacy of Bronchodilator therapy in Bronchiolitis. A meta-analysis. *Arch Pediatr Adolesc Med*. 1996;150(11):1166–72.
- Keren R, Shah SS, Srivastava R, et al. Comparative effectiveness of intravenous vs oral antibiotics for postdischarge treatment of acute osteomyelitis in children. *JAMA Pediatr*. 2015;169(2):120–8.
- Kolyvas E, Ahronheim G, Marks MI, et al. Oral antibiotic therapy of skeletal infections in children. *Pediatrics*. 1980;65(5):867–71.
- Le Saux N, Howard A, Barrowman NJ, et al. Shorter courses of parenteral antibiotic therapy do not appear to influence response rates for children with acute hematogenous osteomyelitis: a systematic review. *BMC Infect Dis*. 2002;2:16.
- Magin EC, Garcia-Garcia JJ, Sert SZ, et al. Efficacy of short-term intravenous antibiotics in neonates with urinary tract infection. *Pediatr Emerg Care*. 2007;23:83–6.
- Mansbach JM, Piedra PA, Teach SJ, et al. MARC-30 Investigators. Prospective multicenter study of viral etiology and hospital length of stay in children with severe bronchiolitis. *Arch Pediatr Adolesc Med*. 2012;166(8):700–6.
- McCulloh R, Koster M, Ralston S, et al. Use of intermittent vs continuous pulse oximetry for nonhypoxic infants and young children hospitalized for bronchiolitis: a randomized clinical trial. *JAMA Pediatr*. 2015;169(10):898–904.
- Miller EK, Gebretsadik T, Carroll KN, et al. Viral etiologies of infant bronchiolitis, croup, and upper respiratory illness during 4 consecutive years. *Pediatr Infect Dis J*. 2013;32(9):950–5.
- Mischler M, Ryan M, Leyenaar J, et al. Epidemiology of bacteremia in previously healthy febrile infants: a follow-up study. *Hosp Pediatr*. 2015;5(6):293–300.
- Morgan DJ, Dhruva SS, Wright SM, Korenstein D. Update on medical overuse: a systematic review. *JAMA Intern Med*. 2016;176(11):1687–92.
- Mower WR, Sachs C, Nicklin EL, et al. Effect of routine emergency department triage pulse oximetry screening on medical management. *Chest*. 1995;108:1297–302.
- Mullins JA, Lamonte AC, Bresee JS, Anderson LJ. Substantial variability in community respiratory syncytial virus season timing. *Pediatr Infect Dis J*. 2003;22(10):857–62.
- Mussman GM, Parker MW, Statile A, et al. Suctioning and length of stay in infants hospitalized with bronchiolitis. *JAMA Pediatr*. 2013;167(5):414–21.
- National Institutes of Health. National institutes of health consensus development conference on infantile apnea and home monitoring, Sept 29 to Oct 1, 1986. *Pediatrics*. 1987;79(2):292–9.
- Newman TB, Bernzweig JA, Takayama JJ, et al. Urine testing and urinary tract infections in febrile infants seen in office settings: the pediatric research of office settings' febrile infant study. *Arch Pediatr Adolesc Med*. 2002;156(1):44–54.
- Oakley E, Borland M, Neutze J, et al. Paediatric Research in Emergency Departments International Collaborative (PREDICT). Nasogastric hydration versus intravenous hydration for infants with bronchiolitis: a randomised trial. *Lancet Respir Med*. 2013;1:113–20.
- Oakley E, Bata S, Rengasamy S, et al. Nasogastric hydration in infants with bronchiolitis less than 2 months of age. *J Pediatr*. 2016;178:241–245.e1. doi:10.1016/j.jpeds.2016.07.012.
- Peltola H, Unkila-Kallio L, Kallio MJ, Finnish Study Group. Simplified treatment of acute staphylococcal osteomyelitis of childhood. *Pediatrics*. 1997;99(6):846–50.
- Plint AC, Johnson DW, Patel H, et al. Pediatric Emergency Research Canada (PERC). Epinephrine and dexamethasone in children with bronchiolitis. *N Engl J Med*. 2009;360(20):2079–89.
- Principi T, Coates AL, Parkin PC, et al. Effect of oxygen desaturations on subsequent medical visits in infants discharged from the emergency department with bronchiolitis. *JAMA Pediatr*. 2016;170:602–8.
- Quinonez RA, Garber MD, et al. Choosing wisely in pediatric hospital medicine: five opportunities for improved healthcare value. *J Hosp Med*. 2013;8(9):479–85.
- Ralston SL, Lieberthal AS, Meissner HC, et al. American Academy of Pediatrics. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. *Pediatrics*. 2014;134(5):e1474–502.
- Rivetveld S, Colland VT. The impact of severe asthma on schoolchildren. *J Asthma*. 1999;36(5):409–17.
- Roberts KB. The diagnosis of UTI: liquid gold and the problem of gold standards. *Pediatrics*. 2015;135(6):1126–7.
- Roberts KB, et al. Subcommittee on urinary tract infection, steering committee on quality improvement and management. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics*. 2011;128(3):595–610.
- Roman H, Chang P, Shroeder A. Diagnosis and management of bacteremic urinary tract infection in infants. *Hosp Pediatr*. 2015;5(1):1–8.
- Ruebner R, Keren R, Coffin S, et al. Complications of central venous catheters used in the treatment of acute hematogenous osteomyelitis. *Pediatrics*. 2006;117(4):1210–5.
- Schnadower D, Kuppermann N, Macias CG, et al. American Academy of Pediatrics Pediatric Emergency Medicine Collaborative Research Committee. Febrile infants with urinary tract infections at very low risk for adverse events and bacteremia. *Pediatrics*. 2010;126(6):1074–83.
- Schondelmeyer AC, Simmons JM, Statile AM, et al. Using quality improvement to reduce continuous pulse

- oximetry use in children with wheezing. *Pediatrics*. 2015;135(4):e1044–51.
- Schroeder AR, Marmor AK, Pantell RH, Newman TB. Impact of pulse-oximetry and oxygen therapy on length of stay in bronchiolitis hospitalizations. *Arch Pediatr Adolesc Med*. 2004;158(6):527–30.
- Schroeder AR, Chang PW, Shen MW, et al. Diagnostic accuracy of the urinalysis for urinary tract infection in infants <3 months of age. *Pediatrics*. 2015;135(6):965–71.
- Schroeder AR, Shen MW, Biondi EA, et al. Bacteraemic urinary tract infection: management and outcomes in young infants. *Arch Dis Child*. 2016;101:125–30.
- Schuh S, Lalani A, Allen U, et al. Evaluation of the utility of radiography in acute bronchiolitis. *J Pediatr*. 2007;150(4):429–33.
- Schuh S, Freedman S, Coates A, et al. Effect of oximetry on hospitalization in bronchiolitis: a randomized clinical trial. *JAMA*. 2014;312:712–8.
- Skjerven HO, Hunderi JO, Brüggmann-Pieper SK, et al. Racemic adrenaline and inhalation strategies in acute bronchiolitis. *N Engl J Med*. 2013;368(24):2286–93.
- Strohmeier Y, Hodson EM, Willis NS, Webster AC, Craig JC. Antibiotics for acute pyelonephritis in children. *Cochrane Database Syst Rev*. 2014;7:CD003772.
- Swingler GH, Hussey GD, Zwarenstein M. Randomised controlled trial of clinical outcome after chest radiograph in ambulatory acute lower respiratory infection in children. *Lancet*. 1998;351(9100):404–8.
- Tieder JS, Altman RL, Bonkowsky JL, et al. Management of apparent life-threatening events in infants: a systematic review. *J Pediatr*. 2013;163(1):94–9.
- Tieder JS, Bonkowsky JL, Etzel RA, et al. Brief resolved unexplained events (formerly apparent life-threatening events) and evaluation of lower-risk infants. *Pediatrics*. 2016;137(5):e20160590.
- Wainwright C. Acute viral bronchiolitis in children—a very common condition with few therapeutic options. *Paediatr Respir Rev*. 2010;11(1):39–45.
- Wainwright C, Altamirano L, Cheney M, et al. A multicenter randomized, double-blind, controlled trial of nebulized epinephrine in infants with acute bronchiolitis. *N Engl J Med*. 2003;349(1):27–35.
- Wang EE, Milner RA, Navas L, Maj H. Observer agreement for respiratory signs and oximetry in infants hospitalized with lower respiratory infections. *Am Rev Respir Dis*. 1992;145(1):106–9.
- Weisgerber MC, Lye PS, Li SH, et al. Factors predicting prolonged hospital stay for infants with bronchiolitis. *J Hosp Med*. 2011;6:264–70.
- Zaoutis T, Localio AR, Leckerman K, et al. Prolonged intravenous therapy versus early transition to oral antimicrobial therapy for acute osteomyelitis in children. *Pediatrics*. 2009;123(2):636–42.
- Zhang L, Mendoza-Sassi RA, Wainwright C, Klassen TP. Nebulized hypertonic saline solution for acute bronchiolitis in infants. *Cochrane Database Syst Rev*. 2008;4:CD006458.
- Zhang L, Mendoza-Sassi RA, Klassen TP, Wainwright C. Nebulized hypertonic saline for acute bronchiolitis: a systematic review. *Pediatrics*. 2015;136(4):687–701.
- Zorc JJ, Hall CB. Bronchiolitis: recent evidence on diagnosis and management. *Pediatrics*. 2010;125(2):342–9.



Update in Pediatric Infectious Disease

13

Archana Chatterjee and Maya Gogoi

Introduction

In the ever-changing field of pediatric infectious diseases, it is difficult to focus on just a few of them. This chapter will provide an overview and brief summary of a number of emerging issues in pediatric infectious diseases including: the impact of human papillomavirus (HPV) vaccines, despite their relatively poor uptake in the past decade; the ongoing outbreaks of measles in the United States; the rise in *Clostridium difficile* infections in children; the introduction of meningococcal B vaccines; the Zika virus outbreak and its implications; the status and management of methicillin-resistant *Staphylococcus aureus* (MRSA) infections; the role of antibiotic stewardship in pediatric facilities; and the management of congenital cytomegalovirus (CMV) infections.

HPV

HPVs are small dsDNA viruses, classified into ‘high-risk’ genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68), which are related

to the development of cervical, vulvar, vaginal, penile, anal and oro-pharyngeal cancers as well as pre-cancerous lesions, and ‘low-risk’ genotypes (6 and 11) which are associated with 90% of ano-genital warts and recurrent respiratory papillomatosis (RRP) (Forman et al. 2012; Bhatia et al. 2013; Larson and Derkay 2010). Of all HPV-related cancers, approximately 94% occur in women and 88% affect the cervix (Jemal et al. 2011). While screening programs for cervical intraepithelial neoplasia (CIN), a precursor to cervical cancer, have substantially reduced the incidence and mortality from this disease in industrialized countries, such programs are often unavailable in resource-poor settings. Thus, vaccination against HPV is a major advancement, as it offers primary prevention against the infectious agent that is the main cause of the disease, irrespective of the availability or utilization of secondary prevention through cervical cancer screening and HPV testing programs (Bosch et al. 2008, 2011).

HPV vaccination has been recommended for females in the United States (US) since mid-2006 and for males since 2011 (Markowitz et al. 2014). Routine vaccination is recommended for females and males aged 11 or 12 years and for females through age 26 years and males through age 21 years if not previously vaccinated. Three prophylactic HPV vaccines are licensed in the US, and have been shown in clinical trials to have high efficacy for prevention of HPV vaccine-type infection and associated diseases

A. Chatterjee, M.D., Ph.D. (✉) • M. Gogoi
Department of Pediatrics, University of South Dakota
Sanford School of Medicine, Sioux Falls, SD, USA
e-mail: Archana.Chatterjee@SanfordHealth.org;
mrg235@cornell.edu

(Paavonen et al. 2007; FUTURE II Study Group 2007; Joura et al. 2015). The bivalent vaccine (2vHPV) targets HPV-16 and -18; the quadrivalent vaccine (4vHPV) targets HPV-6, -11, -16, and -18; and the 9-valent vaccine (9vHPV) targets HPV-6, -11, -16, and -18 as well as 5 additional HPV types (31, 33, 45, 52, and 58) (Chatterjee 2014).

Although the rates of HPV vaccination have been increasing in the US over the past decade, coverage remains low compared to other vaccines recommended for adolescents (Fig. 13.1) (Reagan-Steiner et al. 2015). In 2014, a national survey found that 60% of 13- to 17-year-old females had received at least 1 dose and 39.7% had received 3 doses of HPV vaccine (Reagan-Steiner et al. 2015). Despite this modest rate of uptake, data from the National Health and Nutrition Examination Surveys (NHANES) demonstrated a 56% decrease in 4vHPV type prevalence among females aged 14–19 years in the first 4 years of the vaccine era (2007–2010)

compared with the pre-vaccine era, with vaccine effectiveness for prevention of infection estimated at 82% (Markowitz et al. 2013). A more recent study shows that between the pre-vaccine and vaccine eras, 4vHPV type prevalence declined from 11.5% to 4.3% among females aged 14–19 years and from 18.5% to 12.1% among females aged 20–24 years with no decrease noted in older age groups (Markowitz et al. 2016). Within the vaccine era, among sexually active females aged 14–24 years, 4vHPV type prevalence was lower in vaccinated (≥ 1 dose) compared with unvaccinated females: 2.1% vs. 16.9%, with no statistically significant changes in other HPV type categories that indicate cross-protection (Markowitz et al. 2016). These compelling data illustrate the population impact of HPV vaccination. Despite the modest uptake of HPV vaccines, after only 6 years of vaccine introduction, there was a 64% decrease in 4vHPV type prevalence among females aged 14 to 19 years and a

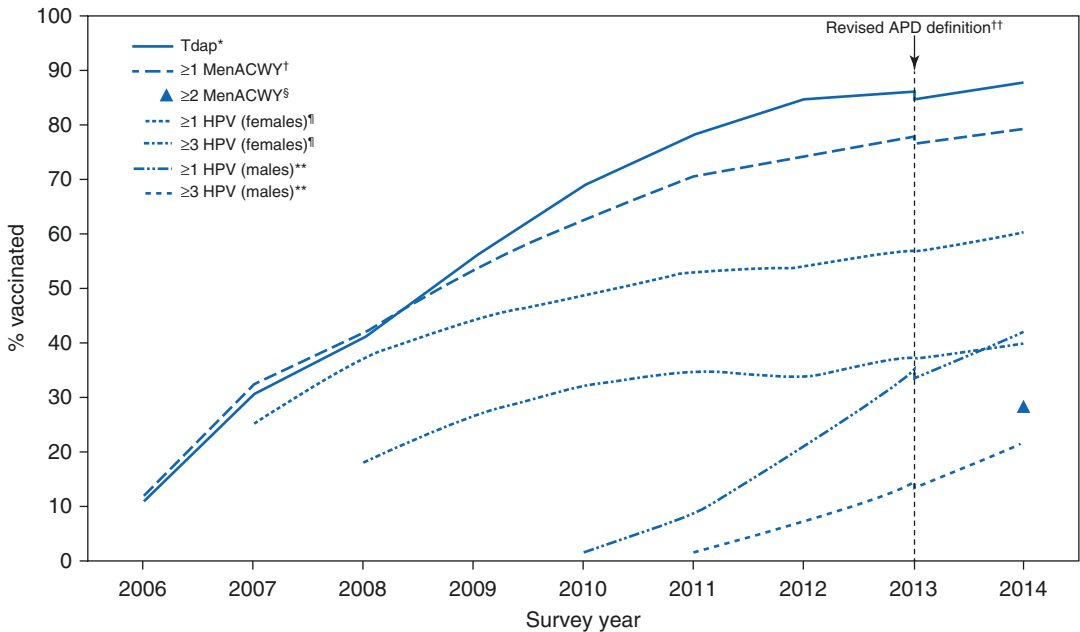


Fig. 13.1 Estimated vaccination coverage with selected vaccines and doses among adolescents aged 13–17 years, by survey year—National Immunization Survey–Teen, United States, 2006–2014. *Tdap* tetanus toxoid, reduced

diphtheria toxoid, and acellular pertussis, *MenACWY* meningococcal conjugate, *HPV* human papillomavirus, *ACIP* Advisory Committee on Immunization Practices, *APD* adequate provider data

34% decrease among those aged 20–24 years (Markowitz et al. 2016).

Some countries, including Australia and the United Kingdom (UK), adopted universal, publicly funded immunization of young women before the onset of sexual activity and, as of 2013, the Australian program has been extended to young men (Chatterjee 2014). The Australian program has had a 73% uptake rate of vaccination among 12- to 13-year-old girls, with the virtual disappearance of genital warts, not only among immunized younger women, but also among unimmunized younger men, presumably as a result of the protective effects of herd immunity (Ali et al. 2013). Australia was also the first to report a significant decline in the rate of high-grade precancerous lesions (Ali et al. 2013). In addition, significant reductions in the prevalence of HPV 16 and 18 DNA have been observed in cervical smear samples from 18- to 24-year-old women (Tabrizi et al. 2012). In England, the prevalence of HPV 16/18 infection in a post-immunization survey in 2013 was 6.5% among 16–18 year olds, compared to 19.1% in the baseline survey prior to the introduction of HPV immunization in 2008 in the UK (Mesher et al. 2013).

Other studies have also confirmed the effectiveness of HPV vaccines. In countries with HPV vaccination coverage of at least 50% in females, HPV type 16 and 18 infections decreased significantly between the pre-vaccination and post-vaccination periods by 68%, with a significant decrease (61%) in ano-genital warts in girls 13–19 years of age, and significant reductions in HPV types 31, 33, and 45 in girls 13–19 years of age, suggesting cross-protection (Drolet et al. 2015). Significant reductions in ano-genital warts were also reported in boys younger than 20 years of age and in women 20–39 years, suggesting herd effects. In countries with HPV vaccination coverage in females lower than 50%, while there were significant reductions in HPV types 16 and 18 infection and in ano-genital warts occurred in girls younger than 20 years of age, there was no indication of cross-protection or herd effects (Drolet et al. 2015).

The introduction of HPV vaccines has encountered some significant hurdles, including an anti-vaccine lobby that has tried to use misinterpreted adverse events in vaccine recipients unrelated to vaccination, as well as adverse events in placebo recipients to suggest that the vaccines are not safe (Chatterjee 2014). In the US, post-licensure vaccine safety monitoring and evaluation indicated that from June 2006 through March 2013, approximately 56 million doses of HPV4 were distributed, and from October 2009 through May 2013, a total of 611,000 doses of HPV2 were distributed (Sudenga et al. 2011; Centers for Disease Control and Prevention (CDC) 2013). Because HPV4 accounts for 99% of the doses distributed in the United States, analysis of vaccine safety data was limited to HPV4. During June 2006 to March 2013, the Vaccine Adverse Event Reporting System (VAERS) received a total of 21,194 adverse event reports occurring in females after receipt of HPV4; 92.1% were classified as non-serious (Centers for Disease Control and Prevention (CDC) 2013). Reporting peaked in 2008 and decreased each year thereafter; the proportion of reports to VAERS that were classified as serious reports peaked in 2009 at 12.8% and decreased thereafter to 7.4% in 2013 (Fig. 13.2) (Centers for Disease Control and Prevention (CDC) 2013). Ongoing safety monitoring for HPV vaccines has shown that most reports are non-serious (Markowitz et al. 2014). The most commonly reported adverse events are injection site pain, swelling and erythema. Among systemic adverse events the most frequently cited are headache, nausea, vomiting, and fever (Markowitz et al. 2014). Syncope continues to be reported following vaccination among adolescents, but adherence to a 15-min observation period after vaccination minimizes this.

It is evident that HPV vaccines are highly effective, and that education about HPV-related diseases and the vaccines to prevent them, is key to their successful deployment. Education regarding HPV-related diseases and vaccines needs to be directed at health care professionals, governments, recipients, parents and schools to ensure effective delivery programs.

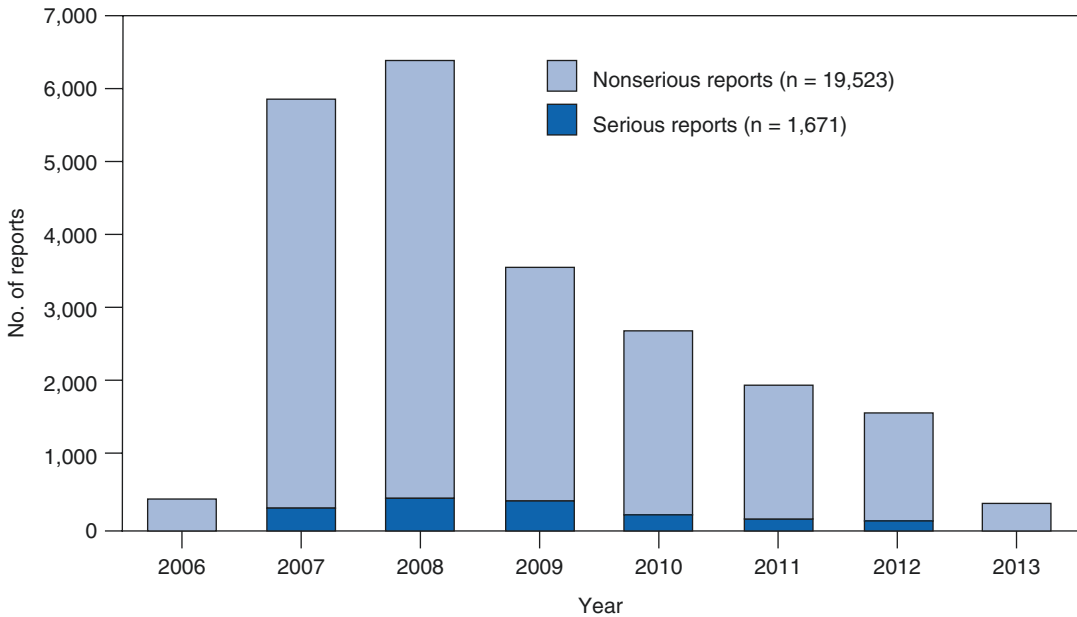


Fig. 13.2 Number of serious and nonserious reports of adverse events after administration of quadrivalent human papillomavirus (HPV4) vaccine in females, by year—Vaccine Adverse Event Reporting System, United States, June 2006 to March 2013. The figure shows the number of reports (serious and nonserious reports) of adverse events after administration of quadrivalent human papillomavi-

rus vaccine in females, by year, in the United States during June 2006 to March 2013. Reporting peaked in 2008 and decreased each year thereafter; the proportion of reports to the Vaccine Adverse Event Reporting System that were classified as serious reports peaked in 2009 at 12.8% and decreased thereafter to 7.4% in 2013

Measles

While many childhood vaccine-preventable diseases have been effectively controlled, recent outbreaks of some of these diseases has prompted concern among clinicians, public health officials, politicians, the media and the public (Whitney et al. 2014; Yang et al. 2015; Halsey and Salmon 2015). One of the best-known is the outbreak of measles in late 2014 that originated at Disneyland in Anaheim, California (Majumder et al. 2015; Clemmons et al. 2015; Chiem 2015). It resulted in 111 cases reported from seven US states, Canada and Mexico (Chiem 2015). Nearly half occurred in unvaccinated individuals, most of who were eligible for vaccination, but intentionally remained unvaccinated (Zipprich et al. 2015). The reasons that some members of the public refuse vaccination for themselves and their children are multifactorial and may be difficult to pinpoint, but the most direct measure of

vaccine refusal is the rate of parents claiming non-medical exemptions to school immunization requirements. Such exemptions have steadily increased in recent years, and shown to be related to the outbreak of measles in California and other states (Majumder et al. 2015; Clemmons et al. 2015; Chiem 2015; Zipprich et al. 2015; Omer et al. 2012).

It is instructive to review the history of measles control and elimination in the US. Measles-containing vaccines were first introduced in the US in 1963, with two intensive elimination efforts over the next two decades. The incidence of measles fell from >300 cases/100,000 population in the pre-vaccine era to a median of 1.3 cases/100,000 from 1982 to 1988 (Hamborsky et al. 2015). A resurgence in measles cases occurred from 1989 to 1992, attributed to suboptimal vaccine coverage among preschool-aged children and vaccine failures after a single dose of measles-containing vaccine. A third elimination

effort was launched in the 1990s, and included the recommendation for a second dose of measles-containing vaccine, which culminated in the successful elimination of measles in the US by 2000 (Katz and Hinman 2004). However, measles outbreaks linked to individuals who acquired it outside the US have persisted, with 23 occurring in 2014, associated with 667 cases of measles (the largest number recorded since elimination) (Centers for Disease Control and Prevention 2015). The US also recorded its first measles-associated death in 12 years (McCarthy 2015).

A recent article reviewed the published literature to examine the association between vaccine delay, refusal, or exemption and the epidemiology of measles (Phadke et al. 2016). Eighteen measles studies were evaluated. A total of 1416 cases ranging in age from 2 weeks to 84 years were reported, with 178 cases occurring in children under 12 months of age, and 56.8% having no history of measles vaccination. Of 970 measles cases for whom detailed vaccination data were available, 574 were unvaccinated despite being vaccine eligible, and 405 (70.6%) had received non-medical exemptions. Unvaccinated individuals made up a greater proportion of measles cases in the index or first generation of a cumulative epidemic curve. Children with vaccine exemptions had a significantly higher risk of acquiring measles than fully vaccinated children, with one study reporting that children with a vaccine exemption were 35 times more likely to contract measles compared to vaccinated children (Salmon et al. 1999). The authors concluded that a substantial proportion of measles cases in the US in the era after elimination occurred in intentionally unvaccinated individuals, and that higher rates of vaccine exemption in a community are associated with greater measles incidence among both the exempt and nonexempt population (Phadke et al. 2016).

This brief discussion of recent measles outbreaks and their causes in the US illustrates the importance of continued vigilance as well as public health efforts and education that are necessary to prevent the resurgence of this potentially deadly disease. Non-medical exemptions obtained by parents who believe they are protecting their

children from harm may in fact, have the opposite effect and put not only them but others at risk for contracting measles and suffering its consequences. As long as measles remains endemic in other parts of the world, maintaining high vaccination rates in the US is imperative.

C. difficile

C. difficile is emerging as an important cause of healthcare- and community-associated diarrhea in children. Originally described as a commensal organism in infants (<1 year of age), *C. difficile* is considered primarily a diarrheal agent of the elderly (Hall and O'Toole 1935). However, epidemiologic studies have demonstrated that up to 71% of children are asymptotically colonized with *C. difficile* and through a paradigm shift over the past decade, it is increasingly being recognized as an important pediatric enteric pathogen (Sammons and Toltzis 2013; Al-Jumaili et al. 1984). Surveillance has revealed that the incidence of *C. difficile* infection (CDI) is increasing in children, including those without traditional risk factors (Benson et al. 2007; Sandora et al. 2011; Kim et al. 2008; Nylund et al. 2011; Zilberberg et al. 2010; Khalaf et al. 2012). Although testing of infants is not recommended, one study reported that up to 26% of children hospitalized with CDIs were infants younger than 1 year, and 5% were neonates (Kim et al. 2008). *C. difficile* carriage rates average 37% for infants 0–1 month of age, 30% between 1 and 6 months of age, 14% at 6–12 months of age and 0–3% by 3 years of age (Jangi and Lamont 2010). Breastfed infants have lower carriage rates than do formula fed infants (14% vs. 30%, respectively) (Benno et al. 1984). Carriage rates in hospitalized children approximate 20% (Cohen et al. 2010).

Recognized risk factors for older children acquiring CDI include antimicrobial therapy, use of proton pump inhibitors, repeated enemas, use of diapers, prolonged nasogastric tube insertion, gastrostomy and jejunostomy tubes, underlying bowel disease, gastrointestinal tract surgery, renal insufficiency, cystic fibrosis and impaired

humoral immunity (Sandora et al. 2011; Schutze et al. 2013; Samady et al. 2014; Pohl et al. 2011). In one study, 67% of pediatric cases had chronic medical conditions including neuromuscular, cardiovascular, respiratory, renal, gastrointestinal, hematologic, immunologic, metabolic, malignancy, or congenital disorders (Kim et al. 2008). CDI is transmitted fecal-orally, through person-to-person contact or contaminated environmental surfaces. The organism has been recovered from the hands of hospital personnel, baby baths, oximeters, electronic thermometers, and hospital floors.

CDI causes a spectrum of symptoms, including asymptomatic colonization; mild, watery diarrhea; and severe pseudomembranous colitis (Khalaf et al. 2012; Pant et al. 2013; Enoch et al. 2011; Sammons et al. 2013; Morris et al. 2013). Infants are usually asymptotically colonized, whereas most symptomatic children experience mild-moderate watery diarrhea, associated with fever, anorexia, or abdominal pain (Khalaf et al. 2012). Approximately 20–30% of children will experience ≥ 1 recurrence following their initial episode and chronic diarrhea may lead to growth retardation (Morinville and McDonald 2005; Sutphen et al. 1983). The NAP1 strain of *C. difficile* which has been described as causing severe disease, including an increased incidence of symptomatic infection, recurrent disease, sepsis, toxic megacolon, bowel perforation, and mortality, has been reported in the pediatric population at lower rates (10–19%) than reported for adults (>50%) (Toltzis et al. 2009). NAP1-associated CDIs occur in children without exposure to health care facilities and/or to antimicrobial agents (Bryant and McDonald 2009).

Evaluation for CDI should be reserved for children with diarrheal symptoms, defined as passage of ≥ 3 loose stools within a 24-h period. Only unformed stools should be tested. Diagnostic methods for CDI in children are evolving (Sammons and Toltzis 2015). Once considered the reference standard, cell culture cytotoxicity neutralization assay (CCNA) has been abandoned by many laboratories because of its slow turnaround time and labor requirements (Peterson et al. 2007). The more common testing

method used for *C. difficile* toxins is the commercially available enzyme immunoassay (EIA), which detects toxins A and/or B. Mean test sensitivities range from 72% to 82%, with mean specificities of 97–98%, compared with the CCNA (Crobach et al. 2009). Molecular assays using nucleic acid amplification tests (NAATs) are approved by the US Food and Drug Administration (FDA) and are now preferred by many laboratories including those in children's hospitals (Schutze et al. 2013). NAATs combine good sensitivity and specificity, and have turnaround times comparable to EIAs. Routine testing for *C. difficile* in children younger than 1 year of age is not recommended because carriage is common in this age group. Testing for *C. difficile* can be considered in children 1–3 years of age with diarrhea, but testing for other causes of diarrhea, particularly viral, is recommended first (Sandora et al. 2011; Schutze et al. 2013). *C. difficile*, its toxins, and genome are shed for long periods after resolution of diarrheal symptoms so EIAs and NAATs should not be used as tests of cure after treatment of CDIs (Schutze et al. 2013).

The management of CDI involves three basic principles:

1. Supportive care.
2. Discontinuing the precipitating antibiotic(s).
3. Initiation of effective anti-*C. difficile* therapy.

Symptomatic support is critical for children, who may require aggressive intravenous hydration. Adjunctive anti-motility agents are discouraged due to concerns of increased intestinal contact time with toxins. Discontinuation of the offending antibiotic(s) may be sufficient for the resolution of mild symptoms and facilitates reconstitution of the normal enteric flora. While no prospective clinical trials for CDI treatment in children have been conducted, for primary mild-moderate CDI in children, oral metronidazole is considered the drug of choice (Khalaf et al. 2012; Schutze et al. 2013; Li et al. 2015). Oral vancomycin or vancomycin administered by enema with or without intravenous metronidazole is indicated as initial therapy for patients with severe disease and for patients who do not

respond to oral metronidazole (Cohen et al. 2010). Pediatric studies evaluating fidaxomicin (approved for use in adults) are ongoing (Khalaf et al. 2012). Up to 30% of patients treated for CDIs experience a recurrence after discontinuing therapy (Schutze et al. 2013). Recurrences represent either relapse with the original isolate or reinfection with a new isolate. For recurrent CDI, a second course of the initially successful antibiotic is recommended with the first recurrence. If this treatment fails, then tapered or pulsed vancomycin regimens can be used (Schutze et al. 2013). Fecal microbiota transplantation or probiotics have been successfully used in case reports of children with CDI (Khalaf et al. 2012; Walia et al. 2014; Goldenberg et al. 2013).

Judicious antibiotic usage, standard plus contact isolation, decontamination of surfaces with sporicidal cleaning agents, and handwashing are critical components of nosocomial prevention of *C. difficile* transmission (Khalaf et al. 2012). Alcohol-based hand sanitizers may not be as effective as handwashing with soap and water because of spore resistance to alcohol.

In summary, *C. difficile* is emerging as an important enteric pathogen in children. Historically considered a commensal in infants, CDI should be considered in the differential diagnosis of older children with diarrhea, particularly those who have risk factors for it. Appropriate testing and treatment modalities should be instituted to manage children with CDI. Further studies investigating the significance of *C. difficile* detection among different age groups, the pathogenesis of CDI, and optimal therapeutic and preventative strategies in children are needed.

Antibiotic Stewardship

A discussion of antibiotic stewardship is probably fitting following the section on CDI. The need for antibiotic stewardship across the spectrum of healthcare has been recognized in the National Action Plan for Combating Antibiotic-Resistant Bacteria issued by the White House in March 2015 (The White House 2015). This plan calls for establishment of antibiotic stewardship

programs (ASPs) in all acute care hospitals by 2020 and for the Centers for Medicare and Medicaid Services to issue a Condition of Participation that participating hospitals develop programs based on recommendations from the Centers for Disease Control and Prevention's (CDC) Core Elements of Hospital Antibiotic Stewardship Programs (Centers for Disease Control and Prevention (CDC) 2014).

Antibiotic stewardship has been defined in a consensus statement from the Infectious Diseases Society of America (IDSA), the Society for Healthcare Epidemiology of America (SHEA), and the Pediatric Infectious Diseases Society (PIDS) as “coordinated interventions designed to improve and measure the appropriate use of [antibiotic] agents by promoting the selection of the optimal [antibiotic] drug regimen including dosing, duration of therapy, and route of administration” (Fishman 2012). The benefits of antibiotic stewardship include improved patient outcomes, reduced adverse events including CDI, improvement in rates of antibiotic susceptibilities to targeted antibiotics, and optimization of resource utilization across the continuum of care. Evidence-based guidelines for implementation and measurement of antibiotic stewardship interventions in inpatient populations were prepared by a multidisciplinary expert panel including clinicians and investigators representing internal medicine, emergency medicine, microbiology, critical care, surgery, epidemiology, pharmacy, and adult and pediatric infectious diseases specialties (Barlam et al. 2016). Selected recommendations from the guidelines (based on the availability of pediatric data) are presented below. These recommendations address the best approaches for antibiotic stewardship programs to influence the optimal use of antibiotics in children.

1. The guidelines recommend preauthorization and/or prospective audit and feedback (PAF), which have been associated with a significant reduction in the use of restricted agents and of associated costs (Metjian et al. 2008). PAF has been effective in children's hospitals by significantly reducing antibiotic use and

- dosing errors, limiting the development of antibiotic resistance, and reducing CDI rates without a negative impact on patient outcomes (Newland et al. 2012; Di Pentima et al. 2011).
2. While recommending against relying solely on didactic educational materials for stewardship, the guidelines do endorse the use of passive educational activities, such as lectures or informational pamphlets, to complement other stewardship activities. Academic medical centers and teaching hospitals are also advised to integrate education on fundamental antibiotic stewardship principles into their preclinical and clinical curricula. Educational strategies should include medical, pharmacy, physician assistant, nurse practitioner, and nursing students and trainees.
 3. Since there is evidence that facility-specific guidelines promote the use of narrower-spectrum antibiotic regimens (Newman et al. 2012), the authors suggest that ASPs develop facility-specific clinical practice guidelines coupled with a dissemination and implementation strategy.
 4. The guidelines suggest incorporation of computerized clinical decision support at the time of prescribing into ASPs, as implementation of computerized decision support systems for prescribers has been associated with improved antibiotic dosing, fewer prescribing errors, and reduced antibiotic costs (Mullett et al. 2001).
 5. Due to limited evidence, the authors give no recommendation about the utility of alternative dosing strategies for vancomycin. However, continuous-infusion vancomycin has been associated with few adverse effects and no nephrotoxicity in children (McKamy et al. 2012).
 6. The authors recommend that ASPs implement guidelines and strategies to reduce antibiotic therapy to the shortest effective duration. One study demonstrated that prescription of shorter courses of antibiotic therapy is associated with outcomes similar to those with longer courses and few adverse events (Saini et al. 2011).
 7. The authors suggest development of stratified antibiograms over solely relying on non-stratified antibiograms to assist ASPs in developing guidelines for empiric therapy. When one institution constructed a pediatric-specific antibiogram for *Escherichia coli* and compared it with antibiograms generated from combined data from both adult and pediatric isolates, there were significant antibiotic susceptibility differences between *E. coli* isolates obtained from pediatric patients vs. the hospital-wide antibiogram data (Boggan et al. 2012). Provision of pediatric-specific data optimized prescribing choice when compared with no antibiogram and also with the hospital-wide antibiogram. Another institution also found age-specific differences with overestimation of resistance in *E. coli* and *S. aureus* for children (Swami and Banerjee 2013).
 8. Although studies of the value of ASP interventions based on rapid testing for respiratory viruses are lacking, some data are available on decreased inappropriate antibiotic use with rapid viral testing. These studies have been performed primarily in pediatric populations such as children presenting to physicians' offices (Jennings et al. 2009) or emergency departments (Bonner et al. 2003; Doan et al. 2009; Wishaupt et al. 2011), children requiring hospitalization (Byington et al. 2002) or immunocompromised children (Kadmon et al. 2013). Based on these, the authors support the use of rapid viral testing for respiratory pathogens to reduce the use of inappropriate antibiotics.
 9. The authors suggest that ASPs develop facility-specific guidelines for fever and neutropenia management in hematology-oncology patients. As an example of the benefits from these, Pakakasama et al. demonstrated that implementation clinical guidelines in pediatric cancer patients resulted in statistically significant reductions in septic shock (intervention vs. control: 3.5% vs. 10.9%; $P = 0.011$), ICU admissions (2.9% vs. 9.4%; $P = 0.016$), and death (0% vs. 6.5%; $P = 0.001$) (Pakakasama et al. 2011).

10. One question in the guideline is devoted to ASPs in the neonatal intensive care unit (NICU). The authors acknowledge that limited evidence is available to determine the most effective ASP strategies in the NICU, but state that general principles should apply (Patel and Saiman 2012). Antibiotic policy and guidelines have been shown to be effective in the NICU (Murki et al. 2010). After implementing a vancomycin guideline, Chiu et al. (2011) saw a 35% reduction in the initiation of vancomycin and a 65% overall decrease in exposure to vancomycin compared with the preimplementation period. Zingg et al. (2011) evaluated antibiotic use after initiating a policy to shorten antibiotic therapy for sepsis and coagulase-negative staphylococcal infection, and to stop pre-emptive treatment if blood cultures were negative. They found an overall 2.8% yearly reduction in antibiotic use ($P < 0.001$) without increasing mortality.

This short discussion of the guidelines for implementing ASPs in pediatric settings is a first step in assisting them to improve the utilization of antibiotics in their facilities. Further research is definitely needed to provide a strong scientific basis for the guidelines.

MRSA

MRSA is a significant cause of both health care-associated and community-associated infections in children, causing a wide spectrum of disease ranging from skin and soft tissue infections to life-threatening systemic infections (Pendleton and Kocher 2015; Vardakas et al. 2013). Invasive MRSA in children is associated with high morbidity, mortality and healthcare costs (Cosgrove et al. 2003; Song et al. 2010). The epidemiology of infections among children is distinct from that in adults e.g. the incidence of invasive infections is relatively high in infants and young children (Klevens et al. 2007). Studies in some centers have shown increases in both invasive and noninvasive community associated (CA) MRSA

infections in children, and a national study showed an increase in the number of hospitalized children with MRSA infection (Gerber et al. 2009; Kaplan et al. 2005). Similarly, numerous outbreaks in NICUs have been attributed to strains of both health care and community origins, and increasing trends in late onset infections in US NICUs caused by MRSA have been reported (Lessa et al. 2009). A retrospective analysis of 25 children's hospitals reported that the incidence of MRSA infections increased 10-fold between 1999 and 2008 (2 cases vs. 21 cases per 1000, $P < 0.001$) with a doubling in the proportion of staphylococcal infections due to MRSA in the same time period (15% vs. 36%) (Herigon et al. 2010). A recent study evaluated reports of invasive MRSA infections in pediatric patients identified from population-based surveillance during 2005–2010 and found that 35% of cases were hospital-onset, 23% were health care-associated community-onset, and 42% were CA-MRSA (Iwamoto et al. 2013). The incidence of invasive CA-MRSA infection per 100,000 children increased from 1.1 in 2005 to 1.7 in 2010. The estimated invasive MRSA incidence in 2010 was higher among infants aged <90 days compared with older infants and children (43.9 vs. 2.0 per 100,000) and among black children compared with other races (6.7 vs. 1.6 per 100,000) (Iwamoto et al. 2013).

Due to the rise in MRSA infections in recent years, the percentage of hospitalized children with *S. aureus* infection that received anti-MRSA antibiotics increased between 1999 and 2008 (52% vs. 79%), while the percentage of hospitalized children receiving beta lactam drugs decreased (66% vs. 30%, $P < 0.001$) (Herigon et al. 2010). During this time period, the percentage of hospitalized children with *S. aureus* infection given clindamycin and linezolid increased (clindamycin, 21% vs. 63%; linezolid, 0% vs. 5%) while vancomycin use remained stable (36% vs. 37%) (Herigon et al. 2010). Current treatment recommendations for infants with MRSA infection based on the clinical practice guidelines by the IDSA vary depending on the site of infection (Liu et al. 2011). For children with minor skin infections (such as impetigo)

and secondarily infected skin lesions (such as eczema, ulcers, or lacerations), mupirocin 2% topical ointment can be used (Liu et al. 2011). For hospitalized children, if the patient is stable without ongoing bacteremia or intravascular infection, empirical therapy with clindamycin 10–13 mg/kg/dose IV every 6–8 h (to administer 40 mg/kg/day) is an option if the clindamycin resistance rate is low ($\leq 10\%$) with transition to oral therapy if the strain is susceptible (Liu et al. 2011). Linezolid 600 mg PO/IV twice daily for children >12 years of age and 10 mg/kg/dose PO/IV every 8 h for children, 12 years of age is an alternative (Liu et al. 2011). First-line treatment is recommended to be with intravenous (IV) vancomycin for severe of MRSA infections (Liu et al. 2011). Alternative antibiotics include clindamycin, linezolid, daptomycin, quinupristin/dalfopristin, rifampin, telavancin, or trimethoprim/sulfamethoxazole (Durand et al. 2014; Gostelow et al. 2014). Over the last 15 years, six drugs have been approved for the treatment of *S. aureus* infections, but PK and safety data in infants are only available for linezolid and daptomycin, while quinupristin/dalfopristin has been studied only in non-infant pediatric populations (Durand et al. 2014).

Recurrent MRSA skin and soft tissue infections (SSTIs) can be a particular problem in children. The following measures are recommended to manage these (Liu et al. 2011):

1. Keep draining wounds covered with clean, dry bandages.
2. Maintain good personal hygiene with regular bathing and cleaning of hands with soap and water or an alcohol-based hand gel, particularly after touching infected skin or an item that has directly contacted a draining wound.
3. Avoid reusing or sharing personal items (e.g., disposable razors, linens, and towels) that have contacted infected skin.
4. Environmental hygiene measures should be considered in patients with recurrent SSTI in the household or community setting by:
 - (a) Focusing cleaning efforts on high-touch surfaces (i.e., surfaces that come into frequent contact with people's bare skin each day, counters, door knobs, bath tubs, and toilet seats) that may contact bare skin or uncovered infections.
 - (b) Using commercially available cleaners or detergents appropriate for the surface being cleaned according to label instructions for routine cleaning of surfaces.
5. Decolonization may be considered in selected cases if:
 - (a) A patient develops a recurrent SSTI despite optimizing wound care and hygiene measures.
 - (b) Ongoing transmission is occurring among household members or other close contacts despite optimizing wound care and hygiene measures.
6. Decolonization strategies should be offered in conjunction with ongoing reinforcement of hygiene measures and may include the following:
 - (a) Nasal decolonization with mupirocin twice daily for 5–10 days.
 - (b) Nasal decolonization with mupirocin twice daily for 5–10 days and topical body decolonization regimens with a skin antiseptic solution (e.g., chlorhexidine) for 5–14 days or dilute bleach baths. (For dilute bleach baths, 1 teaspoon per gallon of water [or ¼ cup per ¼ tub or 13 gallons of water] given for 15 min twice weekly for 3 months can be considered.)
7. Oral antimicrobial therapy is recommended for the treatment of active infection only and is not routinely recommended for decolonization. An oral agent in combination with rifampin, if the strain is susceptible, may be considered for decolonization if infections recur despite above measures.
8. The role of cultures in the management of patients with recurrent SSTIs is limited:
 - (a) Screening cultures prior to decolonization are not routinely recommended if at least one of the prior infections was documented as due to MRSA.
 - (b) Surveillance cultures following a decolonization regimen are not routinely recommended in the absence of an active infection.

In summary, both invasive and non-invasive infections due to MRSA in children remain challenging to manage. Care for pediatric patients with MRSA infections should be optimized by utilizing published evidence-based guidelines for these infections.

Congenital CMV

Congenital CMV (cCMV) infection is the leading nongenetic cause of sensorineural hearing loss (SNHL) in newborns worldwide (Fowler and Boppana 2006; Boppana et al. 2013). The impact of cCMV infection on pediatric health is significant, affecting 0.5–2% of all live-born infants worldwide (Schleiss and Heineman 2005; Manicklal et al. 2013). Although cCMV infection is rare overall, it accounts for 21% of children with hearing loss at birth and 24% of those with hearing loss at 4 years of age (Grosse et al. 2008). An estimated 10% of infected infants exhibit neurological sequelae at birth, while an additional 10–15% of infected infants develop SNHL in the first 2 years of life, up to two thirds have neurologic deficits, and 4% die during the newborn period (Boppana et al. 2013; Schleiss and Heineman 2005). In the United States, approximately 30,000 congenital infections occur annually, of which more than 5000 infections lead to permanent disabilities, including SNHL, growth restriction, seizures, and motor and cognitive disability (Boppana et al. 2013; Schleiss and Heineman 2005).

Proof of cCMV infection requires virologic detection of CMV in urine, oral fluids, respiratory tract secretions, blood, or CSF obtained within 2–4 weeks of birth (Plosa et al. 2015). The analytical sensitivity of CMV DNA detection by PCR assay of dried blood spots is low, so these specimens should not be used for screening for cCMV infection (Boppana et al. 2010). Differentiating between intrauterine and postnatal infection is difficult beyond 2–4 weeks of age unless clinical manifestations such as chorioretinitis or intracranial calcifications occur (Plosa et al. 2015). Serologic methods for diagnosis of

cCMV are not recommended due to their poor specificity (Plosa et al. 2015).

Treatment for cCMV infection with antiviral agents has been controversial. A study conducted by the National Institute of Allergy and Infectious Diseases (NIAID) Collaborative Antiviral Study Group (CASG) reported that among neonates with symptomatic cCMV disease involving the central nervous system (CNS), ganciclovir administered intravenously over a period of 6 weeks was associated with improved audiologic outcomes at 6 months of life, but there was a suggestion that this benefit could wane over the first 2 years of life (Kimberlin et al. 2003). Treated infants had fewer developmental delays, according to Denver Developmental evaluations, than untreated infants (Oliver et al. 2009). In a follow-up study, the CASG determined the dose of oral valganciclovir (the prodrug of ganciclovir) that results in systemic exposure to ganciclovir that is similar to that with intravenous ganciclovir (Kimberlin et al. 2008). Treatment with intravenous ganciclovir or oral valganciclovir for 6 weeks is now an accepted treatment option for patients with symptomatic cCMV disease involving the CNS (Plosa et al. 2015).

A recent randomized, placebo-controlled trial of valganciclovir in neonates with symptomatic cCMV disease, compared 6 months of therapy with 6 weeks of therapy (Kimberlin et al. 2015). A total of 96 neonates underwent randomization, of which 86 had follow-up data at 6 months that could be evaluated. Best-ear hearing at 6 months was similar in the 6-month group and the 6-week group (Kimberlin et al. 2015). Total ear hearing (hearing in one or both ears that could be evaluated) was more likely to be improved or to remain normal at 12 months in the 6-month group than in the 6-week group (73% vs. 57%, $P = 0.01$) (Kimberlin et al. 2015). The benefit in total-ear hearing was maintained at 24 months (77% vs. 64%, $P = 0.04$), and the 6-month group had better neurodevelopmental scores on the Bayley Scales of Infant and Toddler Development (third edition) (Bayley 2006), on the language-composite component ($P = 0.004$) and on the receptive-communication scale ($P = 0.003$) (Kimberlin et al. 2015). Grade 3 or 4 neutropenia occurred in

19% of the participants during the first 6 weeks, and in 21% of the participants during the next 4.5 months of the study in the 6-month group and in 27% of those in the 6-week group ($P = 0.64$) (Kimberlin et al. 2015). The authors concluded that the data from this controlled study suggest that among infants with symptomatic cCMV disease, 6 months of oral valganciclovir therapy has a moderately favorable effect on long-term audiologic and neurodevelopmental outcomes (after adjustment for baseline CNS involvement) without an excess risk of neutropenia or the need to maintain intravenous access for prolonged periods of time (Kimberlin et al. 2015). However, ganciclovir does have toxic effects on the gonads and is carcinogenic in animal models (Roche Pharmaceuticals 2001), and although these toxic effects have not been seen in humans, this information should be conveyed to families of neonates for whom valganciclovir therapy is being considered. It should be noted that the results of the study do not apply to infants with asymptomatic cCMV infection, as there are no controlled studies showing a benefit in this population and the possibility of harm exists (Kimberlin et al. 2015). Since CMV-associated SNHL fluctuates over time in more than one third of patients as part of the natural history of this disease, prospective, controlled trial designs are critical to assess treatment benefit in patients with asymptomatic cCMV infections.

Meningococcal B Vaccines

Meningococcal disease caused by the encapsulated organism *Neisseria meningitidis* remains a feared and devastating illness due to its rapid onset and associated morbidity and mortality (Rouphael and Stephens 2012). Differences in the polysaccharide capsule surrounding the organism allow classification into 12 serogroups, of which A, B, C, W and Y are predominantly responsible for invasive disease (Rouphael and Stephens 2012). Meningococcal disease due to serogroup B (MenB) is endemic in many countries in Europe, the Western Pacific, and the Americas where incidence rates are dynamic

over time. The majority of invasive meningococcal cases across Europe from 2008 to 2009 were caused by serogroup B (71%), and the incidence rate for adolescents aged 15–19 years in 2009 was approximately 1.7 cases per 100,000 population (European Centre for Disease Prevention and Control 2011). Australia and New Zealand report similar incidence rates (Harrison et al. 2009; Communicable Diseases Network Australia: Commonwealth Department of Health and Ageing 2007). Low to moderate endemic rates (of predominant serogroup B) in the Americas range from 0.3 to 4 cases per 100,000 population (Harrison et al. 2009; World Health Organization (WHO) 2011; Jafri et al. 2013). The incidence of MenB disease is stable and low in US adolescents and young adults aged 11–23 years, with approximately 50–60 cases and 5–10 deaths reported annually, the majority (>80%) of which occur in older adolescents and young adults aged 16–23 years (MacNeil et al. 2015). Whereas several outbreaks of MenB disease have occurred in recent years on college campuses in the US, 98% of cases are sporadic (Folaranmi et al. 2015).

Adolescents and young adults are uniquely susceptible to poor outcomes from invasive meningococcal disease and are therefore targeted for vaccination in order to protect them as well as impact carriage rates, thereby leading to ‘herd protection’. While the incidence of meningococcal disease is highest in infants <1 year of age, there tends to be a second peak in adolescents, aged 11–19 years (Jafri et al. 2013). Nasopharyngeal carriage is more prevalent among adolescents (Christensen et al. 2010; Soeters et al. 2015). The high carriage rate and peak of disease incidence in adolescents and young adults is thought to be due largely to factors associated with social behaviors such as close living quarters (e.g. university dormitories, military barracks), crowded venues (e.g. bars, clubs), intimate contact (e.g. kissing, sharing drinks), smoking, and sleep deprivation (Delbos et al. 2013; Broderick et al. 2012).

Conjugate vaccines have been successfully used to protect against disease caused by meningococci with ACWY capsular polysaccharides

(Halperin et al. 2012). This approach has been unfeasible for MenB as its capsular polysaccharide is antigenically similar to the human fetal neural cell adhesion molecule resulting in poor immunogenicity and the potential to induce auto-antibodies (Bai et al. 2011). Consequently, attention has focused on alternative non-capsular vaccine candidates, which are immunogenic, highly conserved and expressed among all meningococci, in order to provide broad protection against diverse MenB strains (Panatto et al. 2011; Tan et al. 2010). Utilizing the natural ability of meningococci to shed outer membrane vesicles (OMV) during growth, initially, monovalent OMV vaccines were developed from local outbreak strains in response to epidemics in Norway, Cuba, Chile and New Zealand (Bai et al. 2011). However, protection induced by these vaccines is generally strain specific and unable to provide protection in areas with heterogeneous epidemiology.

The first broad-spectrum multicomponent vaccine against serogroup B meningococcus (MenB), 4CMenB (Bexsero®), was approved by the European Medicines Agency (EMA) in 2013, for prevention of MenB disease in all age groups, and by the US Food and Drug Administration (FDA) in January 2015 for use in adolescents aged 10–25 years (MacNeil et al. 2015; Seib et al. 2015). A second protein-based MenB vaccine has also been approved in the US for adolescents aged 10–25 years (Trumenba®) (MacNeil et al. 2015; Seib et al. 2015). Both vaccines contain the lipoprotein factor H-binding protein (fHbp), while 4CMenB also contains Neisseria adhesin A (NadA), Neisserial Heparin Binding Antigen (NHBA) fused with GNA1030, and OMV from the New Zealand outbreak strain NZ98/254 (NZ OMV) (Seib et al. 2015; Donnelly et al. 2010; Nolan et al. 2015; Perrett et al. 2015; Findlow 2013). Trumenba® was licensed in the US in October 2014 as a 3-dose series given at 0, 2, and 6 months and has recently received approval for 2 doses at 0 and 6 months (Wyeth Pharmaceuticals Inc 2014). Bexsero® is licensed in the US for 2 doses at 0 and ≥ 1 month (Novartis Vaccines and Diagnostics Inc 2015). Both vaccines produce local and systemic reactions at the

following rates: pain at the injection site (83–85%), headache (33–35%), myalgia (30–48%), fatigue (35–40%), induration (28%), nausea (18%), chills (15%), and arthralgia (13%) (Wyeth Pharmaceuticals Inc 2014; Novartis Vaccines and Diagnostics Inc 2015). The CDC's Advisory Committee on Immunization Practices (ACIP) has recommended that a MenB vaccine series may be administered to adolescents and young adults aged 16–23 years to provide short-term protection against most strains of MenB disease with the preferred age for vaccination being 16–18 years (recommendation Category B) (MacNeil et al. 2015). It states that MenB vaccines may be administered concomitantly with other vaccines indicated for this age, but at a different anatomic site, if feasible (MacNeil et al. 2015). In 2015, the ACIP recommended routine use (recommendation Category A) of MenB vaccines in certain groups of persons at increased risk for MenB disease, including during outbreaks of MenB disease (Folaranmi et al. 2015). College campuses that have recently experienced an outbreak of MenB disease should continue to follow the recommendations for use of MenB vaccines in outbreak settings that recommend vaccination for persons aged ≥ 10 years (Folaranmi et al. 2015).

Thus, while it is encouraging to have new MenB vaccines for adolescents and young adults, they are at present being routinely recommended only for people with increased risk for MenB disease and in outbreak settings. It will be interesting to follow the impact of these vaccines and evaluate changes in the epidemiology of MenB disease over time.

Zika Virus

Zika virus (ZIKV) was discovered in monkeys of the Zika Forest in Uganda in 1947 and was first documented in humans in 1952 (World Health Organization 2016a). Fourteen confirmed cases were documented in African and Asian countries throughout the latter half of the twentieth century (Broutet et al. 2016). In 2007, an outbreak in Micronesia signaled the spread of ZIKV, with 49

confirmed cases and over 50 unconfirmed. From 2013 to 2014 confirmed cases were documented throughout Oceania and in April 2015 a ZIKV outbreak began in Brazil (Roth et al. 2014; Saiz et al. 2016). Since then it has spread to countries in South America, Central America, Mexico, and the Caribbean. For the last half century ZIKV had lurked in the shadows of other mighty mosquito-borne infections such as dengue, yellow fever, West Nile virus and malaria. However it has become clear that ZIKV does in fact pose a great threat to public health due to the concurrent rise in birth defects and Guillian-Barre Syndrome (GBS) associated with it.

ZIKV is an enveloped, icosahedral flavivirus related to dengue, yellow fever, and West Nile viruses (Saiz et al. 2016). It has a non-segmented, positive-sense, ssRNA genome allowing for rapid replication within host cells and subsequent transfer to vectors. Arthropod vectors of ZIKV include at least 15 species of mosquitos from the *Aedes* genus, mainly *A. aegypti* (Americas) and *A. albopictus* (Asia) (Centers for Disease Control and Prevention 2016a). Other modes of transmission include mother to child, sexual contact (virus may reside in sperm unknown period of time), blood transfusions, and laboratory exposure. The exact pathogenesis of ZIKV is still unknown, but is inferred from that of similar flaviviruses.

Most cases of ZIKV are relatively minor with incubation periods of 3–12 days (Brito 2015). About 18% of cases are symptomatic and present with influenza-like features (Saiz et al. 2016). Common symptoms include fever, pink maculopapular rash, joint pain, and conjunctivitis; less common symptoms include vomiting, headaches, edema, and jaundice (Centers for Disease Control and Prevention 2016b). Occasionally, gastrointestinal complications may occur, manifesting as abdominal pain, diarrhea, constipation, or ulcers (Saiz et al. 2016). Symptoms generally resolve within a week, however joint pain and weakness may last up to month post-infection. It appears that there is an epidemiologic link between ZIKV infection and the development of GBS; this association is yet to be confirmed (Centers for Disease Control and Prevention 2016c). No deaths have been reported in ZIKV infected patients with

GBS and the syndrome seems to resolve within a few weeks of onset.

The most alarming complication of ZIKV infection is the development of severe birth defects, including: microcephaly, decreased brain parenchymal volume resulting in ventriculomegaly, lissencephaly, and calcifications in the basal ganglia and subcortical-cortical transition area (Cavalheiro et al. 2016). The most severe birth defects occur upon infection during the first trimester.

Differential diagnoses for ZIKV infection include dengue and chikungunya. Blood or urine tests may confirm ZIKV infection; however, blood tests may produce false positives due to cross-reactivity with antibodies for other flaviviruses (especially dengue and yellow fever) (Petersen et al. 2016). In pregnant women amniocentesis may determine if the infection has spread to the fetus.

There is no specific antiviral therapy for or vaccine to prevent ZIKV infection at this time. General precautions against mosquito exposure should be taken and pregnant women should be advised about the risks of traveling to ZIKV endemic areas. Rest, fluids, and acetaminophen to control fever/pain are the only recommended interventions. NSAIDs should be avoided until dengue can be ruled out to avoid bleeding (Centers for Disease Control and Prevention 2016b). Healthcare providers should monitor pregnant women diagnosed with ZIKV infection through serial ultrasounds and discuss termination of pregnancy on an individual basis. ZIKV guidelines from the CDC and WHO are available for practitioners to follow (Centers for Disease Control and Prevention 2016d; World Health Organization 2016b).

Summary/Conclusion

This chapter has focused on several contemporary topics in pediatric infectious diseases including the impact of HPV vaccines; the ongoing outbreaks of measles in the US; the rise in *C. difficile* infections and their management in children; the role of antibiotic stewardship in pediatric

facilities; the status and management of MRSA infections; the management of congenital CMV infections; the introduction of meningococcal B vaccines; and the Zika virus outbreak and its implications. This sample of subjects exemplifies the dynamic and diverse nature of the subspecialty, as emerging and re-emerging infections keep this field engaged in ongoing research and scholarship.

References

- Ali H, Donovan B, Wand H, et al. Genital warts in young Australians five years into national human papillomavirus vaccination programme: national surveillance data. *BMJ*. 2013;346:f2032.
- Al-Jumaili IJ, Shibley M, Lishman AH, Record CO. Incidence and origin of *Clostridium difficile* in neonates. *J Clin Microbiol*. 1984;19:77–8.
- Bai X, Findlow J, Borrow R. Recombinant protein meningococcal serogroup B vaccine combined with outer membrane vesicles. *Expert Opin Biol Ther*. 2011;11:969–85.
- Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, Srinivasan A, Dellit TH, Falck-Ytter YT, Fishman NO, Hamilton CW, Jenkins TC, Lipsett PA, Malani PN, May LS, Moran GJ, Neuhauser MM, Newland JG, Ohl CA, Samore MH, Seo SK, Trivedi KK. Implementing an Antibiotic Stewardship Program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clin Infect Dis*. 2016;62(10):e51–77.
- Bayley N. Bayley Scales of Infant Development technical manual. 3rd ed. Harcourt Assessment: San Antonio, TX; 2006.
- Benno Y, Sawada K, Mitsuoka T. The intestinal microflora of infants: composition of fecal flora in breast-fed and bottle-fed infants. *Microbiol Immunol*. 1984;28(9):975–86.
- Benson L, Song X, Campos J, Singh N. Changing epidemiology of *Clostridium difficile*-associated in children. *Infect Control Hosp Epidemiol*. 2007;28:1233–5.
- Bhatia N, Lynde C, Vender R, Bourcier M. Understanding genital warts: epidemiology, pathogenesis, and burden of disease of human papillomavirus. *J Cutan Med Surg*. 2013;17(Suppl 2):S47–54.
- Boggan JC, Navar-Boggan AM, Jhaveri R. Pediatric-specific antimicrobial susceptibility data and empiric antibiotic selection. *Pediatrics*. 2012;130:e615–22.
- Bonner AB, Monroe KW, Talley LI, Klasner AE, Kimberlin DW. Impact of the rapid diagnosis of influenza on physician decision-making and patient management in the pediatric emergency department: results of a randomized, prospective, controlled trial. *Pediatrics*. 2003;112:363–7.
- Boppana SB, Ross SA, Novak Z, et al. Dried blood spot real-time polymerase chain reaction assays to screen newborns for congenital cytomegalovirus infection. *JAMA*. 2010;303:1375–82.
- Boppana SB, Ross SA, Fowler KB. Congenital cytomegalovirus infection: clinical outcome. *Clin Infect Dis*. 2013;57(Suppl 4):S178–81.
- Bosch FX. Human papillomavirus: science and technologies for the elimination of cervical cancer. *Expert Opin Pharmacother*. 2011;12(14):2189–204.
- Bosch FX, Castellsague X, de Sanjose S. HPV and cervical cancer: screening or vaccination? *Br J Cancer*. 2008;98(1):15–21.
- Brito C. Zika virus: a new chapter in the history of medicine. *Acta Medica Port*. 2015;28(6):679–80.
- Broderick M, Faix D, Hansen C, Blair P. Trends in meningococcal disease in the United States military, 1971–2010. *Emerg Infect Dis*. 2012;18(9):1430–7.
- Broutet N, Krauer F, Riesen M, Khalakdina A, Almiron M, Aldighieri S, Espinal M, Low N, Dye C. Zika virus as a cause of neurologic disorders. *N Engl J Med*. 2016;374(16):1506–9.
- Bryant K, McDonald LC. *Clostridium difficile* infections in children. *Pediatr Infect Dis J*. 2009;28(2):145–6.
- Byington CL, Castillo H, Gerber K, et al. The effect of rapid respiratory viral diagnostic testing on antibiotic use in a children's hospital. *Arch Pediatr Adolesc Med*. 2002;156:1230–4.
- Cavalheiro S, Lopez A, Serra S, Da Cunha A, da Costa MDS, Moron A, Lederman HM. Microcephaly and Zika virus: neonatal neuroradiological aspects. *Childs Nerv Syst*. 2016;32:1057–60.
- Centers for Disease Control and Prevention (2015) Measles cases and outbreaks. <http://www.cdc.gov/measles/cases-outbreaks.html>. Accessed 10 Jul 2016.
- Centers for Disease Control and Prevention. Zika virus: transmission and risks. 2016a. <https://www.cdc.gov/zika/transmission/index.html> Accessed 12 Jul 2016.
- Centers for Disease Control and Prevention. 2016b Zika virus: symptoms, diagnosis, & treatment. <https://www.cdc.gov/zika/symptoms/index.html> Accessed 12 Jul 2016.
- Centers for Disease Control and Prevention. 2016c Zika and Guillain-Barré syndrome. <http://www.cdc.gov/zika/about/gbs-qa.html> Accessed 12 Jul 2016.
- Centers for Disease Control and Prevention. Zika virus: clinical guidance. 2016d. <http://www.cdc.gov/zika/hc-providers/clinical-guidance.html> Accessed 12 Jul 2016.
- Centers for Disease Control and Prevention (CDC). Human papillomavirus vaccination coverage among adolescent girls, 2007–2012, and postlicensure vaccine safety monitoring, 2006–2013 – United States. *MMWR Morb Mortal Wkly Rep*. 2013;62(29):591–5.
- Centers for Disease Control and Prevention (CDC). Core elements of hospital antibiotic stewardship programs. 2014. <http://www.cdc.gov/getsmart/healthcare/pdfs/core-elements.pdf>. Accessed 10 Jul 2016.
- Chatterjee A. The next generation of HPV vaccines: nonavalent vaccine V503 on the horizon. *Expert Rev Vaccines*. 2014;13(11):1279–90.

- Chiem AT. Infectious disease/CDC update. Measles outbreak – California, December 2014–February 2015. *Ann Emerg Med*. 2015;66(1):82–3.
- Chiu CH, Michelow IC, Cronin J, Ringer SA, Ferris TG, Puopolo KM. Effectiveness of a guideline to reduce vancomycin use in the neonatal intensive care unit. *Pediatr Infect Dis J*. 2011;30:273–8.
- Christensen H, May M, Bowen L, Hickman M, Trotter CL. Meningococcal carriage by age: a systematic review and meta-analysis. *Lancet Infect Dis*. 2010;10(12):853–61.
- Clemmons NS, Gastanaduy PA, Fiebelkorn AP, Redd SB, Wallace GS; Centers for Disease Control and Prevention (CDC). Measles – United States, January 4–April 2, 2015. *MMWR Morb Mortal Wkly Rep*. 2015;64(14):373–6.
- Cohen SH, Gerding DN, Johnson S, et al. Society for Healthcare Epidemiology of America; Infectious Diseases Society of America. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). *Infect Control Hosp Epidemiol*. 2010;31(5):431–55.
- Communicable Diseases Network Australia: Commonwealth Department of Health and Ageing. Guidelines for the early clinical and public health management of meningococcal disease in Australia. Revised ed. Canberra, ACT: Communicable Diseases Network Australia: Commonwealth Department of Health and Ageing; 2007.
- Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, Carmeli Y. Comparison of mortality associated with methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* bacteremia: a meta-analysis. *Clin Infect Dis*. 2003;36(1):53–9.
- Crobach MJ, Dekkers OM, Wilcox MH, Kuijper EJ. European Society of Clinical Microbiology and Infectious Diseases (ESCMID): data review and recommendations for diagnosing *Clostridium difficile*-infection (CDI). *Clin Microbiol Infect*. 2009;15(12):1053–66.
- Delbos V, Lemée L, Bénichou J, Berthelot G, Taha M, Caron F, B14 STOP Study Group. Meningococcal carriage during a clonal meningococcal B outbreak in France. *Eur J Clin Microbiol Infect Dis*. 2013;32:1451–9.
- Di Pentima MC, Chan S, Hossain J. Benefits of a pediatric antimicrobial stewardship program at a children's hospital. *Pediatrics*. 2011;128:1062–70.
- Doan QH, Kissoon N, Dobson S, et al. A randomized, controlled trial of the impact of early and rapid diagnosis of viral infections in children brought to an emergency department with febrile respiratory tract illnesses. *J Pediatr*. 2009;154:91–5.
- Donnelly J, Medini D, Boccadifuoco G, Biolchi A, Ward J, Frasch C, et al. Qualitative and quantitative assessment of meningococcal antigens to evaluate the potential strain coverage of protein-based vaccines. *Proc Natl Acad Sci U S A*. 2010;107(45):19490–5.
- Drolet M, Bénard É, Boily MC, et al. Population-level impact and herd effects following human papillomavirus vaccination programmes: a systematic review and meta-analysis. *Lancet Infect Dis*. 2015;15(5):565–80.
- Durand C, Brueckner A, Sampadian C, Willett KC, Belliveau P. Daptomycin use in pediatric patients. *Am J Health Syst Pharm*. 2014;71(14):1177–82.
- Enoch DA, Butler MJ, Pai S, Aliyu SH, Karas JA. *Clostridium difficile* in children: colonisation and disease. *J Infect*. 2011;63(2):105–13.
- European Centre for Disease Prevention and Control. Surveillance of invasive bacterial diseases in Europe 2008/2009. Stockholm: ECDC; 2011.
- Findlow J. Meningococcal group B vaccines. *Hum Vaccin Immunother*. 2013;9(6):1387–8.
- Fishman N. Policy statement on antimicrobial stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Diseases Society (PIDS). *Infect Control Hosp Epidemiol*. 2012;33:322–7.
- Folaranmi T, Rubin L, Martin SW, Patel M, JR MN, Centers for Disease Control (CDC). Use of Serogroup B meningococcal vaccines in persons aged ≥ 10 years at increased risk for serogroup b meningococcal disease: recommendations of the Advisory Committee on Immunization Practices, 2015. *MMWR Morb Mortal Wkly Rep*. 2015;64(22):608–12.
- Forman D, de Martel C, Lacey CJ, et al. Global burden of human papillomavirus and related diseases. *Vaccine*. 2012;20(Suppl 5):F12–23.
- Fowler KB, Boppana SB. Congenital cytomegalovirus (CMV) infection and hearing deficit. *J Clin Virol*. 2006;35:226–31.
- FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med*. 2007;356(19):1915–27.
- Gerber JS, Coffin SE, Smathers SA, Zaoutis TE. Trends in the incidence of methicillin resistant *Staphylococcus aureus* infection in children's hospitals in the United States. *Clin Infect Dis*. 2009;49(1):65–71.
- Goldenberg JZ, Ma SSS, Saxton JD, Martzen MR, Vandvik PO, Thorlund K, Guyatt GH, Johnston BC. Probiotics for the prevention of *Clostridium difficile*-associated diarrhea in adults and children. *Cochrane Database Syst Rev*. 2013;5:CD006095.
- Gostelow M, Gonzalez D, Smith PB, Cohen-Wolkowicz M. Pharmacokinetics and safety of recently approved drugs used to treat methicillin-resistant *Staphylococcus aureus* infections in infants, children and adults. *Expert Rev Clin Pharmacol*. 2014;7(3):327–40.
- Grosse SD, Ross DS, Dollard SC. Congenital cytomegalovirus (CMV) infection as a cause of permanent bilateral hearing loss: a quantitative assessment. *J Clin Virol*. 2008;41:57–62.
- Hall IC, O'Toole E. Intestinal flora in new-born infants: with a description of a new pathogenic anaerobe, *Bacillus difficilis*. *Am J Dis Child*. 1935;49:390–402.
- Halperin SA, Bettinger JA, Greenwood B, Harrison LH, Jelfs J, Ladhani SN, et al. The changing and dynamic

- epidemiology of meningococcal disease. *Vaccine*. 2012;30(suppl 2):B26–36.
- Halsey NA, Salmon DA. Measles at Disneyland, a problem for all ages. *Ann Intern Med*. 2015;162(9):655–6.
- Hamborsky J, Kroger A, Wolfe S, editors. Measles: epidemiology and prevention of vaccine-preventable diseases (the pink book). 13th ed. Washington, DC: Public Health Foundation; 2015.
- Harrison L, Trotter C, Ramsay M. Global epidemiology of meningococcal disease. *Vaccine*. 2009;27S:B51–63.
- Herigon JC, Hersh AL, Gerber JS, Zaoutis TE, Newland JG. Antibiotic management of *Staphylococcus aureus* infections in US children's hospitals, 1999–2008. *Pediatrics*. 2010;125(6):e1294–300.
- Iwamoto M, Mu Y, Lynfield R, Bulens SN, Nadle J, Aragon D, Petit S, Ray SM, Harrison LH, Dumyati G, Townes JM, Schaffner W, Gorwitz RJ, Lessa FC. Trends in invasive methicillin-resistant *Staphylococcus aureus* infections. *Pediatrics*. 2013;132(4):e817–24.
- Jafri R, Ali A, Messonnier N, Tevi-Benissan C, Durrheim D, Eskola J, et al. Global epidemiology of invasive meningococcal disease. *Popul Health Metrics*. 2013;11:17.
- Jangi S, Lamont JT. Asymptomatic colonization by *Clostridium difficile* in infants: implications for disease in later life. *J Pediatr Gastroenterol Nutr*. 2010;51(1):2–7.
- Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA Cancer J Clin*. 2011;61(2):69–90.
- Jennings LC, Skopnik H, Burckhardt I, Hribar I, Del Piero L, Deichmann KA. Effect of rapid influenza testing on the clinical management of paediatric influenza. *Influenza Other Respir Viruses*. 2009;3:91–8.
- Joura EA, Giuliano AR, Iversen OE, et al. Broad Spectrum HPV Vaccine Study. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. *N Engl J Med*. 2015;372(8):711–23.
- Kadmon G, Levy I, Mandelboim M, et al. Polymerase-chain-reaction-based diagnosis of viral pulmonary infections in immunocompromised children. *Acta Paediatr*. 2013;102:e263–8.
- Kaplan SL, Hulten KG, Gonzalez BE, et al. Three-year surveillance of community acquired *Staphylococcus aureus* infections in children. *Clin Infect Dis*. 2005;40(12):1785–91.
- Katz SL, Hinman AR. Summary and conclusions: measles elimination meeting, 16–17 March 2000. *J Infect Dis*. 2004;189(Suppl 1):S43–7.
- Khalaf N, Crews JD, DuPont HL, Koo HL. *Clostridium difficile*: an emerging pathogen in children. *Discov Med*. 2012;14(75):105–13.
- Kim J, Smathers SA, Prasad P, Leckerman KH, Coffin S, Zaoutis T. Epidemiological features of *Clostridium difficile*-associated disease among inpatients at children's hospitals in the United States, 2001–2006. *Pediatrics*. 2008;122(6):1266–70.
- Kimberlin DW, Lin CY, Sánchez PJ, et al. Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. *J Pediatr*. 2003;143:16–25.
- Kimberlin DW, Acosta EP, Sánchez PJ, et al. Pharmacokinetic and pharmacodynamics assessment of oral valganciclovir in the treatment of symptomatic congenital cytomegalovirus disease. *J Infect Dis*. 2008;197:836–45.
- Kimberlin DW, Jester PM, Sánchez PJ, Ahmed A, Arav-Boger R, Michaels MG, Ashouri N, Englund JA, Estrada B, Jacobs RF, Romero JR, Sood SK, Whitworth MS, Abzug MJ, Caserta MT, Fowler S, Lujan-Zilbermann J, Storch GA, RL DB, Han JY, Palmer A, Weiner LB, Bocchini JA, Dennehy PH, Finn A, Griffiths PD, Luck S, Gutierrez K, Halasa N, Homans J, Shane AL, Sharland M, Simonsen K, Vanchiere JA, Woods CR, Sabo DL, Aban I, Kuo H, James SH, Prichard MN, Griffin J, Giles D, Acosta EP, Whitley RJ, National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Valganciclovir for symptomatic congenital cytomegalovirus disease. *N Engl J Med*. 2015;372(10):933–43.
- Klebens RM, Morrison MA, Nadle J, et al. Active Bacterial Core surveillance (ABCs) MRSA Investigators. Invasive methicillin resistant *Staphylococcus aureus* infections in the United States. *JAMA*. 2007;298(15):1763–71.
- Larson DA, Derkey CS. Epidemiology of recurrent respiratory papillomatosis. *APMIS*. 2010;118(6–7):450–4.
- Lessa FC, Edwards JR, Fridkin SK, Tenover FC, Horan TC, Gorwitz RJ. Trends in incidence of late-onset methicillin-resistant *Staphylococcus aureus* infection in neonatal intensive care units: data from the National Nosocomial Infections Surveillance System, 1995–2004. *Pediatr Infect Dis J*. 2009;28(7):577–81.
- Li R, Lu L, Lin Y, Wang M, Liu X. Efficacy and safety of metronidazole monotherapy versus vancomycin monotherapy or combination therapy in patients with *Clostridium difficile* infection: a systematic review and meta-analysis. *PLoS One*. 2015;10(10):e0137252.
- Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis*. 2011;52(3):e18–55.
- MacNeil JR, Rubin L, Folaranmi T, Ortega-Sanchez IR, Patel M, Martin SW. Use of Serogroup B meningococcal vaccines in adolescents and young adults: recommendations of the Advisory Committee on Immunization Practices, 2015. *MMWR Morb Mortal Wkly Rep*. 2015;64(41):1171–6.
- Majumder MS, Cohn EL, Mekar SR, Huston JE, Brownstein JS. Substandard vaccination compliance and the 2015 measles outbreak. *JAMA Pediatr*. 2015;169(5):494–5.
- Manicklal S, Emery VC, Lazzarotto T, Boppana SB, Gupta RK. The “silent” global burden of congenital cytomegalovirus. *Clin Microbiol Rev*. 2013;26:86–102.
- Markowitz LE, Hariri S, Lin C, et al. Reduction in human papillomavirus (HPV) prevalence among

- young women following HPV vaccine introduction in the United States, National Health and Nutrition Examination Surveys, 2003–2010. *J Infect Dis*. 2013;208(3):385–93.
- Markowitz LE, Dunne EF, Saraiya M, et al. Centers for Disease Control and Prevention (CDC). Human papillomavirus vaccination: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2014;63(RR-05):1–30.
- Markowitz LE, Liu G, Hariri S, Steinau M, Dunne EF, Unger ER. Prevalence of HPV after introduction of the vaccination program in the United States. *Pediatrics*. 2016;137(3):e20151968.
- McCarthy M. US sees first measles death in 12 years. *BMJ*. 2015;351:h3653.
- McKamy S, Chen T, Lee M, Ambrose PJ. Evaluation of a pediatric continuous infusion vancomycin therapy guideline. *Am J Health Syst Pharm*. 2012;69:2066–71.
- Meshor D, Soldan K, Howell-Jones R, et al. Reduction in HPV 16/18 prevalence in sexually active young women following the introduction of HPV immunisation in England. *Vaccine*. 2013;32:26–32.
- Metjian TA, Prasad PA, Kogon A, Coffin SE, Zaoutis TE. Evaluation of an antimicrobial stewardship program at a pediatric teaching hospital. *Pediatr Infect Dis J*. 2008;27:106–11.
- Morinville V, McDonald J. *Clostridium difficile*-associated diarrhea in 200 Canadian children. *Can J Gastroenterol*. 2005;19:497–501.
- Morris O, Tebruegge M, Pallett A, Green SM, Pearson AD, Tuck A, Clarke SC, Roderick P, Faust SN. *Clostridium difficile* in children: a review of existing and recently uncovered evidence. *Adv Exp Med Biol*. 2013;764:57–72.
- Mullett CJ, Evans RS, Christenson JC, Dean JM. Development and impact of a computerized pediatric anti-infective decision support program. *Pediatrics*. 2001;108:E75.
- Murki S, Jonnala S, Mohammed F, Reddy A. Restriction of cephalosporins and control of extended spectrum beta-lactamase producing gram negative bacteria in a neonatal intensive care unit. *Indian Pediatr*. 2010;47:785–8.
- Newland JG, Stach LM, DeLurgio SA, et al. Impact of a prospective-audit-with feedback antimicrobial stewardship program at a children's hospital. *J Pediatr Infect Dis*. 2012;1:179–86.
- Newman RE, Hedican EB, Herigon JC, Williams DD, Williams AR, Newland JG. Impact of a guideline on management of children hospitalized with community acquired pneumonia. *Pediatrics*. 2012;129:e597–604.
- Nolan T, O'Ryan M, Wassil J, Abitbol V, Dull P. Vaccination with a multicomponent meningococcal B vaccine in prevention of disease in adolescents and young adults. *Vaccine*. 2015;33(36):4437–45.
- Novartis Vaccines and Diagnostics Inc. Bexsero [package insert]. Cambridge, MA: Novartis Vaccines and Diagnostics Inc; 2015. <http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM431447.pdf>. Accessed 11 Jul 2016
- Nylund CM, Goudie A, Garza JM, Fairbrother G, Cohen MB. *Clostridium difficile* infection in hospitalized children in the United States. *Arch Pediatr Adolesc Med*. 2011;165(5):451–7.
- Oliver SE, Cloud GA, Sánchez PJ, et al. Neurodevelopmental outcomes following ganciclovir therapy in symptomatic congenital cytomegalovirus infections involving the central nervous system. *J Clin Virol*. 2009;46(Suppl 4):S22–6.
- Omer SB, Richards JL, Ward M, Bednarczyk RA. Vaccination policies and rates of exemption from immunization, 2005–2011. *N Engl J Med*. 2012;367(12):1170–1.
- Paavonen J, Jenkins D, Bosch FX, et al. HPV PATRICIA study group. Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial. *Lancet*. 2007;369(9580):2161–70.
- Pakakasama S, Surayuthprecha K, Pandee U, et al. Clinical practice guidelines for children with cancer presenting with fever to the emergency room. *Pediatr Int*. 2011;53:902–5.
- Panatto D, Amicizia D, Lai PL, Gasparini R. *Neisseria meningitidis* B vaccines. *Expert Rev Vaccines*. 2011;9:1337–51.
- Pant C, Deshpande A, Altaf MA, Minocha A, Sferra TJ. *Clostridium difficile* infection in children: a comprehensive review. *Curr Med Res Opin*. 2013;29(8):967–84.
- Patel SJ, Saiman L. Principles and strategies of antimicrobial stewardship in the neonatal intensive care unit. *Semin Perinatol*. 2012;36:431–6.
- Pendleton A, Kocher MS. Methicillin-resistant *Staphylococcus aureus* bone and joint infections in children. *J Am Acad Orthop Surg*. 2015;23(1):29–37.
- Perrett KP, McVernon J, Richmond PC, Marshall H, Nissen M, August A, Percell S, Toneatto D, Nolan T. Immune responses to a recombinant, four-component, meningococcal serogroup B vaccine (4CMenB) in adolescents: a phase III, randomized, multicentre, lot-to-lot consistency study. *Vaccine*. 2015;33(39):5217–24.
- Petersen E, Wilson ME, Touch S, McCloskey B, Mwaba P, Bates M, Dar O, Mattes F, Kidd M, Ippolito G, Azhar EI, Zumla A. Rapid spread of Zika virus in the Americas—implications for public health preparedness for mass gatherings at the 2016 Brazil Olympic Games. *Int J Infect Dis*. 2016;44:11–5.
- Peterson LR, Manson RU, Paule SM, Hacek DM, Robicsek A, Thomson RB Jr, Kaul KL. Detection of toxigenic *Clostridium difficile* in stool samples by real-time polymerase chain reaction for the diagnosis of *C. difficile*-associated diarrhea. *Clin Infect Dis*. 2007;45:1152–60.
- Phadke VK, Bednarczyk RA, Salmon DA, Omer SB. Association between vaccine refusal and vaccine-preventable diseases in the United States: a review of measles and pertussis. *JAMA*. 2016;315(11):1149–58.
- Plosa EJ, Esbensen JC, Fuller MP, Weitkamp JH. Cytomegalovirus infection. In: Kimberlin DW, Brady

- MT, Jackson MA, Long SS, editors. Red Book: 2015 report of the Committee on Infectious Diseases. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015. p. 317–22.
- Pohl JF, Patel R, Zobell JT, Lin E, Korgenski EK, Crowell K, Mackay MW, Richman A, Larsen C, Chatfield BA. *Clostridium difficile* infection and proton pump inhibitor use in hospitalized pediatric cystic fibrosis patients. *Gastroenterol Res Pract*. 2011;2011:1–4.
- Reagan-Steiner S, Yankey D, Jeyarajah J, Elam-Evans LD, Singleton JA, Curtis CR, MacNeil J, Markowitz LE, Stokley S. national, regional, state, and selected local area vaccination coverage among adolescents aged 13–17 years—United States, 2014. *MMWR Morb Mortal Wkly Rep*. 2015;64(29):784–92.
- Roche Pharmaceuticals. Valganciclovir package insert. Clifton, NJ: Roche Pharmaceuticals; 2001. http://www.accessdata.fda.gov/drugsatfda_docs/label/2001/21304lbl.pdf. Accessed 13 Jul 2016
- Roth A, Mercier A, Lepers C, Hoy D, Duituturaga S, Benyon E, Guillaumot L, Souarès Y. Concurrent outbreaks of dengue, chikungunya and Zika virus infections – an unprecedented epidemic wave of mosquito-borne viruses in the Pacific 2012–2014. *Eur Secur*. 2014;19(41):1–8.
- Rouphael N, Stephens D. *Neisseria meningitidis*: biology, microbiology, and epidemiology. *Methods Mol Biol*. 2012;799:1–20.
- Saini SS, Dutta S, Ray P, Narang A. Short course versus 7-day course of intravenous antibiotics for probable neonatal septicemia: a pilot, open-label, randomized controlled trial. *Indian Pediatr*. 2011;48:19–24.
- Saiz J, Vázquez-Calvo Á, Blázquez AB, Merino-Ramos T, Escribano-Romero E, Martín-Acebes MA. Zika virus: the latest newcomer. *Front Microbiol*. 2016; 7:496.
- Salmon DA, Haber M, Gangarosa EJ, Phillips L, Smith NJ, Chen RT. Health consequences of religious and philosophical exemptions from immunization laws: individual and societal risk of measles. *JAMA*. 1999;282(1):47–53.
- Samady W, Pong A, Fisher E. Risk factors for the development of *Clostridium difficile* infection in hospitalized children. *Curr Opin Pediatr*. 2014;26(5):568–72.
- Sammons JS, Toltzis P. Recent trends in the epidemiology and treatment of *C. difficile* infection in children. *Curr Opin Pediatr*. 2013;25(1):116–21.
- Sammons JS, Toltzis P. Pitfalls in diagnosis of pediatric *Clostridium difficile* infection. *Infect Dis Clin N Am*. 2015;29:465–76.
- Sammons JS, Toltzis P, Zaoutis TE. *Clostridium difficile* infection in children. *JAMA Pediatr*. 2013;167(6):567–73.
- Sandora TJ, Fung M, Flaherty K, Helsing L, Scanlon P, Potter-Bynoe G, Gidengil CA, Lee GM. Epidemiology and risk factors for *Clostridium difficile* infection in children. *Pediatr Infect Dis J*. 2011;30:580–4.
- Schleiss M, Heineman T. C. Progress toward an elusive goal: current status of cytomegalovirus vaccines. *Expert Rev Vaccines*. 2005;4:381–406.
- Schutze GE, Willoughby RE, Committee on Infectious Diseases; American Academy of Pediatrics. *Clostridium difficile* infection in infants and children. *Pediatrics*. 2013;131(1):196–200.
- Seib KL, Scarselli M, Comanducci M, Toneatto D, Maignani V. *Neisseria meningitidis* factor H-binding protein fHbp: a key virulence factor and vaccine antigen. *Expert Rev Vaccines*. 2015;14(6):841–59.
- Soeters HM, McNamara LA, Whaley M, Wang X, Alexander-Scott N, Kanadianian KV, Kelleher CM, MacNeil J, Martin SW, Raines N, Sears S, Vanner C, Vuong J, Bandy U, Sicard K, Patel M, Centers for Disease Control (CDC). Serogroup B meningococcal disease outbreak and carriage evaluation at a college – Rhode Island, 2015. *MMWR Morb Mortal Wkly Rep*. 2015;64(22):606–7.
- Song X, Perencevich E, Campos J, Short BL, Singh N. Clinical and economic impact of methicillin-resistant *Staphylococcus aureus* colonization or infection on neonates in intensive care units. *Infect Control Hosp Epidemiol*. 2010;31(2):177–82.
- Sudenga SL, Royse KE, Shrestha S. Role and uptake of human papillomavirus vaccine in adolescent health in the United States. *Adolesc Health Med Ther*. 2011;2:63–74.
- Sutphen JL, Grand RJ, Flores A, Chang TW, Bartlett JG. Chronic diarrhea associated with *Clostridium difficile* in children. *Am J Dis Child*. 1983;137:275–8.
- Swami SK, Banerjee R. Comparison of hospital-wide and age and location-stratified antibiograms of *S. aureus*, *E. coli*, and *S. pneumoniae*: age- and location-stratified antibiograms. *Spring*. 2013;2:63–7.
- Tabrizi SN, Brotherton JM, Kaldor JM, et al. Fall in human papillomavirus prevalence following a national vaccination program. *J Infect Dis*. 2012;206:1645–51.
- Tan LK, Carlone GM, Borrow R. Advances in the development of vaccines against *Neisseria meningitidis*. *N Engl J Med*. 2010;362:1511–20.
- The White House. National action plan for combating antibiotic-resistant bacteria. 2015. https://www.whitehouse.gov/sites/default/files/docs/national_action_plan_for_combating_antibiotic-resistant_bacteria.pdf. Accessed 10 Jul 2016.
- Toltzis P, Kim J, Dul M, Zoltanski J, Smathers S, Zaoutis T. Presence of the epidemic North American Pulsed Field type 1 *Clostridium difficile* strain in hospitalized children. *J Pediatr*. 2009;154(4):607–8.
- Vardakas KZ, Kontopidis I, Gkegkes ID, Rafailidis PI, Falagas ME. Incidence, characteristics, and outcomes of patients with bone and joint infections due to community-associated methicillin-resistant *Staphylococcus aureus*: a systematic review. *Eur J Clin Microbiol Infect Dis*. 2013;32(6):711–21.
- Walia R, Kunde S, Mahajan L. Fecal microbiota transplantation in the treatment of refractory *Clostridium difficile* infection in children: an update. *Curr Opin Pediatr*. 2014;26(5):573–8.
- Whitney CG, Zhou F, Singleton J, Schuchat A, Centers for Disease Control and Prevention (CDC). Benefits from immunization during the vaccines for children

- program era – United States, 1994–2013. *MMWR Morb Mortal Wkly Rep.* 2014;63(16):352–5.
- Wishaupt JO, Russcher A, Smeets LC, Versteegh FG, Hartwig NG. Clinical impact of RT-PCR for pediatric acute respiratory infections: a controlled clinical trial. *Pediatrics.* 2011;128:e1113–20.
- World Health Organization. The history of Zika virus. Geneva: World Health Organization; 2016a. <http://www.who.int/emergencies/zika-virus/timeline/en/> Accessed 12 Jul 2016
- World Health Organization. Pregnancy management in the context of Zika virus infection: Interim guidance update. Geneva: World Health Organization; 2016b. <http://www.who.int/csr/resources/publications/zika/pregnancy-management/en/> Accessed 12 Jul 2016
- World Health Organization (WHO). Meningococcal vaccines: WHO position paper, November 2011. *Wkly Epidemiol Rec.* 2011;86(47):521–39.
- Wyeth Pharmaceuticals Inc. Trumenba [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals Inc. (Pfizer); 2014. <http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM421139.pdf>. Accessed 11 Jul 2016
- Yang YT, Barraza L, Weidenaar K. Measles outbreak as a catalyst for stricter vaccine exemption legislation. *JAMA.* 2015;314(12):1229–30.
- Zilberberg MD, Tillotson GS, McDonald C. *Clostridium difficile* infections among hospitalized children, United States, 1997–2006. *Emerg Infect Dis.* 2010;16(4):604–9.
- Zingg W, Pfister R, Posfay-Barbe KM, Huttner B, Touveneau S, Pittet D. Secular trends in antibiotic use among neonates: 2001–2008. *Pediatr Infect Dis J.* 2011;30:365–70.
- Zipprich J, Winter K, Hacker J, Xia D, Watt J, Harriman K, Centers for Disease Control and Prevention (CDC). Measles outbreak—California, December 2014–February 2015. *MMWR Morb Mortal Wkly Rep.* 2015;64(6):153–4.



Update in Clinical Genetics and Metabolics

14

Christine M. Armour and Matthew A. Lines

Clinical genetics has undergone unprecedented change in recent years. The increasing sophistication of molecular genetic testing, together with the accelerating tempo of disease gene discovery, has led to greatly enhanced rates of successful clinical diagnosis. New and powerful techniques such as whole-exome sequencing have made it possible to efficiently catalogue most of the protein-coding genetic variation in an individual. At the same time, a great deal has been learned about the clinical spectra of many genetic syndromes; in particular, mild or non-classical presentations of many disorders are becoming increasingly recognized. The field of Metabolics has also advanced due to the increasingly widespread adoption of mass-spectrometry-based expanded newborn screening programs, allowing earlier detection of many treatable metabolic disorders. The role of transplantation, both of solid organs and of hematopoietic stem cells, has continued to expand, as have the roles of enzyme replacement, small-molecule therapy, and novel targeted therapies for many classic genetic disorders.

C.M. Armour, M.D., M.Sc., F.R.C.P.C (✉)
Regional Genetics Unit, Children's Hospital
of Eastern Ontario, 401 Smyth Road, Ottawa,
ON K1H 8L1, Canada
e-mail: carmour@cheo.on.ca

M.A. Lines, M.D, F.R.C.P.C., F.C.C.M.G
Metabolics, Department of Pediatrics, Children's
Hospital of Eastern Ontario, 401 Smyth Road,
Ottawa, ON K1H 8L1, Canada
e-mail: mllines@cheo.on.ca

Updates in Clinical Genetics

The advent of improved genetic testing methods has dramatically changed the landscape of testing options available in the genetics clinic, providing improved rates of diagnosis and providing new insights into many rare conditions. Given the increasing diagnostic power of genetic testing, these techniques seem poised to gradually transition into primary care; providers will need to become more familiar with the capabilities and limitations of these tests.

New test methods that have been developed over recent years include:

1. *High resolution chromosomal microarray* (also called *array comparative genomic hybridization*, aCGH): This test uses a chip technology to assess all of a patient's chromosomes for missing (deleted) or extra (duplicated) material.
2. Massively parallel DNA sequencing, also called *Next Generation Sequencing (NGS)*: These techniques allow tremendous amounts of DNA sequence to be read simultaneously, permitting the simultaneous testing of many genes with high accuracy and efficiency. NGS-based tests include 'gene panel' tests (genes grouped together by common phenotype, e.g. genes associated with ciliopathies or intellectual disability) and *whole-exome sequencing (WES)*, which attempts to read the coding regions of all or most protein-coding genes. WES has recently become

available in some jurisdictions. *Whole-genome sequencing* (WGS) is available primarily on a research basis.

As with any test, it is essential that the fundamentals of these tests are understood prior to applying them in patient care. Consideration should be given to appropriate clinical indications, limitations of the test, and the uncommon, but real chance of *incidental findings*. Incidental findings (also referred to as *secondary findings*) are highly predictive of a medically actionable condition, but are *unrelated* to the primary indication for testing. One example of an *incidental finding* could be the detection of a mutation for an adult-onset cancer predisposition (e.g. *BRCA1* mutation) when ordering a test for developmental delay. Further details on specific technologies are discussed below.

Chromosomal Microarray

Chromosomal microarray (CMA) has become an integral tool in the first line of investigations for a number of common clinical presentations, such as developmental delay/intellectual disability, autism spectrum disorders and congenital anomalies in many jurisdictions (Miller et al. 2010; Michelson et al. 2011; Moeschler et al. 2014). As described above, the term ‘chromosomal microarray’ refers to a group of technologies that allows detailed analysis of chromosomes to assess for duplicated or deleted segments of chromosome. Such duplications or deletions are referred to as ‘copy number variants’ (CNVs).

Chromosome variants may be either *benign* (without medical significance) or *pathogenic* (disease-causing), and this distinction is not always straightforward. The gene content and location of the CNV are important factors in assessing its pathogenicity. Many smaller CNVs may be found in healthy individuals. On the other hand, CNVs may be the clear cause of the presenting complaints (e.g. the microdeletion responsible for 22q11.2 microdeletion syndrome). Other CNVs are variable in their *expressivity* (severity of

symptoms) and/or *penetrance* (likelihood of causing any symptoms). To aid in interpretation of the results, the reporting clinical laboratory provides an interpretation of any findings, classifying each CNV as one of: pathogenic, a *variant of unknown significance* (VOUS), or likely benign. Common, or relatively common, benign CNVs are not usually reported. Reporting standards vary by jurisdiction.

Pathogenic copy number variants (deletions or duplications) are thought to account for approximately 8–20% of the cases of global developmental delay and/or multiple congenital anomalies (Michelson et al. 2011; Miller et al. 2010).

The main advantage of CMA over conventional karyotyping is the ability to detect much smaller deletions or duplications. For example, depending on the specific type of array used, CMA may detect CNVs above 40–100 kilobases (kb) in size, whereas traditional karyotype typically detects only changes above 4–6 megabases (Mb). As with traditional karyotypes, complete trisomy or loss of an entire chromosome (e.g. trisomy 18 or Turner syndrome), are also detected by CMA.

There are some important limitations of CMA:

1. CMA cannot detect *balanced* rearrangements (those which produce no net loss or gain of chromosomal material). Practically speaking, this is not typically of major concern in the evaluation of patients with intellectual disability, autism or MCA.
2. Arrays are not a sensitive method for assessing mosaicism, particularly mosaicism below approximately 20–30% (Miller et al. 2010).
3. Like karyotypes, CMA does not inspect individual genes in detail, and will not detect single point mutations, trinucleotide repeat expansions, or very small deletions/duplications below the resolution of the CMA. Other technologies are required for this level of detail.

The two most commonly-used array types are *oligonucleotide* arrays and the *single nucleotide polymorphism* (SNP) arrays, the latter being the more commonly used in many laboratories at present. While both types of array can provide information about CNVs, SNP arrays also have the advantage of highlighting genomic intervals which are homozygous (i.e. where both maternal and paternal chromosomes contain identical material). SNP analysis is useful in the detection of uniparental disomy (which may lead to imprinting disorders), parental consanguinity, and triploidy (in which an individual has three sets of all chromosomes); such information cannot be obtained from oligonucleotide array. Many laboratories will report the loss of heterozygosity (LOH) in terms of the amount and location that is identified. The ordering provider should be aware of the type of array being used so that they understand the limits and information gained.

While the reason for offering CMA to a patient remains identification of the cause of the phenotype, it is imperative to be aware of the other types of findings that may arise, so that the patient/parents/guardians are appropriately counselled so that they are adequately informed prior to deciding on proceeding, or not. This may become relevant for example for insurance purposes.

Incidental findings are occasionally identified on CMA. Rates vary by study, but incidental findings may occur in approximately 0.3–1.0% of cases (Pichert et al. 2011; Boone et al. 2013). Examples of incidental findings on CMA could include detection of a deletion encompassing a cancer-predisposition gene, or identification of a heterozygous deletion in the *DMD* gene in a female, implying that her male offspring would be at risk of Duchenne muscular dystrophy. When ordering an array, pre-test counselling should include the possibility of incidental finding(s), and the potential outcomes of information found (e.g. insurance discrimination). Although obvious, it bears mention that the individual tested should be the affected individual, rather than an asymptomatic relative (e.g. parent).

Pre-test and post-test counselling should include (but is not limited to):

- A brief explanation of what the test can and cannot detect (e.g. segments of chromosomes but not gene level data)
- The likelihood of identifying a pathogenic finding, which varies by indication
- The likelihood of identifying an incidental finding
- The implication of an incidental finding in your jurisdiction (e.g. insurance bias)
- Whether or not one is able to ‘opt out’ of incidental findings
- Follow up testing that may be indicated, as in the case of variants of uncertain significance
- Overall benefits and drawbacks of testing

Sequencing-Based Technologies

General Principles

Next Generation Sequencing (NGS) is a high-throughput sequencing technology that allows many millions of molecules of DNA to be amplified and analyzed in a shorter time frame than earlier methods (e.g. Sanger sequencing). The volume of data from NGS is orders of magnitude greater than from earlier forms of genetic testing. With this comes the need for better bioinformatic methods to interpret the many thousands of genetic variants potentially observed in a given patient. There are a number of general principles that ought to be considered when ordering a NGS based test, many of which are similar to those described for CMA. As for other tests in medicine, if unfamiliar with the test methods and/or its interpretation, it is often better not to order the test, and to instead refer the patient.

Appropriate use

1. An important current principle is that of limiting sequencing to testing of Mendelian conditions (single gene). At present, the clinical utility of performing genetic testing for apparently multifactorial conditions (e.g.

hypertension, myocardial infarction) has not been established (Boycott et al. 2015).

2. For single-gene disorders, it is appropriate to analyze the pertinent gene individually, as opposed to using a broader test (e.g. panel). However, as the cost of sequencing decreases, and bioinformatics methods improve, this may become less of an issue.
3. As the number of genes examined increases, the likelihood of incidental findings and/or variants of unclear significance also increases.

Sorting natural variation from pathogenicity

In interpreting NGS data, it is important to appreciate that there is significant natural variation amongst humans at the level of DNA sequence, and only a very small proportion of this variation is clinically relevant (Cooper and Shendure 2011). In making its interpretation, the laboratory must select only those few variants which are likely to be disease-causing, from this enormous natural background variation. Non-specialists and patients commonly over-ascribe clinical significance to reported variants which may or may not be meaningful.

Limitations

A critical limitation of NGS is that some types of genetic alterations (large deletions or duplications, trinucleotide repeats, etc.) cannot be easily detected. Examples of relevant conditions that would not be detected using current NGS methods include chromosomal disorders in general, Fragile X syndrome, and Myotonic Dystrophy, among many others. Diseases with multiple genetic etiologies, such as with Angelman syndrome (which can arise from deletions, uniparental disomy, or single gene changes), may or may not be detected.

The reliability of an NGS result depends on several technical factors. The regions targeted for sequencing (e.g. the genes of interest) may or may not be covered in their entirety, and/or the *depth* of coverage (the average number of sequence 'reads' corresponding to a given region) may or may not be adequate to ensure that mutations are successfully identified (Sims et al. 2014). For example, if 99% of the target is covered to an average depth of 20-fold, this indicates that 99% of the DNA bases in the gene have been sequenced at least 20 times. The remaining 1% of base pairs have been

sequenced fewer than 20 times, and may contain mutations which have gone undetected.

Appropriate pre- and post-test counselling

The counselling for NGS is similar to that for CMA, with the addition of details pertinent to the level of DNA sequence.

Pre-test and post-test counselling for NGS-based testing should include (but is not limited to):

- Overall benefits and drawbacks of testing
- A brief explanation of what the test can and cannot detect
- The likelihood of identifying a pathogenic finding (odds of a diagnostic test result), which varies by indication
- The possibility of one or more incidental finding(s)
- Whether or not one is able to 'opt out' of incidental findings

Follow-up testing that may be indicated, as in the case of variants of uncertain significance.

Pre-test and post-test counselling for NGS-based testing should include (but is not limited to):

- Overall benefits and drawbacks of testing
- A brief explanation of what the test can and cannot detect
- The likelihood of identifying a pathogenic finding (odds of a diagnostic test result), which varies by indication
- The possibility of one or more incidental finding(s)
- Whether or not one is able to 'opt out' of incidental findings
- Follow-up testing that may be indicated, as in the case of variants of uncertain significance.

Types of Applications

There are a number of ways in which NGS can be used to examine genes. The two principal clinical

uses are ‘gene panels’, which are in use in many laboratories for a wide variety of indications, and whole-exome sequencing (WES), which is offered by an increasing number of laboratories worldwide.

Gene Panels

Multiple genes associated with similar phenotypes are often co-analyzed as part of an NGS panel. One such example is the Noonan syndrome spectrum, which is caused by mutations of several genes in a common biological pathway, the RAS/mitogen-activated protein kinase (Ras/MAPK) signalling pathway (reviewed in Aoki et al. 2016). There are numerous gene panels for many different phenotypes available through many academic and commercial laboratories.

Panels vary in their contents, and ‘more is not always better’; when ordering, one should be aware of the genes included on the panel, and consider if they are all well-associated with the condition. Some laboratories include genes that may be only loosely associated with the condition in question. In addition, some panels may ‘lump together’ a variety of phenotypically diverse conditions which would not usually be co-considered clinically. For example, if a investigating a child with apparently non-syndromic hearing loss, some panels may include syndromic forms of hearing loss with other medical implications beyond hearing alone (e.g. a variant of unknown significance in a gene for Alport syndrome may lead to additional screening and/or insurance bias).

“Gene panels are currently best suited to presentations that are relatively specific in regard to their clinical features and do not have very high genetic heterogeneity” (CCMG statement, Boycott et al. 2015).”

Whole-Exome Sequencing (WES)

WES refers to the sequencing of the coding regions (exons) of most or all protein-coding genes (Boycott et al. 2015). Non-coding sequences, such as introns and regulatory regions are not examined.

Often only variants in genes with a known clinical phenotype are reported. It is currently estimated that humans have approximately 19,000–25,000 genes (International Human Genome Sequencing Consortium 2004; Ezkurdia et al. 2014). Of these, current estimates suggest that about 5000 are known to be associated with a condition (OMIM 2016). It is unclear what, if any, clinical importance should be ascribed to variants in genes of unknown function (outside of a research context). WES is a very powerful tool for novel disease gene discovery in the context of research (discussed below). WES has become available for clinical use in some jurisdictions, but access may be limited in some cases by its relatively high present cost.

While very powerful, WES does not diagnose all patients, or even all patients with a Mendelian disorder. Diagnostic yield for the technique depends heavily on numerous factors, such as the clinical presentation, the point in the diagnostic workup at which WES is employed, and the experience and technical capabilities of the laboratory. Importantly, WES is more likely to yield a specific molecular diagnosis when the analysis is carried out as a ‘trio’ of the proband and their biological parents, as parental data enhance the classification of variants in the proband (Retterer et al. 2016).

WES is used primarily for the diagnosis of Mendelian conditions and there is little evidence to support its use for multifactorial conditions. Factors suggestive of a single-gene disorder include family history consistent with Mendelian inheritance (autosomal dominant, autosomal recessive, X-linked recessive, etc.), consanguinity (recessive disorders), familial recurrence, or unusually severe and/or young-onset phenotypes. Some medical conditions (e.g. retinitis pigmentosa) are both heterogeneous and almost exclusively genetic; the yield of WES is likely to be highest in this group (Boycott et al. 2015).

The overall diagnostic yield of WES is often approximately 30%, varying greatly by clinical features and indication (Boycott et al. 2015; Retterer et al. 2016).

Incidental Findings in WES

Incidental or secondary findings are medically relevant results which are unrelated to the clinical indication. At present, there are limited data about the overall rate of incidental findings in WES; estimates in broad groups of patients are in the range of approximately 4.6–6.2% (Lee et al. 2014; Yang et al. 2014; Retterer et al. 2016). Professional bodies have issued statements regarding disclosure of incidental findings; these have been not without controversy, and vary by jurisdiction.

- The European Society of Human Genetics (ESHG) has recommended the analysis of NGS data (the ‘bioinformatic pipeline’) include filtering of known genetic variants with limited or no clinical utility to exclude genetic variants in genes unrelated to the primary indication to minimise inadvertent diagnosis (van El et al. 2013). At the same time, they recommended that if a variant with serious health implications is identified (either for the patient tested or a close relative), it should be reported back to the patient. They also recommended that guidelines around consent for such testing needed to be developed.
- The American College of Medical Genetics (ACMG) detailed a minimum list of 56 genes they deemed medically actionable for which laboratories should report pathogenic variants regardless of the clinical indication for testing (Green et al. 2013). They originally recommended that these 56 genes should be analyzed on all samples undergoing genome-wide sequencing, with mandatory reporting to the ordering clinician. They later amended their recommendations to allow patients to opt-out of receiving such results, or any incidental findings (ACMG 2015).
- The Canadian College of Medical Genetics (CCMG) stated that they do not ‘endorse intentional clinical analysis of disease genes unrelated to the primary indication, even if the results might be medically actionable’,

and recommended that the sequence data be filtered so as to minimize incidental findings (Boycott et al. 2015). They endorsed the ability of consenting adults to decline to be informed, while supporting the disclosure (to parents) of all incidental results in highly-penetrant genes that are medically actionable during childhood.

It behooves physicians ordering NGS-based tests to be well versed in the policies of their jurisdiction, and of the laboratory from which they are ordering the testing, regarding incidental findings, and to convey those to the patient and family accurately during the consent process. Guidelines are likely to continue to evolve as the medical community gains experience with the use of these techniques.

In summary, WES is a powerful technology which is changing the practice of clinical genetics. In using WES, the technical and ethical considerations implicit in its use must be borne in mind. Practitioners making use of WES should be well-acquainted with the technology, its limitations, and the patient’s unique clinical context, prior to deciding whether it is the most appropriate test to offer the patient.

Whole-Genome Sequencing

WGS refers to the sequencing of an almost all of an individual’s genome (Boycott et al. 2015). While WGS yields a great deal more sequence information than even WES, practical applications for WGS are currently few, as the large majority of detected variants reside in non-coding regions (i.e. outside of recognized genes), and are without obvious medical significance. The volume of data generated by WGS is enormous, and manipulation and storage of the data are additional concerns. There are only a few clinical laboratories worldwide offering clinical WGS, and its use is not yet well-integrated into the clinic.

Research Testing

While WES, and to a much lesser degree WGS, has emerged into clinical use in some

jurisdictions, many research studies are ongoing to study the use of these techniques, to apply them in different clinical scenarios, and to share data between multiple institutions in order to accelerate the discovery of novel disease genes. To this end, a research study may be a viable option for some patients, particularly those who may not have access to clinical testing. The Canadian College of Medical Geneticists has also endorsed “the option of having coded or anonymised genome-wide and phenotypic data deposited and stored in an international database to assist in interpretation of genome-wide studies of themselves and other patients” and to “understand the relationship of genome-wide variants found in them and clinical abnormalities” (Boycott et al. 2015).

Management of Genetic Diseases

Although genetic diseases are innate to the individual and have historically been challenging to treat, many genetic conditions do have specific management. At minimum, specific surveillance measures (imaging, specialist clinical surveillance, etc.) and/or developmental supports (physical therapy, occupational therapy, speech/language therapy) exist for many genetic syndromes. Many metabolic disorders have specific dietary or pharmacological treatments, and these are discussed in the metabolics section below. Moreover, a few classical genetic syndromes have in recent years received specific (pathway-directed) small-molecule treatments. Selected examples include:

- Treatment of the *aortopathies* (e.g. Marfan syndrome, Loeys-Dietz syndrome) with β -blockers or angiotensin-converting enzyme inhibitors. Angiotensin II receptor antagonists may mitigate dilatation of the aorta (Lacro et al. 2014).
- Treatment of rapidly growing renal angiolipomas in Tuberous Sclerosis with mTOR inhibitors is now considered clinical first-line therapy (Kingswood et al. 2016).

An exhaustive review of medical therapy for genetic disorders is beyond the scope of this chapter, and the reader is encouraged to refer to the literature on a case-by-case basis, as needed.

Many high-quality resources exist to guide practitioners with respect to the care of patients with genetic syndromes. For example, the American Academy of Pediatrics has produced a series of free online guidelines for health care supervision of a number of more common syndromes such as Fragile X or Williams syndrome (AAP Committee on Genetics 2001; Hersh et al. 2011). Likewise, the National Center for Biotechnology Information (US) hosts a clinically-oriented review series, ‘GeneReviews’, which is a ‘one stop’ shop for diagnosis, management and counseling guidelines for many disorders [<https://www.ncbi.nlm.nih.gov/books/NBK1116/>].

Gene Therapy

In most jurisdictions gene therapy remains in the research realms and/or entering clinical trials. A detailed discussion of gene therapy is beyond the scope of this chapter but specific examples of advancements in gene therapy include:

- recent approval of ‘Strimvelis’, a type of gene therapy approved for Adenosine deaminase (ADA) deficiency which leads to severe combined immune deficiency, by the European Medicines Agency (Hoggatt 2016).
- numerous promising trials are ongoing that trial gene therapy for hemophilia A and B, with more success currently being observed with Hemophilia B (reviewed in Ward and Walsh 2016).

Updates in Metabolics

The human genome encodes thousands of enzymes and transporters, each of which has evolved over evolutionary time to fulfil a specific metabolic role. With that complexity in mind, this section aims to provide a *general* overview of inborn errors of metabolism (IEMs), with emphasis on recent developments in the field. For

greater detail on specific disorders, the reader is referred to any of several encyclopedic references (Valle et al. 2016; Saudubray et al. 2016; Nyhan et al. 2012; Pagon et al. 1993). *Vademecum Metabolicum* is a useful pocket reference which is also available both online and as a free mobile ‘app’ (Zschocke and Hoffmann 2011).

General Clinical Paradigms

IEMs can be roughly divided into two main groups (Table 14.1):

- (a) *Small-molecule disorders of intermediary metabolism.*
- (b) *Organellar diseases.*

In general and with many exceptions, *small-molecule disorders* follow a (sub)acute or episodic course, exhibit relatively nonspecific clinical symptoms and signs, and require use of the biochemical laboratory for diagnosis. In contrast, *organellar diseases* are chronic conditions which often exhibit characteristic clinical

symptoms and signs; recognition is largely clinical, and laboratory tests serve to *confirm* the clinical impression. *Small-molecule disorders* and *organellar diseases* can be further subclassified into ‘families’ of disorders (Tables 14.2 and 14.3, respectively) on the basis of the affected pathway (e.g. ‘urea cycle disorders’, ‘fatty acid oxidation disorders’), and/or the specific laboratory test employed for diagnosis (e.g. ‘organic acidurias’).

‘Small-Molecule’ Disorders

Small-molecule IEMs are characterized by deficiency of an enzyme, enzyme cofactor, or transporter, with a resulting ‘block’ in one or more metabolic pathway(s). This, in turn, results in either (1) toxic accumulation of ‘upstream’ substrate(s), and/or (2) deficiency of the pathway’s ‘downstream’ product(s) (Fig. 14.1). Although some *small-molecule* disorders present with recognizable symptoms and signs, presentations are more typically nonspecific. Some *small-molecule* IEMs present suggestive findings on routine laboratory studies (blood gases, electrolytes, CBC, glucose, lactate, ammonia, etc.);

Table 14.1 General clinical paradigms in metabolism

| | ‘Small-molecule’ disorders | ‘Organellar’ diseases |
|---|--|---|
| Course | Acute or episodic > chronic | Chronic +/- initial normal period |
| Clinical presentation | Nonspecific | Often suggestive or specific |
| ‘Routine’ lab investigations ^a | Often suggestive (when patient symptomatic) (Table 14.4) | Normal or non-specifically abnormal |
| ‘Metabolic’ lab investigations | – ‘Small molecule metabolic screen’ ^b – Specific enzyme or metabolite tests – Genetic testing | – Specific metabolite tests for each condition – Specific enzyme test – Genetic testing |
| Newborn screening | Some disorders targeted | Few disorders targeted |
| Typical treatments | Varies by condition, may include: – Supportive measures – Modified diet – Vitamin/cofactor supplements – Drugs – HSCT – Solid organ (e.g. liver) transplantation | Varies by condition, may include: – Supportive measures – HSCT – ERT – Drugs |

ERT enzyme replacement therapy, *HSCT* hematopoietic stem cell transplantation

^aTypically: Complete blood count, blood gas, electrolytes, glucose, lactate, ammonia (free-flowing venous sample, transport on ice, analyze promptly)

^bTypically: Plasma amino acids, total homocysteine, urine organic acids, plasma acylcarnitine profile, free and total carnitine, other tests as indicated clinically

Table 14.2 Major categories of small-molecule IEMs

| Group | Examples | Typical presentations | Key investigations |
|--|--|--|---|
| Amino acidopathies | PKU Tyrosinemia type I MSUD Homocystinuria (CBS) NKH | Various | Amino acids Homocysteine (CBS) |
| Organic acidurias | 'Classic' OAs (MMA, PA, IVA, etc.) | Acute metabolic crisis, high-anion-gap metabolic acidosis, neutropenia | Urine organic acids Acylcarnitine profile Ammonia |
| | 'Cerebral' OAs (GA-I, Canavan, etc.) | Acute and/or chronic encephalopathy | Brain MRS Urine organic acids Acylcarnitine profile |
| Urea cycle | OTC Citrullinemia (I + II) ASA lyase Arginase deficiency HHH CPS NAGS | Hyperammonemic crises, protein intolerance | Ammonia Plasma amino acids Urine orotic acid |
| Fatty acid oxidation disorders and carnitine shuttle | MCAD VLCAD LCHAD/MTP CPT 1a, CPT 2 CACT MADD/GA2 | Variously, any of: Fasting hypoketotic hypoglycemia, cardiomyopathy, rhabdomyolysis, neuropathy, retinopathy, or multiple organ systems failure | Acylcarnitine profile Free, total carnitine Urine organic acids Beta-hydroxybutyrate Free fatty acids |
| Disorders of vitamin and cofactor metabolism | Cobalamin disorders (several) BTD PDE Biopterin defects Cerebral folate deficiency | Various | Various |
| Carbohydrate disorders | Classical galactosemia | Acute liver failure, gram-negative sepsis | Galactose-1-phosphate GALT activity |
| | HFI | Postprandial hypoglycemia, hepatic injury | Glucose, lactate, uric acid, ALT, AST (when symptomatic) Molecular testing |
| Glycogen storage diseases (excl. Pompe) | GSD I (Von Gierke), III, VI, IX | Predominantly hepatic, e.g. hepatomegaly, fasting intolerance, hypoglycemia with ketosis | Glucose, lactate, triglycerides, uric acid, Abdominal U/S |
| | GSD V (McArdle), VII | Predominantly muscle, e.g. postexertional rhabdomyolysis | CK Non-ischemic forearm test or cycle ergometry |
| | GSD 0 (glycogen synthase) | Postprandial hyperglycemia and fasting hypoglycemia | Molecular testing |
| Porphyrias | AIP PCT EPP | Episodic delirium and/or Cutaneous photosensitivity | Urine PBG and ALA (when obtunded) Plasma, urine, and/or stool porphyrins, or free erythrocyte protoporphyrin |
| Metal metabolism | Menkes disease | Developmental delay, steel-wool hair, cutis laxa, bladder diverticulae | Copper Ceruloplasmin Bladder U/S |

(continued)

Table 14.2 (continued)

| Group | Examples | Typical presentations | Key investigations |
|----------------------------------|-------------------------|--|---|
| Purine and pyrimidine metabolism | Lesch-Nyhan ADA-SCID | Hematological, neurological, and/or joint symptoms | Urine purines, pyrimidines Uric acid |
| Pentose phosphate pathway | G6PD | Hemolytic anemia | G6PD screen |
| Neurotransmitter disorders | Various | Encephalopathy | CNS neurotransmitters |

List is not comprehensive: Only selected disease categories are shown, and only selected ‘classical’ examples are shown for each category. For all disorders, genetic testing may be considered in parallel with other investigations. For brevity, the word ‘deficiency’ has been omitted. ADA-SCID: Adenosine deaminase deficiency/severe combined immunodeficiency; AIP: Acute intermittent porphyria; ALA: delta-aminolevulinic acid; ASA: Argininosuccinic acid; BTM: Biotinidase; CACT: Carnitine-acylcarnitine translocase; CBS: Cystathionine beta-synthase; CPS: Carbamoyl phosphate synthetase; CPT: Carnitine palmitoyltransferase; EPP: Erythropoietic protoporphyria; G6PD: Glucose-6-phosphate dehydrogenase; GA-I: Glutaric aciduria type I; GA-II: Glutaric aciduria type II; GALE: Galactose epimerase; GALT: Galactose-1-phosphate uridylyltransferase; GSD: Glycogen storage disease; HFI: Hereditary fructose intolerance; HHH: Hyperammonemia-hyperornithinemia-homocitrullinuria syndrome; IVA: Isovaleric acidemia; LCHAD: Long chain hydroxyacyl-coA dehydrogenase deficiency; MADD: Multiple acyl-coA dehydrogenase; MCAD: Medium-chain acyl-coA dehydrogenase; MRS: Magnetic resonance spectroscopy; MSUD: Maple syrup urine disease; MMA: Methylmalonic aciduria; MTP: Mitochondrial trifunctional protein deficiency; NAGS: N-acetylglutamate synthase; NKH: Nonketotic hyperglycinemia; OA: Organic aciduria; OTC: Ornithine transcarbamoylase; PA: Propionic acidemia; PBG: Porphobilinogen; PCT: Porphyria cutanea tarda; PDE: Pyridoxine-dependent epilepsy; PKU: Phenylketonuria; VLCAD: Very long-chain acyl-coA dehydrogenase

Table 14.3 Major categories of organellar diseases

| Group | Examples | Typical presentations | Key investigations |
|---------------|---|---|--|
| Mitochondrial | Leigh syndrome Alpers syndrome MELAS MERRF NARP SANDO Kearns-Sayre syndrome Pearson syndrome | High clinical and genetic heterogeneity (Reviewed in Vafai and Mootha 2012) Progressive involvement of one or more highly-oxidative tissues (CNS, retina, peripheral nerves, myocardium, skeletal muscle, pancreatic beta cell, liver, etc.) | Lactate Plasma amino acids (Ala, Pro, Gly) Acylcarnitine profile Urine organic acids GDF-15 (Davis et al. 2016) Consider muscle biopsy ^a |
| | Gaucher type I ^b | Splenomegaly, bruising, short stature with Erlenmeyer flask deformity of tibiae, ‘bone crises’, ‘spleen crises’ | Beta-glucosidase activity in WBCs |
| | CNS sphingolipidoses (e.g. GM1, GM2, NPA/B, MLD, Krabbe, Gaucher types II/III, etc.) | Neurological plateau/regression +/- cherry red macular spots, macrocephaly, hepatosplenomegaly, or implacable crying episodes (Krabbe) | Specific enzyme test in WBCs (most) or fibroblasts (NPA/B) ^c |
| | Mucopolysaccharidoses (e.g. Hurler/MPS I, Hunter/MPS II) Oligosaccharidoses Mucopolysaccharidoses | Dysostosis multiplex, organomegaly, macrocephaly, contractures, coarse features, developmental delay/regression, +/- any of: corneal clouding, cardiac (valvular) disease, angiokeratomata | Urine MPS spot Urine MPS fractionation Urine oligosaccharides |
| | Pompe (GSD II) (infantile form) | Skeletal myopathy with massive myocardial hypertrophy | ECG, echo Acid maltase activity |
| | Neuronal ceroid lipofuscinoses | Retinopathy, seizures, neurological decline | Skin biopsy for EM PPT1, TPP1 enzymologies |
| Cystinosis | Photophobia, proximal renal tubulopathy, rickets | WBC cystine Slit-lamp exam (corneal crystals) Urinalysis, urine amino acids, urine phosphate | |

Table 14.3 (continued)

| Group | Examples | Typical presentations | Key investigations |
|---------------------------------------|--|--|---|
| Peroxisomal | Peroxisomal biogenesis (Zellweger spectrum) D-bifunctional protein ('pseudo-Zellweger') | Hypotonia, dysmorphism (large fontanelle, midface hypoplasia, broad nasal bridge), CNS, hepatic, and renal disease | VLCFAs RBC plasmalogens Bile acids in urine by FAB-MS |
| | X-ALD | Behavioural/cognitive decline, white matter changes, and/or adrenal insufficiency, and/or myelopathy | VLCFAs Head MRI |
| | RCDP | Rhizomelic limb shortening, calcific stippling of epiphyses | RBC plasmalogens |
| Congenital disorders of glycosylation | N-linked CDGs – Type I (endoplasmic reticulum) – Type II (Golgi) | Highly heterogeneous (reviewed in Sparks and Krasnewich 2005) (CGD Ia): Abnormal cutaneous fat pads | Transferrin IEF (not sensitive) N-linked glycans by MS |
| | O-linked CDGs (e.g. Walker-Warburg, Muscle-Eye-Brain) | Neuronal migration defects, congenital myopathy | CK Brain MRI O-linked glycans by MS |
| Lipid disorders | SLO CTX | Various | 7-dehydrocholesterol (SLO) Cholestanol (CTX) |

List is not comprehensive: Only selected disease categories are shown, and only selected 'classical' examples are shown for each category. For all disorders, genetic testing may be considered in parallel with other investigations. For brevity, the word 'deficiency' has been omitted. CDG: Congenital disorder of glycosylation; CK: Creatine kinase; CTX: Cerebrotendinous xanthomatosis; EM: Electron microscopy; FAB: Fast atom bombardment; GDF-15: Growth/Differentiation factor 15; GM1: GM1 gangliosidosis; GM2: GM2 gangliosidosis (Tay-Sachs disease/Sandhoff); IEF: Isoelectric focusing; MELAS: Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes; MERRF: Myoclonic epilepsy with ragged red fibres

MLD: Metachromatic leukodystrophy; MPS: Mucopolysaccharidosis; MS: Mass spectrometry; NARP: Neuropathy, ataxia, and retinitis pigmentosa; NPA/B: Niemann-Pick disease type A/B; PPT1: Protein palmitoylthioesterase-1; RBC: Red blood cells; RCDP: Rhizomelic chondrodysplasia punctata; SANDO: Sensory ataxic neuropathy, dysarthria, and ophthalmoparesis; SLO: Smith-Lemli-Opitz syndrome; TPP1: Tripeptidyl peptidase-1; WBC: White blood cell; X-ALD: X-linked adrenoleukodystrophy

^aOften second-line if genetic panel testing is normal, or first-line if clinical suspicion for large mitochondrial DNA deletion(s) or depletion

^bDistinguished here from the other pediatric-onset sphingolipidoses by lack of CNS involvement (type I only)

^cFalse-positives due to pseudodeficiency are common in the evaluation of MLD; confirm with a second method (e.g. DNA test)

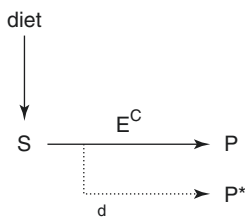


Fig. 14.1 A model metabolic pathway. (After Clarke 2006, Fig. 11). In the above example, substrate S, which is essential in the diet, is metabolized to product P via enzyme E and enzyme cofactor C. Deficiency of E or C will cause S to accumulate with concurrent deficiency of P. In an alternative pathway (dashed arrow), drug d can react with S to form an alternative product, P*. Potential treatment strategies could include: Restricting S in the diet, supplementing P, supplying drug d, replacing E by enzyme replacement, or enhancing E's activity with supra-physiologic amounts of C. All of these strategies are used clinically in the treatment of small-molecule IEMs

when present, these patterns (Table 14.4) should prompt evaluation for an IEM. In contrast, other small-molecule IEMs (such as phenylketonuria, maple syrup urine disease, glutaric aciduria type I, etc.) may present no clues on routine lab investigations even during an acute metabolic crisis; specific biochemical investigations are required. In the patient with undifferentiated symptoms (e.g. acute encephalopathy), many practitioners employ a 'small molecule screen' (at least: CBC, blood gases, electrolytes, glucose, lactate, ammonia, plasma amino acids, total homocysteine, urine organic acids, plasma acylcarnitine profile, and other tests depending on the clinical situation). This workup, ideally performed while the patient is acutely symptomatic, will identify many (not all) treatable small-molecule IEMs.

Once a particular IEM is suspected, the diagnosis can be confirmed by proving a deficient activity of the pertinent enzyme or transporter activity, and/or (increasingly) by identifying mutation(s) in the corresponding gene(s).

It is important to recognize that some *small-molecule* disorders are specifically treatable

(with dietary modification, drugs, supplements or cofactors, by solid organ (e.g. liver) transplantation, or, less commonly, by hematopoietic stem cell transplantation (HSCT) or enzyme replacement therapy (ERT) (Table 14.5). A subset of these disorders are targets of newborn screening in industrialized countries (see below).

Table 14.4 High-value ‘routine’ laboratory findings in metabolism

| Key finding | Metabolic Ddx | Metabolic investigations |
|---|--|---|
| Hyperammonemia (exclude factitious) ^a | UCDs OAs HHH LPI FAODs HI/HA | Plasma amino acids Urine organic acids and orotic acid Urine amino acids Acylcarnitine profile Free and total carnitine |
| Hypoglycemia (hypoketotic) ^b (exclude factitious) ^c | FAODs Carnitine shuttle (CPT1a) Ketogenesis defects (e.g. HMG-CoA) Hyperinsulinism ^d | Plasma acylcarnitine profile Free and total carnitine Free fatty acids Beta-hydroxybutyrate Insulin, growth hormone, cortisol Urine organic acids |
| Hypoglycemia (ketotic) | GSDs (esp. I, III, VI, IX, 0) Gluconeogenesis defects (e.g. F-1,6-BP) Ketolytic defects Hypopituitarism ^d ‘Benign ketotic hypoglycemia’ ^d | Abdominal ultrasound (hepatomegaly) CBC, lactate, uric acid, ALT/AST, triglycerides (GSDI) Genetic testing if high suspicion |
| Hypoglycemia (immediately postprandial) | HFI | Dietary history: sweets avoidance Uric acid, transaminases (during symptoms) Genetic testing if high suspicion |
| High anion gap metabolic acidosis (unexplained) ^e | OAs Cobalamin disorders Ketolytic defects | Urine organic acids Acylcarnitine profile Total homocysteine Ammonia CBC |
| Lactic acidosis | Mitochondrial PDH (postprandial) PC (fasting) Krebs cycle GSD type I (fasting, with hepatomegaly) | Lactate, uric acid, ALT/AST, triglycerides (GSDI) Plasma amino acids Urine organic acids Acylcarnitine profile Consider PDH, PC activities in skin fibroblasts (skin biopsy) Consider muscle biopsy Consider first-line genetic testing (mitochondriopathy panel or clinical whole exome) |
| Anemia (macrocytic) | Cobalamin disorders Folate cycle | Total homocysteine Plasma amino acids Urine organic acids Acylcarnitine profile Folate B12 |

Table 14.4 (continued)

| Key finding | Metabolic Ddx | Metabolic investigations |
|--------------|---|--|
| Coagulopathy | Galactosemia Tyrosinemia I | Galactosemia screen/GALT activity Succinylacetone Plasma amino acids |

List is not comprehensive. Some treatable IEMs may present with normal routine lab results. For all disorders, genetic investigations (e.g. single-gene or panel-based sequencing) may be considered in parallel with biochemical testing
Abbreviations: CPT1a: Carnitine palmitoyltransferase 1a deficiency; Ddx: Differential diagnosis; F-1,6-BP: Fructose-1,6-bisphosphatase deficiency; FAODs: Fatty acid oxidation disorders; GALT: Galactose-1-phosphate uridylyltransferase; GSDs: Glycogen storage diseases (includes GSD0, glycogen synthase deficiency); HHH: Hyperammonemia-hyperornithinemia-homocitrullinuria syndrome; HFI: Hereditary fructose intolerance; HI/HA: Hyperinulinism-hyperammonemia syndrome; HMG-CoA: 3-hydroxy-3-methylglutaryl-coA lyase deficiency; LPI: Lysinuric protein intolerance; OAs: Organic Acidurias; PDH: Pyruvate dehydrogenase deficiency; PC: Pyruvate Carboxylase deficiency; UCDs: Urea cycle defects

^aCollect free-flowing venous (or arterial) sample, on ice, and analyze promptly

^bie. Ketosis is less than expected given the degree of hypoglycemia. See also: Fig. 14.1 (nomogram: free fatty acids versus beta-hydroxybutyrate) in [PMID#8869190]

^cConfirm with laboratory glucose measurement

^dEtiologically heterogeneous

^ei.e. $([Na^+] - [Cl^-] - [HCO_3^-]) > 16$ mmol/L, not fully accounted for by lactate and/or ketones

Table 14.5 Therapeutic approaches in metabolism

| Approach | Examples |
|--|---|
| Correct the underlying mutation ('gene therapy') | – ADA-SCID |
| Correct the underlying mutation in selected tissue(s) by transplantation | – HSCT transplantation for Hurler syndrome, X-ALD, etc. – Liver transplantation for urea cycle defects – Combined Liver/kidney transplant for MMA |
| Pharmacological replacement of the deficient enzyme activity ('enzyme replacement therapy') | – ERT for Gaucher type I |
| (Cofactor defects) Replacement of missing enzyme cofactor | – IM Hydroxocobalamin for disorders of intracellular cobalamin metabolism |
| (Partial enzyme defects) | |
| • Pharmacological induction of the relevant gene's expression | – Hydroxyurea in sickle-cell disease |
| • Pharmacological enhancement of enzyme activity with supraphysiological doses of the enzyme's cofactor | – Tetrahydrobiopterin (BH4) for BH4-responsive phenylketonuria |
| • Pharmacological stabilization of an unstable mutant enzyme with a chemical chaperone | – N/A |
| (Deficiency syndromes) Supplementation of a deficient product or alternative | – Uncooked cornstarch therapy for GSD Ia |
| (Intoxication syndromes) | – Phenylalanine restriction in phenylketonuria (PKU) |
| • Dietary restriction of a dietarily-essential substrate or precursor | |
| • Pharmacological inhibition of a preceding pathway step to block formation of the toxic substrate in question | – Nitisinone therapy (prevents succinylacetone accumulation) in tyrosinemia type I |
| • Removal of toxic product by hemodialysis (acutely) | – HD for hyperammonemia in UCDs |
| • Removal of toxic product with detoxifying drugs (acutely or chronically) | – Sodium benzoate and sodium phenylacetate therapy for hyperammonemia in UCDs |
| • Block transport of toxic product into end organ(s) of interest | – Large neutral amino acid supplementation in PKU (block brain transport of phenylalanine) |

Abbreviations (unlisted disease abbreviations are as per Table 14.2): ERT: Enzyme replacement therapy; HD: Hemodialysis; HSCT: Hematopoietic stem cell transplantation; NTBC: Nitisinone

Organellar Diseases

In contrast to *small-molecule* disorders, *organellar diseases* are primarily recognized clinically on the basis of characteristic clinical symptoms and signs. Organellar disorders are quite variable in their presentations but common signs may include: Dymorphic features, organomegaly, skeletal and/or connective tissue abnormalities, developmental regression, macrocephaly, progressive white matter disease, cherry-red macular spots, etc. (Tables 14.3 and 14.6). Organellar diseases can be sub-classified by affected organelle, into: *mitochondrial diseases*, *peroxisomal disorders*, *lysosomal storage diseases*, and *congenital disorders of glycosylation types I and II (involving endoplasmic reticulum and Golgi, respectively)* (Table 14.3); *lysosomal* disorders are further subdivided by type

of *storage material*. Once the clinical suspicion of a particular *organellar disease* has been raised, the diagnosis is confirmed by specific biochemical and/or enzymological testing, and/or by molecular testing of the relevant gene(s). Because many organellar diseases are dreaded, life- and family-altering diagnoses, it is often prudent to ‘prove’ one’s clinical suspicion using several independent test methods before conferring a diagnosis. A handful of organellar diseases are treatable by HSCT, ERT, or with drugs (Table 14.5), although the effect of treatment is generally partial at best, and many conditions are entirely without disease-modifying treatment. Until recently, organellar diseases have not been targeted for neonatal screening; a few such disorders are now being targeted, as discussed below.

Table 14.6 Selected classical ‘syndromic’ presentations in metabolism

| Symptom complex | Major metabolic DDx | Biochemical investigations |
|---|--|---|
| Hypotonia, CNS malformations, enlarged anterior fontanelle | Peroxisomal (Zellweger spectrum, DBP) | VLCFA Bile acid precursors Red cell plasmalogens |
| Rhizomelia Calcific epiphyseal stippling | Peroxisomal (Rhizomelic chondrodysplasia punctata) | Red cell plasmalogens |
| Dysostosis multiplex, macrocephaly, organomegaly, hernias/hydroceles, +/- corneal clouding, angiokeratomata | Mucopolysaccharidoses Oligosaccharidoses Mucopolipidosis III GM1 gangliosidosis MSD | Urine MPS spot ^a Urine MPS fractionation Urine oligosaccharides Specific enzyme assay |
| Cherry-red macular spots and developmental deceleration/regression +/- macrocephaly, organomegaly | Sphingolipidoses (GM1, GM2 [Tay-Sachs/Sandhoff], Niemann-Pick A/B, MLD, MSD, sialidosis, others) | Specific enzyme activities in WBCs or cultured fibroblasts |
| Nonimmune, non-hematological fetal hydrops | Various lysosomal | Urine MPS spot ^b Urine MPS fractionation Urine oligosaccharides Urine sialic acid Blood smear/bone marrow Consider NGS panel or WES |
| Abnormal fat pads on thighs/buttocks, inverted nipples | CDG-N, esp. CDG Ia | Isoelectric focusing of serum transferrin |
| Dysmorphism, congenital anomalies (various) with CNS involvement | CDG-N | Transferrin IEF N-linked glycans by FAB-MS in urine |
| Polymicrogyria, occipital encephalocele | CDG-O (Walker-Warburg, Muscle-eye-brain) | CK O-linked glycans by FAB-MS in urine |

Table 14.6 (continued)

| Symptom complex | Major metabolic DDx | Biochemical investigations |
|---|--|---|
| Midface hypoplasia, short PFs, periventricular cysts, +/- cardiomyopathy and multisystem involvement | Energy metabolism (esp. PDH, mitochondrial disorders) | Lactate Plasma amino acids (Ala, Pro, Gly) Acylcarnitine profile Urine organic acids Brain MRS Lactate:pyruvate ratio, PDH, PC enzymologies (skin fibroblasts) Consider muscle biopsy, incl. Respiratory chain enzymology |
| Dysmorphism, cardiomyopathy, multiple renal cysts, +/- CNS malformations | Energy metabolism (esp. GA-II, Carnitine shuttle, FAODs) | Acylcarnitine profile Free and total carnitine Urine organic acids |
| Hypotonia, steel-wool hair, bladder diverticulae | Menkes | Serum copper Ceruloplasmin |
| Microcephaly, growth retardation, hypospadias, Y-shaped 2-3 syndactyly of toes, polydactyly, heart and structural anomalies | Smith-Lemli-Opitz | Serum 7-dehydrocholesterol |

Only selected conditions are shown. In each case, genetic testing (single-gene or panel) can also be considered alongside biochemical investigations

CDG: congenital disorders of glycosylation (–N: N-linked; –O: O-linked); CK: Creatine kinase; CNS: Central nervous system; DBP: D-bifunctional protein deficiency; FAODs: Fatty acid oxidation disorders; FAB-MS: Fast atom bombardment-mass spectrometry; GA-II: Glutaric aciduria type II; IEF: Isoelectric focusing; MPS: Mucopolysaccharides; MRS: Magnetic resonance spectroscopy; MSD: Multiple sulphatase deficiency; MLD: Metachromatic leukodystrophy; NGS: Next-generation sequencing; PDH: Pyruvate dehydrogenase deficiency; PC: Pyruvate carboxylase deficiency; PFs: Palpebral fissures; VLCFAs: Very long chain fatty acids; WBCs: White blood cells

^aAbsent in some conditions

^bNeither specific nor sensitive

The Expanding Role of Newborn Screening

The aim of newborn screening (NBS) is *secondary prevention*, i.e. to identify children at increased risk of having a treatable IEM, prior to the onset of clinical symptoms. Cost and other practical considerations limit NBS programs to a specific list of (relatively few) targeted conditions; criteria for selecting appropriate targets have been constructed (Andermann et al. 2008; Wilson and Jungner 1968). In general, valid targets are conditions which are medically serious, display a presymptomatic phase during which treatment is beneficial, and for which robust (e.g. highly predictive), practical, and cost-effective test(s) are available.

In most highly-industrialized countries, *tandem mass spectrometry* (MS:MS), which can rapidly measure the abundance of multiple compounds in a dried blood spot card or other stable sample, has become the primary platform for NBS (Charrow et al. 2000). MS:MS-based NBS programs now screen for dozens of treatable IEMs in addition to ‘classic’ targets such as phenylketonuria and congenital hypothyroidism. The structure of the NBS system and the list of disorders screened varies by jurisdiction; many programs use some variation of the U.S. Department of Health and Human Services’ Recommended Uniform Screening Panel (RUSP), which currently includes 31 disorders (U.S. D.H.H.S. 2015). Classically, screened conditions have tended to be small-molecule IEMs (e.g. phenylketonuria) and/or endocrinological

disorders (e.g. congenital hypothyroidism) readily amenable to medical and/or dietary therapy. Recently, however, the RUSP has recently added X-linked adrenoleukodystrophy and Hurler syndrome (both treatable via early HSCT), and Pompe disease (treatable by ERT). NBS has also been tried for Krabbe disease (Globoid cell leukodystrophy), another lysosomal storage disease, although outcomes have been disappointing (Wasserstein et al. 2016). In general, targeted lysosomal therapies (e.g. ERT and HSCT) are complex and resource-intensive, and in some disorders/cases the magnitude of clinical benefit may be unclear. Although lab methods for multiplexed lysosomal disease screening by MS continue to develop (Elliott et al. 2016), there are a number of medical, technical, ethical, economic, and health systems considerations to be carefully weighed.

As end-users of NBS programs, pediatricians and primary care providers should be aware of (1) the limitations of screening, and (2) what to do in the event of a positive screen. With respect to the former: Firstly, many treatable IEMs (e.g. most urea cycle disorders) are not targeted for screening for technical or practical reasons (e.g. lack of an appropriate test). Other disorders (e.g. classical galactosemia, urea cycle defects, organic acidurias, severe fatty acid oxidation defects) may present symptomatically during the first days of life, before the screen's results have been reported. As with any laboratory test, false-positive and false-negative results may occur, as may sample mis-collection, mishandling, or misidentification (e.g. of twin samples). With respect to the latter: In the event of a positive screen, physicians should recognize that the situation is *potentially an emergency even if* the child is initially well-appearing. Clinicians should know where to locate appropriate management resources and/or diagnostic algorithms; these are often provided by the NBS program itself, or alternatively can be found online courtesy of the American College of Medical Geneticists (ACMG) (ACMG 2001). It will likely be necessary to contact the appropriate pediatric consulting service (e.g. metabolics, endocrinology, immunology) for expert advice.

Increasing Reliance on DNA-Based Testing

Classically, clinical diagnosis of an IEM involves the following steps: A clinical phenotype compatible with an IEM is recognized; one or more metabolites are measured at abnormal concentration(s); a corresponding enzyme activity is shown to be deficient; and mutation(s) are confirmed in a corresponding gene. Ideally the clinical presentation, metabolite measurements, enzymology, and genetic results are all congruent, so that the diagnosis has been secured by several independent means. Recent advances in molecular genetic testing appear poised to upend the classical approach. As described earlier in this chapter, NGS is a disruptive technology which permits the simultaneous testing of tens to thousands of genes efficiently and at low cost. In theory, NGS offers several advantages over 'standard' biochemical testing, namely: (1) convenient sampling (nearly all testing can be performed using peripheral blood), (2) state-independence (results are unaffected by illness, dietary status, medications, etc.), (3) standardization and relative ease of use, (4) direct applicability of results to genetic counselling, if desired, and, importantly, (5) low clinical bias, i.e. improved recognition of very rare or atypically-presenting disorders. In contrast, many biochemical tests are methodologically complex, limited to few centers worldwide, and/or have collection requirements which are either state-specific (e.g. during illness) or invasive (e.g. tissue biopsy, lumbar puncture). DNA-based tests are therefore becoming increasingly accepted as 'first-line' investigations for many metabolic disorders. Situations where first-line genetic testing for IEMs may be appropriate could include:

- Avoidance of invasive testing: For example, up to ~25–50% of patients with a primary mitochondrial disorder can be diagnosed via NGS, obviating the need for diagnostic muscle biopsy (Calvo et al. 2012; Lieber et al. 2013).
- Nonspecific clinical presentations with a very broad associated genetic/metabolic differential

diagnosis (e.g. nonimmune fetal hydrops) (Shamseldin et al. 2015)

- Where pretest probability of an IEM is high, a definitive genetic diagnosis is required urgently, and/or where prenatal (e.g. amniocentesis) or preimplantation genetic diagnosis may later be considered.

Disease-Modifying Therapy for IEMs

IEMs should, in theory, be treatable using a wide variety of therapeutic strategies (Table 14.5), of which *gene therapy* (*in vivo* reconstitution of the missing gene, e.g. using engineered virus vectors) should be the most definitive. Currently, the promise of clinical gene therapy remains largely unrealized, and important technical, safety, and ethical/legal obstacles remain to be addressed before it enters widespread use in clinical genetics (Ginn et al. 2013; ‘Gene-therapy trials’ (Editorial, *Nature*), 2016). Specific forms of gene therapy, for instance in the context of autologous stem cell transplantation, are used currently (e.g. in the treatment of severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID) (Gaspar 2012)). Many IEMs characterized by intoxication should be particularly amenable to gene therapy, as most enzymes function very efficiently and only a few percent of the usual activity (in liver, for instance) may be needed to prevent toxic substrate accumulation. It will be exciting to see how this area evolves over the coming years.

Another (arguably more pedestrian) means of ‘replacing’ a missing enzyme or transporter is by allogeneic organ or stem cell transplantation. In patients post-HSCT, cells derived from donor hematopoietic stem cells engraft not only in the recipient’s bone marrow but also in the brain (as microglia); some of the lysosomal enzymes expressed by these cells are secreted and endocytosed by neighbouring host cells. This ‘lysosomal cross-correction’ (Fratantoni et al. 1968) is the basis of HSCT for Hurler syndrome (Boelens et al. 2013). Liver-based small-molecule IEMs, e.g. the urea cycle defects, some organic acidurias, and hepatically-based glycogen storage diseases, are greatly improved by liver (or

liver/kidney) transplantation, such that patients may become asymptomatic (at least from a hepatic point of view) on a normal diet (Yu et al. 2015; Niemi et al. 2015; Matern et al. 1999). For enzymes expressed mainly (but not exclusively) in the liver, *domino transplantation* (in which the patient’s explanted liver is donated to another individual) is an interesting option to address the issue of organ scarcity, but care must be taken to ensure safety of recipients of IEM patient organs (Popescu and Dima 2012).

ERT products are an expanding pharmaceutical market and many products have been brought to market in recent years. Products are available for Gaucher and Fabry diseases, several of the mucopolysaccharidoses (MPS I, II, IVa, VI, and VII), hypophosphatasia, acid lipase deficiency, and for ADA-deficiency SCID, among others. For some disorders, e.g. Gaucher disease type I, ERT is highly effective in mitigating the principal disease manifestations; for others, the effect may be partial or even subtle. A major limitation of ERT for many lysosomal disorders is that existing products do not penetrate the blood-brain barrier. Another limitation is cost: In general, the agents are very costly, and this is a concern to patients and to the health-care system even in highly industrialized countries.

A number of small-molecule strategies (beyond simple dietary supplementation) are employed in the treatment of IEMs. *Cofactor therapy* (providing an enzyme with pharmacological doses of a necessary cofactor to enhance its activity) is used in several conditions. Patients with *biopterin-responsive* PKU can be given a more liberal diet while taking tetrahydrobiopterin (BH4) supplementation, BH4 being a prosthetic group for the deficient enzyme (phenylalanine hydroxylase) (Somaraju and Merrin 2015). *Substrate reduction therapy* (SRT), in which the *biosynthesis* of an offending compound is blocked pharmacologically, is a treatment option in Gaucher disease and Niemann-Pick disease type C (Platt and Jeyakumar 2008). *Chaperone therapy*, that is, small molecules designed to bind to enzymes and improve their stability *in vivo*, is another theoretical option which has not yet entered routine clinical use.

Future Directions

'Targeted' Versus 'Untargeted' Metabolomics

As the genome is the sum of all genetic information in an individual, the *metabolome* is the sum of the (many thousands of) compounds transformed by the body's metabolism. *Metabolomics* is the simultaneous measurement of many metabolites in order to gain insight into a biological system. Commonly-used biochemical lab tests are a form of *targeted metabolomics*, focused on specific subsets of clinically-useful compounds (amino acids, organic acids, acylcarnitines, etc.). In contrast, *untargeted metabolomics* aims to measure as many metabolites as possible (using specialised MS instruments); in many cases, the compounds identified may be novel and/or their precise structure unknown. In general, targeted metabolomics methods are *hypothesis-testing*, whereas untargeted metabolomics may be thought of as *hypothesis-generating*. Untargeted metabolomics is new even in comparison with WES, and is just entering clinical use (Miller et al. 2015); it promises to greatly expand the chemical 'space' surveyed by clinical metabolics, to identify new IEMs, and to yield new insights into the pathophysiology of already-recognized IEMs.

Diagnostic Approach to the 'Genetic' or 'Metabolic' Patient

Geneticists are, largely, specialists in the diagnosis of rare and obscure disorders. The diagnostic workup of genetics and metabolic patients tends to be highly individualized, and thus difficult to express algorithmically. As always, the mainstay of assessment begins with the medical history, family history (including three-generation history for consanguinity, congenital anomalies, major medical or developmental concerns, miscarriages and neonatal/childhood deaths), and physical examination. A simplified diagnostic

algorithm is demonstrated in Fig. 14.2, and general clinical approaches for some of the more common referrals are described below.

The Patient Suspected of a Specific Genetic Syndrome

Patients with a clinically-recognized symptom complex represent the minority of referrals, and the testing approach in these patients will necessarily depend on the diagnosis in question. For example, in a patient with suspected Down syndrome, a karyotype is the appropriate test, as this will confirm the diagnosis and provide useful information about chromosome structure (presence or absence of mosaicism, or a Robertsonian translocation). On the other hand, in a patient with a conotruncal heart defect, hypocalcemia, and absent thymus, a microarray is appropriate, to demonstrate the expected chromosome 22q11 microdeletion. For disorders caused by point mutations within gene(s), sequencing and/or deletion testing of the appropriate genes will likely be indicated.

The Patient with an Undifferentiated Syndrome

Patients with multiple congenital anomalies and/or dysmorphic features are relatively likely to have an unrecognized syndrome, developmental sequence, infectious/teratogenic cause, or *association*. Initial investigations in these patients will typically include a chromosome microarray, imaging studies to identify associated malformations, and dysmorphology examination by a geneticist or pediatrician. Many IEMs may present as a dysmorphic syndrome (Table 14.6), and metabolic conditions should also be considered in the evaluation of this group. In patients with a normal microarray, the next test of choice will often be an NGS panel or whole exome (ideally a trio of the patient and both parents), resources permitting.

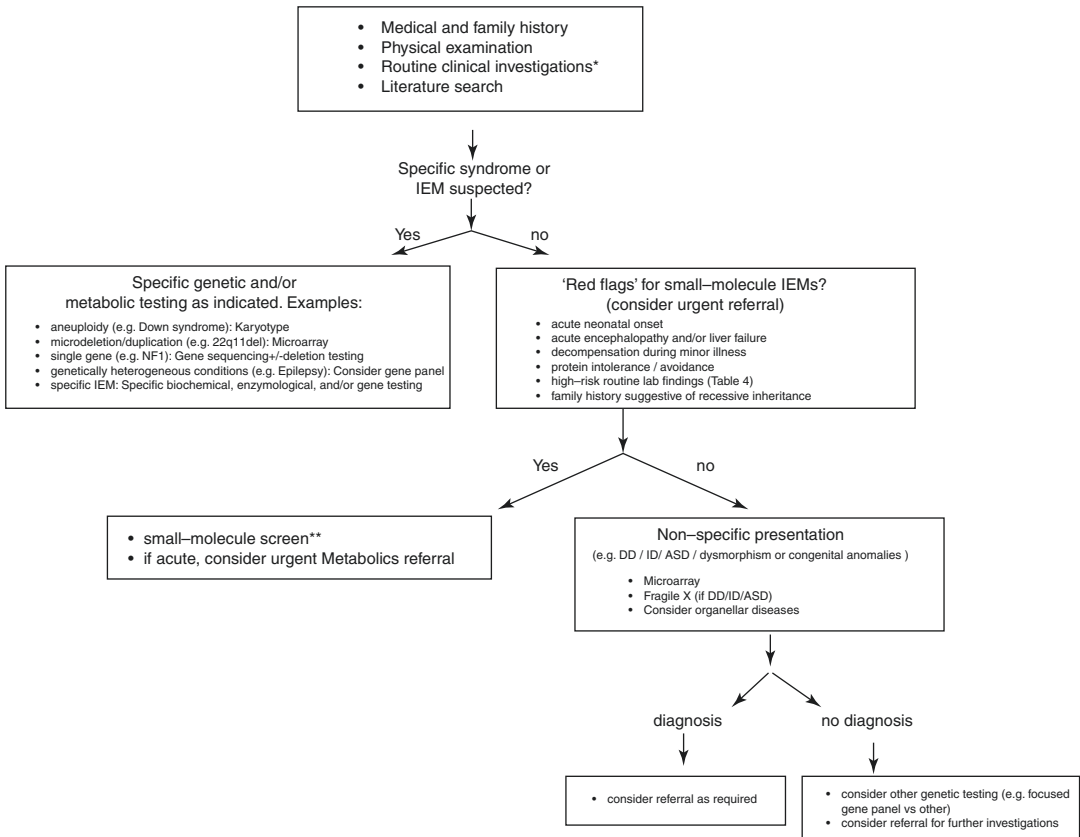


Fig. 14.2 A generalized approach to the child with possible genetic/metabolic syndrome. For detailed discussion see text in section ‘Clinical Approach’. *DD* developmental delay, *ID* intellectual disability, *ASD* autism spectrum disorder. (*Asterisk*) As indicated clinically as part of routine assessment, e.g.: MRI head (if focal neurological

findings); thyroid hormone indices, etc. (*Double asterisks*) At minimum: CBC, blood gases, electrolytes, glucose, lactate, ammonia, plasma amino acids, urine organic acids, plasma acylcarnitine profile, free and total carnitine, other tests as indicated for the clinical presentation

The Patient with Undifferentiated Developmental Delay and/or Autism-Spectrum Disorder

This group comprises a large portion of clinic referrals, and the diagnostic yield in nondysmorphic patients with a normal examination is relatively low, perhaps on the order of 10–25%. The standard workup of these patients includes a microarray and Fragile X testing (both boys and girls); some specialists advocate uniform metabolic screening (van Karnebeek and Stockler-Ipsiroglu 2014). NGS panels for nonsyndromic intellectual disability are becoming increasingly used, and useful, in this group of patients.

The Patient with Metabolic ‘Red Flags’

Acute medical illness in a neonate should prompt consideration of IEMs alongside other conditions such as sepsis. Other ‘Red flags’ which should prompt the pediatrician or general practitioner to consider small-molecule disorders include intolerance of illness, fasting, or certain foods (e.g. proteins, sweets), parental consanguinity, or abnormal lab studies (Table 14.4). The diagnostic yield of small-molecule screening investigations is likely to be higher in these patients than in patients with (for instance) undifferentiated developmental delay.

References

- ACMG Board of Directors. ACMG policy statement: updated recommendations regarding analysis and reporting of secondary findings in clinical genome-scale sequencing. *Genet Med*. 2015;17(1):68–9.
- American Academy of Pediatrics Committee on Genetics. Health care supervision for children with Williams syndrome. *Pediatrics*. 2001;107(5):1192–204. Erratum in: *Pediatrics* 2002;109(2):329
- American College of Medical Geneticists. ACMG ACT sheets and confirmatory algorithms [Internet]. Bethesda, MD: ACMG; 2001. <http://www.ncbi.nlm.nih.gov/books/NBK55827/>. Accessed 11 Nov 2016
- Andermann A, Blancquaert I, Beauchamp S, Déry V. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. *Bull World Health Organ*. 2008;86(4):317–9.
- Aoki Y, Niihori T, Inoue S, Matsubara Y. Recent advances in RASopathies. *J Hum Genet*. 2016;61(1):33–9.
- Boelens JJ, Aldenhoven M, Purtill D, Ruggeri A, Defor T, Wynn R, et al. Outcomes of transplantation using various hematopoietic cell sources in children with Hurler syndrome after myeloablative conditioning. *Blood*. 2013;121(19):3981–7.
- Boone PM, Soens ZT, Campbell IM, Stankiewicz P, Cheung SW, Patel A, Beaudet AL, Plon SE, Shaw CA, McGuire AL, Lupski JR. Incidental copy-number variants identified by routine genome testing in a clinical population. *Genet Med*. 2013;15(1):45–54.
- Boycott K, Hartley T, Adam S, Bernier F, Chong K, Fernandez BA, Friedman JM, Geraghty MT, Hume S, Knoppers BM, Laberge AM, Majewski J, Mendoza-Londono R, Meyn MS, Michaud JL, Nelson TN, Richer J, Sadikovic B, Skidmore DL, Stockley T, Taylor S, van Karnebeek C, Zawati MH, Lauzon J, Armour CM, Canadian College of Medical Geneticists. The clinical application of genome-wide sequencing for monogenic diseases in Canada: position statement of the Canadian College of Medical Geneticists. *J Med Genet*. 2015;52(7):431–7.
- Calvo SE, Compton AG, Hershman SG, Lim SC, Lieber DS, Tucker EJ, et al. Molecular diagnosis of infantile mitochondrial disease with targeted next-generation sequencing. *Sci Transl Med*. 2012;4(118):118ra10.
- Charrow J, Goodman SI, McCabe ERG, Rinaldo P. (American College of Medical Genetics/American Society of Human Genetics Test and Technology Transfer Committee Working Group). Tandem mass spectrometry in newborn screening. *Genet Med*. 2000;2(4):267–9.
- Clarke JTR. A clinical guide to inherited metabolic diseases. 3rd ed. New York, NY: Cambridge University Press; 2006.
- Cooper GM, Shendure J. Needles in stacks of needles: finding disease-causal variants in a wealth of genomic data. *Review Nat Rev Genet*. 2011;12(9):628–40.
- Davis RL, Liang C, Sue CM. A comparison of current serum biomarkers as diagnostic indicators of mitochondrial diseases. *Neurology*. 2016;86(21):2010–5.
- Editorial. Gene-therapy trials must proceed with caution. *Nature*. 2016;534(7609):590.
- van El CG, Cornel MC, Borry P, Hastings RJ, Fellmann F, Hodgson SV, Howard HC, Cambon-Thomsen A, Knoppers BM, Meijers-Heijboer H, Scheffer H, Tranebjaerg L, Dondorp W, de Wert GM, Public Professional Policy Committee ESHG. Whole-genome sequencing in health care: recommendations of the European Society of Human Genetics. *EJHG*. 2013;21:580–4.
- Elliott S, Buroker N, Courmoyer JJ, Potier AM, Trometer JD, Elbin C, et al. Pilot study of newborn screening for six lysosomal storage diseases using Tandem Mass Spectrometry. *Mol Genet Metab*. 2016;118(4):304–9.
- Ezkurdia I, Juan D, Rodriguez JM, Frankish A, Diekhans M, Harrow J, Vazquez J, Valencia A, Tress ML. Multiple evidence strands suggest that there may be as few as 19,000 human protein-coding genes. *Hum Mol Genet*. 2014;23(22):5866–78.
- Fratantoni JC, Hall CW, Neufeld EF. Hurler and Hunter syndromes: mutual correction of the defect in cultured fibroblasts. *Science*. 1968;162(3853):570–2.
- Gaspar HB. Gene therapy for ADA-SCID: defining the factors for successful outcome. *Blood*. 2012;120(18):3628–9.
- Ginn SL, Alexander IE, Edelstein ML, Abedi MR, Wixon J. Gene therapy clinical trials worldwide to 2012- an update. *J Gen Med* 2013;15(2):65–77
- Green RC, Berg JS, Grody WW, Kalia SS, Korf BR, Martin CL, McGuire AL, Nussbaum RL, O'Daniel JM, Ormond KE, Rehm HL, Watson MS, Williams MS, Biesecker LG, American College of Medical Genetics and Genomics. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med*. 2013;15:565–74.
- Hersh JH, Saul RA, Committee on Genetics. Health supervision for children with fragile X syndrome. *Pediatrics*. 2011;127(5):994–1006.
- Hoggatt J. Gene therapy for "Bubble Boy" disease. *Cell*. 2016;166(2):263.
- International Human Genome Sequencing Consortium. Finishing the euchromatic sequence of the human genome. *Nature*. 2004;431(7011):931–45.
- van Karnebeek CD, Stockler-Ipsiroglu S. Early identification of treatable inborn errors of metabolism in children with intellectual disability: the treatable intellectual disability endeavor protocol in British Columbia. *Paediatr Child Health*. 2014;19(9):469–71.
- Kingswood JC, Bissler JJ, Budde K, Hulbert J, Guay-Woodford L, Sampson JR, Sauter M, Cox J, Patel U, Elmslie F, Anderson C, Zonnenberg BA. Review of

- the tuberous sclerosis renal guidelines from the 2012 consensus conference: current data and future study. *Nephron*. 2016;134(2):51–8.
- Lacro RV, Dietz HC, Sleeper LA, Yetman AT, Bradley TJ, Colan SD, Pearson GD, Selamet Tierney ES, Levine JC, Atz AM, Benson DW, Braverman AC, Chen S, De Backer J, Gelb BD, Grossfeld PD, Klein GL, Lai WW, Liou A, Loeys BL, Markham LW, Olson AK, Paridon SM, Pemberton VL, Pierpont ME, Pyeritz RE, Radojewski E, Roman MJ, Sharkey AM, Stylianou MP, Wechsler SB, Young LT, Mahony L, Pediatric Heart Network Investigators. Atenolol versus losartan in children and young adults with Marfan's syndrome. *N Engl J Med*. 2014;371(22):2061–71.
- Lee H, Deignan JL, Dorrani N, et al. Clinical exome sequencing for genetic identification of rare Mendelian disorders. *JAMA*. 2014;312:1880–7.
- Lieber DS, Calvo SE, Shanahan K, Slate NG, Liu S, Hershman SG, et al. Targeted exome sequencing of suspected mitochondrial disorders. *Neurology*. 2013;80(19):1762–70.
- Matern D, Starzl TE, Arnaout W, Barnard J, Bynon JS, Dhawan A, Emond J, Haagsma EB, Hug G, Lachaux A, Smit GP, Chen YT. Liver transplantation for glycogen storage disease types I, III, and IV. Review. *Eur J Pediatr*. 1999;158(Suppl 2):S43–8.
- Michelson DJ, Shevell MI, Sherr EH, Moeschler JB, Gropman AL, Ashwal S. Evidence report: genetic and metabolic testing on children with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology*. 2011;77(17):1629–35.
- Miller DT, Adam MP, Aradhya S, Biesecker LG, Brothman AR, Carter NP, Church DM, Crolla JA, Eichler EE, Epstein CJ, Faucett WA, Feuk L, Friedman JM, Hamosh A, Jackson L, Kaminsky EB, Kok K, Krantz ID, Kuhn RM, Lee C, Ostell JM, Rosenberg C, Scherer SW, Spinner NB, Stavropoulos DJ, Tepperberg JH, Thorland EC, Vermeesch JR, Waggoner DJ, Watson MS, Martin CL, Ledbetter DH. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet*. 2010;86(5):749–64.
- Miller MJ, Kennedy AD, Eckhart AD, Burrage LC, Wulff JE, Miller LA, et al. Untargeted metabolomics analysis for the clinical screening of inborn errors of metabolism. *J Inher Metab Dis*. 2015;38(6):1029–39.
- Moeschler JB, Shevell M, Committee on Genetics. Comprehensive evaluation of the child with intellectual disability or global developmental delays. *Pediatrics*. 2014;134(3):e903–18.
- Niemi AK, Kim IK, Krueger CE, Cowan TM, Baugh N, Farrell R, et al. Treatment of methylmalonic acidemia by liver or combined liver-kidney transplantation. *J Pediatr*. 2015;166(6):1455–61.e1.
- Nyhan WL, Hoffman GF, Barshop BA, Al-Aqeel AI. Atlas of inherited metabolic diseases. 3rd ed. London: Hodder Arnold; 2012.
- OMIM. Online Mendelian inheritance in man, OMIM®. Baltimore, MD: McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University; 2016. <http://omim.org/>
- Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, LJH B, et al., editors. GeneReviews [Internet]. Seattle, WA: University of Washington, Seattle; 1993. <http://www.ncbi.nlm.nih.gov/books/NBK1116/>. Accessed 9 Nov 2016
- Pichert G, Mohammed SN, Ahn JW, Ogilvie CM, Izatt L. Unexpected findings in cancer predisposition genes detected by array comparative genomic hybridisation: what are the issues? *J Med Genet*. 2011;48(8):535–9.
- Platt FM, Jeyakumar M. Substrate reduction therapy. Review. *Acta Paediatr*. 2008;97(457):88–93.
- Popescu I, Dima SO. Domino liver transplantation: how far can we push the paradigm? Review. *Liver Transpl*. 2012;18(1):22–8. <https://doi.org/10.1002/lt.22443>.
- Retterer K, Juusola J, Cho MT, Vitazka P, Millan F, Gibellini F, Vertino-Bell A, Smaoui N, Neidich J, Monaghan KG, McKnight D, Bai R, Suchy S, Friedman B, Tahilian J, Pineda-Alvarez D, Richard G, Brandt T, Haverfield E, Chung WK, Bale S. Clinical application of whole-exome sequencing across clinical indications. *Genet Med*. 2016;18(7):696–704.
- Saudubray JM, Baumgartner MR, Walter J, editors. Inborn metabolic diseases: diagnosis and treatment. 6th ed. Heidelberg: Springer-Verlag; 2016.
- Shamseldin HE, Tulbah M, Kurdi W, Nemer M, Alsaah N, Al Mardawi E, et al. Identification of embryonic lethal genes in humans by autozygosity mapping and exome sequencing in consanguineous families. *Genome Biol*. 2015;16:116.
- Sims D, Sudbery I, Ilott NE, Heger A, Ponting CP. Sequencing depth and coverage: key considerations in genomic analyses. *Nat Rev Genet*. 2014;15(2):121–32.
- Somaraju UR, Merrin M. Sapropterin dihydrochloride for phenylketonuria. *Cochrane Database Syst Rev*. 2015;3:CD008005.
- Sparks SE, Krasnewich DM. Congenital disorders of N-linked glycosylation pathway overview. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, LJH B, et al., editors. GeneReviews® [Internet]. Seattle, WA: University of Washington, Seattle; 2005. <http://www.ncbi.nlm.nih.gov/books/NBK1332/>.
- U. S. Department of Health and Human Services Advisory Committee on Heritable Disorders in Newborns and Children. Recommended Uniform Screening Panel 2015. <http://www.hrsa.gov/advisorycommittees/mch-badvisory/heritabledisorders/recommendedpanel/>. Accessed on 10 Nov 2016.

- Vafai SB, Mootha VK. Mitochondrial disorders as windows into an ancient organelle. *Rev Nat.* 2012;491(7424):374–83.
- Valle D, Beaudet AL, Vogelstein B, Kinzler KW, Antonarakis SE, Ballabio A, et al., editors. *The online metabolic and molecular bases of inherited disease* [Internet]. New York, NY: McGraw-Hill Medical; 2016. <http://ommbid.mhmedical.com/ommbid-index.aspx> (with authorized username and password). Accessed 9 Nov 2016
- Ward P, Walsh CE. Current and future prospects for hemophilia gene therapy. *Expert Rev Hematol.* 2016;9(7):649–59.
- Wasserstein MP, Andriola M, Arnold G, Aron A, Duffner P, Erbe RW, et al. Clinical outcomes of children with abnormal newborn screening results for Krabbe disease in New York State. *Genet Med.* 2016;18(12):1235–43. <https://doi.org/10.1038/gim.2016.35>.
- Wilson JMG, Jungner G. *Principles and practice of screening for disease*. Geneva: WHO; 1968. <http://www.who.int/bulletin/volumes/86/4/07-050112BP.pdf>
- Yang Y, Muzny DM, Xia F, et al. Molecular findings among patients referred for clinical whole-exome sequencing. *JAMA.* 2014;312:1870–9.
- Yu L, Rayhill SC, Hsu EK, Landis CS. Liver transplantation for urea cycle disorders: analysis of the United Network for Organ Sharing Database. *Transplant Proc.* 2015;47(8):2413–8.
- Zschocke J, Hoffmann GF. *Vademecum metabolicum*. 3rd ed. Friedrichsdorf: Milupa Metabolics GmbH; 2011. <http://evm.health2media.com/#/start>



Darcy Weidemann and Martin Bitzan

Introduction

Pediatric nephrology is a relatively young field which emerged as a distinct discipline in the 1950s–1970s. Several critical discoveries, including the use of glucocorticoids in the treatment of childhood idiopathic nephrotic syndrome, the development of the technique of percutaneous renal biopsy which permitted classification of glomerular disease and recognition of immunological factors as key to its pathogenesis, and innovation of advanced renal replacement therapies of dialysis and kidney transplantation are all scientific advances that established pediatric nephrology as a pediatric subspecialty (Chesney 2002). Pediatric nephrology as a discipline continues to evolve rapidly. The last few decades have seen remarkable advancements in the epidemiology, etiology, pathogenesis, and treatment of children with kidney diseases. There is now a greater understanding of factors contributing to

abnormal renal development and congenital anomalies of the kidney and urological tract (CAKUT), in particular progenitors of renal development, branching morphogenesis and its various factors and co-factors. There is an explosion of the so-called “omics” approaches which include genomics, transcriptomics, proteomics, and metabolomics, all of which have led to exponential increases in available experimental data and development of large clinical databases (Hanna et al. 2016). New approaches to renal and urinary tract imaging have allowed for improved diagnosis of acute and chronic kidney injury. The development and validation of novel biomarkers for acute and chronic kidney disease is an active area of research with the promise of earlier diagnosis, improved assessment of duration or severity of kidney diseases, and prediction of disease progression and adverse clinical outcomes (Fassett et al. 2011). Evidence-based clinical practice guidelines by a variety of professional organizations including the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) and Kidney Disease Improving Global Outcomes (KDIGO) aim to enhance the diagnosis and management of children with kidney disease through evidence-based recommendations. The obesity epidemic has largely changed the landscape of diagnosis and management of pediatric hypertension. This chapter will discuss several important recent clinical advances in the field of pediatric nephrology.

D. Weidemann (✉)
Section of Pediatric Nephrology,
Department of Pediatrics,
University of Missouri – Kansas City School
of Medicine, Children’s Mercy Hospital and Clinics,
Kansas City, MO, USA
e-mail: dkweidemann@cmh.edu

M. Bitzan
Division of Nephrology, Department of Pediatrics,
McGill University Health Center, Montreal
Children’s Hospital, Montreal, QC, Canada
e-mail: martin.bitzan@mcgill.ca

Evaluation and Management of Urinary Tract Infections in Children

Background

Urinary tract infections (UTI) are now one of the most common causes of serious bacterial infection in children, accounting for about 5% of children ages 2–24 months of age with fever without a clinically apparent focus (Subcommittee on Urinary Tract Infection SCoQI, Management and Roberts 2011). Throughout childhood the cumulative incidence is approximately 10% in girls and 3% in boys, with a recurrence risk of 8–30% (Conway et al. 2007). Febrile UTIs have the highest incidence during the first year of life in girls and uncircumcised boys. UTIs in infants and young children generally present as unilateral or bilateral (febrile) pyelonephritis. Infections limited to the bladder (cystitis) are typically seen in teenage girls, are afebrile, and easily treated with a short course of oral antibiotics. Concern about serious long-term consequences, renal scarring, hypertension, and progressive chronic kidney disease, have historically led to intensive evaluation and treatment of children with UTIs. Children with UTIs were routinely exposed to invasive diagnostic imaging tests, received long-term antibiotic prophylaxis, or underwent surgery for underlying anatomic abnormalities, specifically for vesicoureteral reflux (VUR). Controversies about direct links between renal scarring and UTI, and UTI and chronic kidney disease (CKD), resulted in new guidelines for the management of UTIs emphasizing a more selective approach to diagnostic imaging and questioning of the value of long-term antibiotic prophylaxis (Subcommittee on Urinary Tract Infection SCoQI, Management and Roberts 2011; Mori et al. 2007).

Pathogenesis

Urinary tract infection is usually due to ascending enteric pathogens following periurethral

colonization, although a minority of infections (4–9%) are thought to result from bacteremia, predominantly in the neonatal period (Hoberman et al. 1999; Smellie et al. 1994). The most frequently identified uropathogens in several recent pediatric studies are *Escherichia coli* (54–67%), *Klebsiella* (6–17%), *Proteus* (5–12%), *Enterococcus* (3–9%), and *Pseudomonas* spp. (2–6%) (Zhanet al. 2005; Prelog et al. 2008). Uropathogenic bacteria have several virulence factors which facilitate ascending infection into the bladder and kidney. One of the best studied factors in *E. coli* are pili, hair-like appendages on the bacterial cell surface that facilitate adherence to the uroepithelium and are thought to generate a local inflammatory response.

Several risk factors for UTI have been identified in children. UTIs appear to be more common in Caucasians compared to other ethnic groups and in boys <1 year and girls <4 years (Shaikh et al. 2008). Although uncircumcised boys have a four- to eightfold higher prevalence of UTI (Shaikh et al. 2008), most uncircumcised infants do not develop UTIs, and a recent systemic review found that 111 circumcisions are needed to prevent one UTI (Singh-Grewal et al. 2005). Children with obstructive urological disease are at high risk of developing UTIs due to urine stasis, which favors multiplication and adherence of uropathogens. Anatomical obstruction (posterior urethral valves, ureteropelvic junction obstruction, strictures), nephrolithiasis and neurogenic bladder dysfunction all predispose to UTI. Underlying bladder and bowel dysfunction (BBD) has recently been recognized as an important but often overlooked risk factor for UTI. A combined analysis of 181 children with first or second UTI enrolled in the longitudinal “Randomized Intervention for Children with Vesicoureteral Reflux” (RIVUR) and “Careful Urinary Tract Infection Evaluation” (CUTIE) studies demonstrated a remarkably high prevalence of 54% children with underlying BBD and identified BBD as one of the most important factors for UTI recurrence (Shaikh et al. 2016).

Clinical Presentation

Fever can be the only presenting symptom of UTI in young infants (Shaikh et al. 2007; Zorc et al. 2005), although irritability, emesis, poor feeding, or lethargy may also be elicited. Older, verbal children are more likely to report urinary symptoms such as dysuria, urgency, frequency, and suprapubic abdominal pain. A recent meta-analysis identified the following risk factors as the most relevant in identifying children <24 months with UTIs: suprapubic tenderness (likelihood ratio [LR] 4.4), temperature > 40 °C (LR 3.2), uncircumcised (LR 2.8), history of UTI (LR 2.3), and fever >24 h (LR 2.0) (Shaikh et al. 2007). Pyelonephritis should be considered when patients demonstrate fever, chills, flank pain, or costovertebral angle tenderness. Parental report of malodorous urine is not a reliable indicator (Gauthier et al. 2012).

Diagnosis

The diagnosis of UTI should be based on a urinalysis demonstrating pyuria (urine dipstick positive for leukocyte esterase, with or without nitrite positivity, or urine microscopy demonstrating the presence of white blood cells) and a positive urine culture. Recent guidelines emphasize the importance of a non-contaminated urine culture. Due to the unacceptably high false positive urine culture rate of urine bags applied to the perineum in non-toilet trained children, urine culture should be obtained by either suprapubic bladder aspiration or urethral catheterization (Subcommittee on Urinary Tract Infection SCoQI, Management and Roberts 2011). For toilet-trained children, a midstream urine collection is acceptable although appropriate cleansing of the perineal region is critical to avoid contamination. The diagnostic cut-off level for a UTI is the growth of more than 10^5 colony forming units (CFU) per mL. Lower thresholds of $>10^4$ CFU/mL are accepted for catheter specimens, acknowledging that this can increase the sensitivity while decreasing speci-

ficity for true UTI (Subcommittee on Urinary Tract Infection SCoQI, Management and Roberts 2011; Bell and Mattoo 2009).

Treatment of Acute UTI

Timely antibiotic administration is the cornerstone of treatment for acute UTIs, although there has been some disagreement regarding the choice of antibiotic, mode of administration, and duration of therapy. All febrile neonates should be treated with parenteral antibiotics pending urine, blood, and cerebrospinal fluid culture results. American Academy of Pediatrics (AAP) and (British) National Institute for Health and Clinical Excellence (NICE) guidelines emphasize that oral and parenteral antibiotic treatment is as equally efficacious for most children. The choice of antibiotics should depend on local resistance patterns, although cephalosporins and amoxicillin-clavulanic acid are frequently used empirically (Montini et al. 2011). NICE recommends 10 days of treatment, whereas the AAP acknowledges that there is insufficient scientific evidence to state whether 7, 10, or 14 days is preferred.

Urinary Tract Imaging

The evolution of urinary tract imaging technology over the past decades has influenced UTI management and become part of the controversy in this field. Traditionally, it was recommended that all patients undergo renal and bladder ultrasound and voiding cystourethrography (VCUG), often complemented by nuclear renal scan to assess for parenchymal scarring. The aim of these, often repeated diagnostic investigations was to identify children with vesicoureteral reflux (VUR), treat them with long-term antibiotic prophylaxis regardless of the VUR grade, and monitor longitudinally. Surgical correction of VUR was considered standard of care. However, recent AAP and NICE guidelines recommend a more conservative approach for the imaging of children

with febrile UTI under the age 2–3 years. AAP recommends renal and bladder ultrasound in all young children with febrile UTIs, but reserves VCUG for children with recurrent febrile UTIs or ultrasonographically detected anatomic abnormalities (Subcommittee on Urinary Tract Infection SCoQI, Management and Roberts 2011). NICE recommends renal and bladder ultrasound and VCUGs for infants <6 months and older children if they have atypical or recurrent UTIs (Mori et al. 2007). NICE recommends nuclear imaging such as dimercaptosuccinic acid (DMSA) scans 4–6 months after an acute infection in children <3 years with recurrent or atypical infections. Neither guideline recommends DMSA renal scan as part of routine clinical evaluation of first, uncomplicated UTIs.

The role of routine VCUG in the evaluation of UTIs remains contentious. Advocates generally cite a strong association between the severity of VUR and the presence of renal scarring (Shaikh et al. 2010; Coulthard 2009), and argue that early detection of reflux remains important given the ability to provide medical or surgical intervention to prevent adverse outcomes (Wan et al. 2012; Hoberman et al. 2003). Opponents who argue for a more selective approach argue that VCUG is an invasive procedure with exposure to unnecessary radiation and risk of iatrogenic UTI due to urethral catheterization (Roberts et al. 2012), and that detection of lower grades of reflux with VCUG is not essential (Hannula et al. 2011). A review of the yield, economic, and radiation costs of five different guideline algorithms concluded that more aggressive protocols have a high sensitivity for detection of VUR and scarring but at the expense of increased radiation and financial costs with uncertain benefit (La Scola et al. 2013).

Update in Vesicoureteral Reflux

Introduction

Vesicoureteral reflux is defined as the abnormal backflow of urine from the urinary bladder into one or both ureters and/or the renal pelvis. The

most widely used nomenclature of the International Reflux Study in Children defines five grades of reflux, where grade I corresponds to reflux of contrast medium into the distal ureter, and (maximal) grade V reflects gross dilation and tortuosity of the ureter and renal pelvis with blunting of the calyces (Lebowitz et al. 1985). The prevalence of VUR in the general pediatric population is estimated at 1–2% (Chand et al. 2003). Positive family history is an important risk factor for VUR with a prevalence of 27.4% in asymptomatic siblings and 35.7% in offspring (Skoog et al. 2010). However, routine screening of asymptomatic siblings is no longer practiced (MacNeily and Afshar 2006).

Diagnosis

VCUG involves the instillation of a radiopaque or radioactive contrast medium into the bladder via urethral catheterization followed by serial imaging during filling and voiding, and remains the gold standard imaging test for the diagnosis of VUR. Widespread adoption of prenatal ultrasound screening has led to the emergence of another population of individuals at risk for VUR, infants with prenatally diagnosed urinary tract dilation (UTD). 12–38% of children with prenatally diagnosed UTD and approximately 40% with postnatal UTD have VUR by VCUG (Lee et al. 2006; Passerotti et al. 2011; Ismaili et al. 2002).

Multiple classification schemes exist for the grading of UTD, which include descriptive (mild—moderate—severe hydronephrosis) and quantitative, such as the anterior-posterior renal pelvic diameter (Grignon et al. 1986) or semi-quantitative such as the Society for Fetal Ultrasound SFU (grade 0–4) (Fernbach et al. 1993). In 2014 a multidisciplinary consensus panel devised a uniform classification system with standard terminology for the diagnosis and management of prenatal and postnatal UTD (Nguyen et al. 2014). A management scheme was proposed, stratifying ultrasound results as UTD P1: low risk, UTD P2: intermediate risk, and

UTD P3: high risk, based on size of the anterior-posterior renal pelvic diameter, central or peripheral calyceal dilatation, and appearance of ureters, bladder, and renal parenchyma. VCUG is recommended only for infants with UTD P3, and the choice to proceed with VCUG for UTD P1 and P2 is left to the discretion of the clinician.

Antibiotic Prophylaxis

The stated main purpose of subjecting children with VUR to continuous antibiotic prophylaxis (CAP) is to reduce the risk of UTI recurrence and of new or additional renal scarring. For decades, children with VUR have been treated with CAP, despite poor clinical evidence, although the scientific justification for this practice was largely based on anecdotal or small case series demonstrating equivocal results (Tullus 2015), and this practice has come under close scrutiny. Recent randomized controlled trials failed to show that CAP is beneficial in children with mild to moderate VUR (Garin et al. 2006; Pennesi et al. 2008; Montini et al. 2008a), and the 2012 Cochrane review of 20 randomized controlled trials of 2324 children with VUR concluded that CAP did not significantly reduce the risk of UTI recurrence and that it was associated with a threefold increase in bacterial drug resistance (Nagler et al. 2011). The “Randomized Intervention for Children with Vesicoureteral Reflux” (RIVUR) trial (Investigators et al. 2014) was the largest multicenter randomized double blind placebo-controlled study involving low-dose trimethoprim/sulfamethoxazole in 607 children ages 2–72 months with grades I–IV VUR and a first or second symptomatic UTI. The study demonstrated a 50% reduced risk of UTI (hazard ratio 0.5, 95% CI 0.34–0.74) although no difference in the development of renal scarring (12% versus 10%) and a significantly increased risk of antibiotic resistance of bacteria isolated during subsequent UTIs. The greatest benefit was observed in children with underlying bowel and bladder dysfunction and those who

presented with a febrile UTI. The “Prevention of Recurrent Urinary Tract Infection in Children with Vesicoureteric Reflux and Normal Renal Tracts” (PRIVENT) trial (Craig et al. 2009) and the Swedish reflux trial (Brandstrom et al. 2010) both demonstrated modest benefit of CAP in reducing the risk of UTI recurrence. A Swedish study demonstrated that in girls >1 year of age with dilating VUR (grade 3 and 4), CAP also reduced new renal parenchymal damage compared with surveillance only, while endoscopic injection (see below) reduced the risk of UTI recurrence but not of new renal scars (Brandstrom et al. 2011). In the current American Urological Association VUR clinical guidelines, CAP is recommended in high risk groups including children <1 year of age, those with dilating VUR (grades 3–5) and/or a history of febrile UTIs, and those >1 year of age with BBD (Peters et al. 2010).

Surgical Intervention

VUR tends to spontaneously improve or resolve during childhood years, with the exception of (rare) grade V reflux (McLorie et al. 1990). Indications for surgical correction of VUR vary and need to be revised. A 2011 meta-analysis concluded that surgical correction of VUR did not reduce the risk of symptomatic UTIs compared with CAP (Nagler et al. 2011). Children with high-grade VUR or recurrent break-through infections while receiving CAP should be considered for surgical intervention (Peters et al. 2010; Fonseca et al. 2012). Traditional open ureteral reimplantation with success rates of 95–98% (Elder 2000) has been largely replaced by endoscopic injection of bulking agents (viscous gel of dextranomer microspheres) as a minimally invasive alternative. The Food and Drug Administration approved the dextranomer hyaluronic acid polymer Deflux® in 2001 for endoscopic correction of VUR grades II–IV VUR, and has reported success rates of 60–90% which are dependent on degree of VUR and the absence of BBD (Lendvay et al. 2006).

Glomerular Diseases in Children

Introduction

Glomerulonephritis (GN) is a generic term to denote non-infectious inflammatory lesions and glomerular injury. The pathogenesis of glomerulonephritides is only partially understood. Most cases are thought to be due to aberrant immunological responses of the host to a variety of etiological triggers. GN can be classified as acute, chronic, and in a small, but important subset as rapidly progressive glomerulonephritis (RPGN). The majority of cases of acute GN in children is due to post-infectious glomerulo-

nephritis, IgA vasculitis (IgAV; previously Henoch-Schönlein Purpura (HSP)), lupus nephritis, and vasculitides such as microscopic polyangiitis and granulomatosis with polyangiitis (formerly known as Wegener’s granulomatosis). Important chronic glomerulonephritides include membranoproliferative glomerulonephritis (MPGN), membranous GN, and IgA nephropathy. Major clinical features of three common forms of GN in children are outlined in Table 15.1. Focal segmental glomerulosclerosis (FSGS) and minimal change disease (MCD) can be characterized as chronic (or recurrent) glomerulopathies with no apparent glomerular inflammation.

Table 15.1 Comparison of clinical features, treatment, and prognosis common acute glomerulonephritides in children

| Clinical features | Post-streptococcal GN | IgA nephropathy | HSP nephritis (IgA vasculitis) |
|------------------------|--|--|---|
| Trigger | Nephritogenic beta hemolytic streptococcal infection 10–14 days preceding onset of symptoms | “Synpharyngitic hematuria”: Viral URI often seen 24–74 h prior to onset of gross hematuria | Prodrome (often viral URI) seen in majority of patients; clustering in fall/spring |
| Clinical features | Hypertension, hyperkalemia, oliguria, and mild azotemia common; microscopic hematuria can persist for up to one year after presentation | Microscopic hematuria and/or low-level proteinuria may persist between episodes of gross hematuria | Rash (lower extremity palpable purpura); arthralgias, abdominal pain (bloody stools, intussusception); renal manifestations can be noted within a few days to ~6 weeks after initial presentation |
| Serum complement C3 | Transiently reduced | Normal | Normal |
| Kidney biopsy findings | Enlarged hypercellular glomeruli, “starry sky” granular deposits of C3 and IgG on immunofluorescence; sub-epithelial “humps”—electron-dense deposits | Mesangial cell and matrix proliferation, mesangial IgA deposits on immunofluorescence, ± IgG and C3 deposits Mesangial IgA, IgG, and C3 deposits Histological features of IgAN and HSP nephritis are indistinguishable | |
| Treatment | Supportive (high-dose methylprednisolone may be considered in rare cases of RPGN), in addition to diuretics and antihypertensives | ACE-I/ARB; lack of evidence-based data although immunotherapy sometimes considered in progressive disease, often with large proteinuria severe cases (glucocorticoids, mycophenolate mofetil); omega3 supplements | Supportive; lack of evidence-based data but various immunotherapy considered in severe cases (glucocorticoids, cyclophosphamide, azathioprine, mycophenolate mofetil) |
| Prognosis | Majority self-limited; excellent prognosis | Chronic illness with long-term risk of CKD and hypertension | Many patients recover spontaneously but subset with long-term risk of CKD and hypertension |

Epidemiology

The most common form of GN in children is acute post-infectious (mainly: post streptococcal) GN affecting as much as 472,000 patients worldwide with 5000 deaths annually according to the World Health Organization estimates (Carapetis et al. 2005). Although its incidence has been steadily declining in the United States and Europe over the past 40–50 years, it remains a substantial cause of morbidity and mortality particularly in both developed and under-resourced countries (Sims Sanyahumbi et al. 2016). The incidence of IgAV/HSP is ~20.4 per 100,000 population per year (Gardner-Medwin et al. 2002), primarily in children <10 years of age, and tends to cluster in the fall and spring. As indicated by the new nomenclature, HSP differs from classical IgA nephropathy by the pathognomonic purpuric rash. They demonstrate virtually indistinguishable lesions in kidney biopsies and may represent different manifestations of the same underlying disease process (Kamei et al. 2016). Recent population-based Medicaid claims data from the US estimate the incidence of lupus nephritis as 0.72 cases per 100,000 children per year, and a prevalence of 3.6 cases per 100,000 children (Hiraki et al. 2012).

Clinical Manifestations

Glomerulonephritis presents clinically with hematuria, proteinuria, edema, renal dysfunction, and occasionally hypertension and nephrotic syndrome. Acute post-infectious, usually post-streptococcal GN (APIGN/APSGN) occurs 7–21 days after the onset of pharyngotonsillitis or Group A streptococcal impetigo, whereas IgA nephropathy presents with painless gross hematuria within 1–3 days of an upper respiratory infection (synpharyngitic hematuria). IgAV/HSP is a form of leukocytoclastic vasculitis, characterized by palpable purpura classically over the buttocks and lower extremities, but occasionally extending to the trunk and upper extremities,

abdominal pain, arthritis, and renal disease (nephritis) in up to 30–40% of cases (Davin and Coppo 2014).

Diagnosis

Laboratory evaluation for suspected APIGN includes measurements of serum C3 and C4, and anti-streptolysin O and anti-DNAse B titers. Serum C3 is usually profoundly depressed in the presence of normal C4 levels. Renal biopsies are not necessary in most children with suspected APIGN and HSP nephritis, but should be performed in patients with rapidly progressive renal dysfunction (RPGN), the persistence of significant or progressive proteinuria, or non-resolving renal failure (Davin and Coppo 2014). The diagnosis of IgA nephropathy requires a kidney biopsy, which demonstrates predominantly IgA deposits by immunofluorescence; staging is according to the Oxford classification (Working Group of the International Ig ANN et al. 2009) which includes mesangial cellularity, segmental sclerosis, endocapillary hypercellularity, and tubulointerstitial atrophy. Renal biopsy is also considered essential in the diagnosis of lupus nephritis (Weening et al. 2004), as treatment is largely dictated by histopathological features demonstrated in the biopsy.

Management

The goals of therapy are to reduce glomerular inflammation, minimize proteinuria, improve kidney function (if decreased), as well as symptomatic control of complications of fluid overload, which can manifest as hypertension or edema. Loop diuretics help decreasing serum potassium levels in patients with mild hyperkalemia and/or fluid overload. Sodium restriction is often recommended, particularly if patients are hypertensive or treated with glucocorticoids. The treatment of (mild) post-streptococcal GN and HSP nephritis is symptomatic and supportive. Although antibiotics do not alter the clinical

course of APSGN, elimination of the nephritogenic strain of group A beta-hemolytic streptococci may minimize further spread of the disease in the community. Various degrees of immunotherapy have been trialed in many cases of moderate to severe GN, although high-quality evidence-based data, in particular double-blind, randomized, placebo-controlled trials, are lacking. Glucocorticoids have shown no benefit in prevention of HSP nephritis (Ronkainen et al. 2006) but may improve renal involvement in select patients (Ronkainen et al. 2006). A 2007 meta-analysis concluded that early glucocorticoid therapy reduced the odds of developing persistent renal disease (OR = 0.43, 95% CI 0.19–0.96) (Weiss et al. 2007). Although there is no clear consensus on the optimal treatment of IgA nephropathy, moderate to large proteinuria $>0.5 \text{ g}/1.73 \text{ m}^2$ per day is associated with accelerated decline of kidney function and an indication to initiate long-term ACE-I/ARB therapy (Reid et al. 2011). The use of glucocorticoids is controversial; some evidence exists that high-dose short-term therapy favors long-term renal protection while daily low-dose long-term prednisone use does not (Lv et al. 2012). Omega3 fatty acid supplementation (fish oil) may decrease proteinuria in IgA nephropathy, although it has not been shown to prevent kidney function decline (Chou et al. 2012).

Prognosis

Long-term prognosis of post-streptococcal GN is excellent. Hypertension and azotemia resolve within the first 2 weeks of illness, and microscopic hematuria and proteinuria resolve in the majority of cases within the first 3–6 months. In a systemic review of 1133 children with HSP, hematuria/proteinuria were seen in $\sim 1/3$ of cases, although almost 20% had some evidence of long-term kidney impairment (Narchi 2005). Spontaneous remission has been well-documented in IgA nephropathy (Shima et al. 2013; Hogg 1988); persistence of proteinuria is considered a marker for

progression to ESRD by 20 years in 20–25% of pediatric cases (Wyatt and Julian 2013).

Acute Kidney Injury in Children

Introduction

Acute Kidney Injury (AKI) is defined as the sudden decrease in glomerular filtration rate (GFR) that compromises the normal regulation of fluid, electrolyte, and acid-base homeostasis. The term AKI has largely replaced acute renal failure (ARF). The new term emphasizes the continuum of renal dysfunction without overt organ failure, which is clinically relevant and linked to morbidity and mortality. ARF now often implies the need for renal replacement therapy. In clinical practice, AKI is defined by an elevation of serum creatinine concentrations over an individual's baseline creatinine and/or the sustained reduction in urine output. Despite its widespread use, serum creatinine is a poor marker for kidney function in AKI, which only correlates with the GFR in steady state. Patients with acute, severe AKI with a markedly reduced GFR may still show normal or mildly elevated creatinine concentrations due to insufficient time for creatinine accumulation in the serum. The increase in serum creatinine may be delayed by up to 48 h after kidney damage has occurred.

Definition

The described limitations of serum creatinine have hampered clinical studies in the field (Thomas et al. 2015; Ricci et al. 2008) and resulted in a large variability in reported incidence, morbidity, and mortality estimates. This deficit was remedied, in part, by consensus definitions, known as RIFLE, AKI network (AKIN), and Kidney Disease Improving Global Outcomes (KDIGO) Classifications (Sutherland et al. 2015) (Table 15.2). The RIFLE criteria were developed by an international consensus panel in 2004 and were intended for use in critically ill adults

Table 15.2 Acute kidney injury definitions

| pRIFLE | | AKIN | | KDIGO | |
|------------------------------|---|-------|---|-------|---|
| Stage | Criteria | Stage | Criteria | Stage | Criteria |
| Risk (R) | eCrCl ↓ 25% | 1 | ↑ SCr ≥ 0.3 mg/dL (26.5 μM) or ↑ SCr | 1 | ↑ SCr ≥ 0.3 mg/dL (26.5 μM) or ↑ SCr ≥ 1.5–2× ^b |
| | UOP < 0.5 mL/kg/h × 8 h | | ≥1.5–2 × ^a | | UOP < 0.5 mL/kg/h × 8 h |
| | | | UOP < 0.5 mL/kg/h × 6 h | | |
| Injury (I) | eCrCl ↓ 50% | 2 | ↑ SCr ≥ 2–3× | II | ↑ SCr ≥ 2–3× |
| | UOP < 0.5 mL/kg/h × 16 h | | UOP < 0.5 mL/kg/h × 12 h | | UOP < 0.5 mL/kg/h × 16 h |
| Failure (F) | eCrCl ↓ 75% or CrCl < 35 mL/min/1.73 m ² | 3 | ↑ SCr ≥ 3–4× or SCr > 4 (within 0.5 in 48 h) or RRT initiated | III | ↑ SCr ≥ 3–4× or SCr > 4 (and meets criteria for AKI) or RRT initiated or eGFR < 35 in patients < 18 years old |
| | UOP < 0.5 mL/kg/h × 24 h or anuria for 12 h | | UOP < 0.5 mL/kg/h × 24 h or anuria × 12 h | | UOP < 0.5 mL/kg/h × 24 h or anuria × 12 h |
| Loss (L) | Failure > 4 weeks | N/A | | N/A | |
| End stage kidney disease (E) | Failure > 3 months | N/A | | N/A | |

UOP: urine output ^awithin 48 h; ^bwithin 7 days

(Bellomo et al. 2004). RIFLE classifies increasing severity of AKI into five different categories: (R) Risk, (I) Injury, (F) Failure, (L) Loss of kidney function, and (E) End stage renal disease, based on magnitude and duration of change in creatinine/GFR, urine output, and the length of renal replacement therapy (RRT). This classification system was subsequently modified for children (pRIFLE), which also uses changes in the estimated creatinine clearance as a measure of GFR (Akcan-Arikan et al. 2007). The AKIN criteria were developed next and are based on changes in serum creatinine; AKIN stage 1 describes patients who experience a ≥0.3 mg/dL (26.4 μM) increase in serum creatinine over a 48 hour period (Mehta et al. 2007). Although AKIN was not adjusted for children, it has been used in research in pediatric AKI, as has the most recent KDIGO definition (Workgroup 2012), which utilizes a more flexible timeline than AKIN and has a specific modification for children. Although each new definition has refined prior classifications, no universal consensus

exists as to the preferred pediatric AKI definition (Sutherland et al. 2015; Lafrance and Levin 2013). An area of active research is the study of novel biomarkers with the goal of identifying kidney injury in critically ill children before changes in serum creatinine occur and of allowing prevention and possibly earlier intervention. Biomarkers under investigation and validation include urinary neutrophil gelatinase-associated lipocalin (NGAL), serum cystatin C, urinary kidney injury molecule (KIM)-1, urinary interleukin (IL)-18, and urinary liver-type fatty acid binding protein (L-FABP) (Schiffel and Lang 2012; Vanmassenhove et al. 2013). Apart from cystatin C, none of these markers has yet become part of routine clinical practice.

Etiology

Kidney function becomes impaired when adequate blood supply and oxygenation, parenchymal integrity and patency of the urinary tract are

interrupted. Consequently, AKI can be viewed as caused primarily by prerenal, intrinsic renal and postrenal factors. Despite substantial overlap, analysis of the likely cause is essential for remediation and treatment.

Epidemiology

The epidemiology of AKI has evolved significantly over the years. Common etiologies, such as infections and sepsis, volume depletion, and primary renal diseases (acute glomerulonephritis, hemolytic uremic syndrome) (Lameire et al. 2016) experience a shift to frequently multifactorial events and complications of advanced technological procedures, such as cardiac surgeries, exposure to nephrotoxic drugs, etc. (Hui-Stickle et al. 2005). Nephrotoxic agents contribute to at least 25% of AKI in the intensive care unit (Mehta et al. 2004). AKI is common in preterm infants, seen in up to 50% of neonates with asphyxia (Aggarwal et al. 2005), children undergoing cardiac surgery (around 30–50%) (Bucholz et al. 2015; Mishra et al. 2005) and after bone marrow transplantation (Kist-van Holthe et al. 1998). The overall incidence of AKI in pediatric intensive care units is around 5% (Bailey et al. 2007), although a more recent retrospective analysis of PICU discharges estimates the incidence of pediatric AKI in the intensive care unit between 25% and 50% (Sutherland et al. 2015; Selewski et al. 2014). AKI has been shown to be an independent risk factor for mortality in children in the ICU. A large international prospective observational study, “Assessment of Worldwide Acute Kidney Injury, Renal Angina, and Epidemiology” (AWARE) (Basu et al. 2015) was launched in 2014 and aims to follow more than 5,000 critically-ill children worldwide.

Treatment

General measures to prevent AKI include restoration of intravascular volume, avoidance of hypotension and renal ischemia by providing inotropic support in critically ill children follow-

ing volume repletion (i.e. early goal-directed therapy in children with sepsis), and careful readjustment of nephrotoxic medications based on close monitoring of drug levels and renal function. Several pharmacological agents including mannitol, loop diuretics, low-dose dopamine, fenoldopam, and N-acetylcysteine have been studied in pediatric AKI with no convincing evidence of benefit, but potential adverse side effects; none is routinely recommended to prevent AKI or its progression.

Management of AKI includes judicious fluid administration to maintain euvolemia, treatment of electrolyte disarray including hyperkalemia, metabolic acidosis, hyperphosphatemia, and hypocalcemia, and treatment of coexistent hypertension if present. Loop diuretics are often used to induce diuresis in the setting of volume overload or for hyperkalemia, but have not been shown to prevent AKI or substantially alter the natural history of AKI other than enhancing urine output in the few nephrons that remain functional. Restriction of sodium, potassium, and phosphate delivery may be indicated, as may sodium polystyrene sulfonate for hyperkalemia and oral phosphate binders for hyperphosphatemia. Metabolic acidosis should be corrected carefully; the exchange of plasma protein-bound hydrogen ions with calcium can result in a decrease in available ionized calcium and result in tetany. Frequent dose adjustments of renally eliminated or potentially nephrotoxic medications are necessary, and a multidisciplinary approach with intensivists, nephrologists, and specialized pharmacists is recommended.

Indications and Timing of RRT

Renal replacement therapy (RRT) is considered early when conservative measures fail. Typical indications include fluid overload (10–20% excess), hyperkalemia or severe acidosis unresponsive to pharmacological therapy, uremia (typically blood urea nitrogen [BUN] > 100 mg/dL (30 mM) or symptomatic), or an inability to provide adequate nutrition (Selewski and Symons 2014). Volume overload has been recognized as a

predictor of unfavorable outcome, and the degree of volume overload at RRT initiation is independently associated with increased mortality—specifically fluid overload greater than 20% (Sutherland et al. 2010), leading to an overall trend in many centers towards earlier initiation of RRT (Basu et al. 2011). RRT modalities include peritoneal dialysis (PD), hemodialysis (HD), and continuous renal replacement therapy (CRRT); their choice is dictated largely by the patient's clinical aspects as well as the availability of equipment and expertise (Walters et al. 2009). The Prospective Pediatric CRRT (ppCRRT) registry demonstrated no difference in overall outcomes based on modality or dose of CRRT used (Flores et al. 2008) in bone marrow transplant recipients. Peritoneal dialysis is advantageous in younger children and neonates and in resource-limited countries, with no requirements for systemic/regional anticoagulation, vascular access, or specialized equipment or personnel. Hemodialysis offers the advantage of rapidly correcting fluid or electrolyte imbalances but requires patients to tolerate a large extracorporeal volume, and therefore CRRT may be preferred in children with multisystem organ dysfunction or hemodynamic instability: it permits gentler fluid removal rates with less dynamic fluid shifts than HD while allowing full total enteral or parenteral nutrition.

Prognosis

The overall mortality for AKI in the U.S. is around 15% (Sutherland et al. 2013); it is lower in non-ICU compared with ICU settings ranging from 1.5% to 9.5% (Sutherland et al. 2013, 2015). The ppCRRT registry of patients requiring RRT reports a mortality of 42%. Survival was lowest in patients <10 kg and those with liver disease/transplant (31%), pulmonary disease/transplant (45%), and bone marrow transplant (45%) (Symons et al. 2007). Patients who survive AKI have an increased risk for hypertension, CKD, and ESRD. A prospective cohort study of pediatric AKI survivors demonstrated that more than 10% had CKD after 3 years, defined as presence

of albuminuria and/or GFR <60 mL/min/1.73 m², and nearly 50% were classified as at risk of CKD (mildly decreased GFR of 60–90 mL/min/1.73 m², hypertension, and/or hyperfiltration) (Mammen et al. 2012).

Chronic Kidney Disease in Children

Introduction

As of 2015 estimates, chronic kidney disease (CKD) is currently estimated to affect 14% of the U.S. population (Saran et al. 2016). CKD is defined as abnormal kidney function based on laboratory, urinalysis and/or imaging tests. Although children comprise only a small proportion of the total CKD population, pediatric kidney function decline appears to be more rapid compared with adults. Extra-renal manifestations and long-term outcome are uniquely different between pediatric and adulthood CKD due to the essential role of normal kidney and related organ functions on the child's physical and brain development. Young adults with ESKD suffer significant comorbidities, with as much as a 10- to 100-fold increased risk of coronary artery calcifications, left ventricular hypertrophy, carotid arteriopathy, infectious complications, and metabolic bone disease (Goodman et al. 2000; Groothoff et al. 2005; McDonald and Craig 2004; Oh et al. 2002). Age-specific mortality rates of dialyzed children are more than 130-fold higher than of the general US population (Saran et al. 2015). There is a growing awareness of the impact of cardiovascular disease in children with CKD. The cardiovascular mortality of children with ESKD is 1000-fold higher than that of the general pediatric population (Parekh et al. 2002). The overall burden of ESKD on the US healthcare system is staggering, with over \$31 billion in Medicare spending in 2013, representing over 7% of the entire annual budget (Saran et al. 2016). Improvement of early diagnosis, intervention, and long-term outcomes of patients, including children with CKD is a major goal of the International Society of Nephrology, the National Kidney Foundation and other organizations.

Multi-center prospective studies and ongoing reports of retrospective registry data have contributed significantly to the CKD literature over the last several years.

Definition

In 2003 the National Kidney Foundation proposed a new definition and staging of CKD in children (Table 15.3) (Hogg et al. 2003) which was slightly adapted in 2013 by the Kidney Disease Improving Global Outcomes (KDIGO) workgroup (Andrassy 2013). Chronic kidney disease is defined as functional or structural damage to the kidneys or decrease in glomerular filtration rate (GFR) to less than 60 mL/min/1.73 m² for at least three months. Importantly, the GFR may be normal or near-normal in the early stages of CKD when it is most important to prevent progression and adequately treat comorbidities frequently encountered with pediatric CKD. Although diabetes and hypertension account for the vast majority of CKD in adults, approximately two thirds of childhood CKD are attributed to congenital abnormalities of the kidney and urinary tract (CAKUT) including renal dysplasia/hypoplasia and various cause of obstructive uropathy (Harambat et al. 2012). Other common causes include focal segmental glomerulosclerosis (FSGS), chronic GN (lupus nephritis, IgA nephropathy, membranoproliferative glomerulo-

Table 15.3 CKD classification in children

| Stage | GFR (mL/min/1.73 m ²) | |
|-------|-----------------------------------|------------------------|
| | K/DOQI definition | KDIGO definition |
| 1 | ≥90 | ≥90 |
| 2 | 60–89 | 60–89 |
| 3 | 30–59 | 3a: 45–59 3b: 30–44 |
| 4 | 15–29 | 15–29 |
| 5 | <15 | <15 |

nephritis, HSP), ciliopathies (nephronophthisis, autosomal recessive polycystic kidney disease), hemolytic uremic syndrome, cystinosis, and Alport's syndrome.

New Equations to Estimate GFR

The original Schwartz formula to estimate GFR in children was developed in the mid-1970s using serum creatinine, height, and an empiric constant for age and gender. However, the serum creatinine assay has changed from the Jaffe chromogen reaction to the enzymatic method, requiring a refinement of pediatric GFR estimating formulas. The equation was updated in 2009 based on results from the prospective observational multi-center study Chronic Kidney Disease in Children (CKiD), which measured GFR through the plasma disappearance of iohexol (Schwartz et al. 2009):

$$eGFR = 39.1 \times [\text{height} / \text{SCr}]^{0.516} \times [1.8 / \text{cystatin C}]^{0.294} \times [30 / \text{BUN}]^{0.169} \times [1.099]^{\text{Male}} \times [\text{height} / 1.4]^{0.188}$$

Additionally, a simplified estimating equation was derived—the so-called bedside CKiD equation—which included an updated constant of 0.413: eGFR = 0.413 × height (cm)/serum creatinine (in mg/dL); for SI units, the constant is 36.5: eGFR = 36.5 × height/serum [μmol/L]. Although the equation has been shown to perform reasonably well in children with moderate CKD with 88% of the estimated GFR values falling within 30% of measured iohexol GFR (Schwartz et al. 2009), the bedside CKiD equation underestimates GFR particularly in male adolescents and children with a true GFR greater than 90 mL/

min/1.73 m² (Staples et al. 2010). Further studies are planned in children and adolescents with normal kidney function and earlier stages of CKD.

Advances in Markers of CKD Progression

Several advances have been made in the recognition of modifiable risk factors to delay CKD progression. Hypertension is frequently present and often poorly controlled; the CKiD study has shown that over half of children had a systolic

or diastolic blood pressure ≥ 95 percentile or use of a current antihypertensive medication at enrollment (Flynn et al. 2008). More recent investigations have demonstrated a prevalence of masked hypertension in 35% (Samuels et al. 2012). Twenty percentage of these children with masked hypertension had left ventricular hypertrophy (LVH) compared with 34% of children with confirmed hypertension (Mitsnefes et al. 2010). The ESCAPE trial (Group et al. 2009), published in 2009, demonstrated that achieving 50th percentile blood pressure targets from an intensified blood pressure regimen with ACE-I delayed CKD progression. Proteinuria is another recognized and potentially modifiable risk factor for CKD progression in children; in a recent longitudinal analysis of CKiD data, nephrotic-range proteinuria (urine protein to creatinine ratio >2 mg/mg) was shown to be one of the strongest risk factors for CKD progression (Warady et al. 2015). Therefore, renin-angiotensin-aldosterone system blockade with ACE-I or ARB is considered first-line therapy for hypertension or proteinuria in children with CKD. Other novel risk factors for CKD progression which have recently been explored include low birth weight and prematurity (Carmody and Charlton 2013), exposure to secondhand smoke (Omoloja et al. 2013), oxidative stress (Cachofeiro et al. 2008), and hyperuricemia (Rodenbach et al. 2015).

Update in Pediatric Hypertension

Introduction

Hypertension in children is defined as a sustained systolic or diastolic blood pressure ≥ 95 percentile for age, gender, and height according to normative data derived from large databases of blood pressure readings obtained in healthy children. One of the most commonly used sources for normal blood pressure tables is the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents Fourth Report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents (National High Blood Pressure

Education Program Working Group on High Blood Pressure in C, Adolescents 2004). The epidemiology, diagnosis, and management of childhood hypertension has changed greatly in the last decade, in part fueled by the rising obesity epidemic. The current fourth report guidelines are in the process of revision with the intention to reflect the changing trends in pediatric hypertension management with expectation of final guideline publication in 2017.

Epidemiology

Historically, hypertension in children was thought to be rare, and when present usually secondary to an underlying condition, most commonly renal parenchymal disease. However, the worldwide obesity epidemic has had a dramatic impact on obesity-related conditions including hypertension, and essential hypertension is now thought to be the most common form of hypertension during children and adolescence (Lurbe et al. 2010). Using data from the US National Health and Nutrition Examination Survey (NHANES), an increase in the prevalence of prehypertension by 2.3% and hypertension by 1% was observed from 1963 to 1999 (Din-Dzietham et al. 2007). Prehypertension progresses to hypertension at the rate of 7% per year (Expert Panel on Integrated Guidelines for Cardiovascular H, Risk Reduction in C, Adolescents, National Heart L, Blood I 2011). More recent and alarming analysis of NHANES survey data from 1999–2008 revealed that 14% of adolescents ages 12–19 years have pre-hypertension or hypertension, in addition to several other metabolic risk factors with 22% elevated low-density lipoprotein cholesterol and 15% with impaired glucose tolerance (May et al. 2012). The entire distribution of childhood blood pressure trends has shifted upward by 1.4 mmHg for systolic BP and 3.3 mmHg for diastolic blood pressure from 1988 to 2000 (Muntner et al. 2004). The most current estimates suggest that the prevalence of prehypertension has reached around 10% and hypertension 4% in all children, with hypertension prevalence in obese children reported at 11–47% (Flynn 2013).

Diagnosis

Blood pressure is usually measured via indirect methods, either through auscultation or oscillometric devices. Auscultative blood pressure assessment is considered the gold standard and is what is used for all pediatric normative data. Oscillometric devices calculate blood pressure by proprietary unpublished formulas, and are known to overestimate blood pressure in children by as much as 5–10 mmHg (Clark et al. 2002). Although the use of oscillometric blood pressure assessment has become widespread, caution should be used when diagnosing hypertension with an automated device in children and elevated readings should be confirmed by manual auscultation.

Twenty-four hour ambulatory blood pressure monitoring (ABPM) is increasingly used in the diagnosis of hypertension in children. In adults ABPM has been shown to be superior to clinical BP monitoring in predicting cardiovascular morbidity and mortality (Metoki et al. 2006). In children, ABPM offers the advantages of distinguishing white coat from true hypertension, evaluating for the presence of masked hypertension, and of more precisely characterizing changes in blood pressure during daily activities and while asleep (Graves and Althaf 2006). In 2014 the American Heart Association published a Scientific Statement regarding the use of APBM in children, affirming its utility in the diagnosis and management of hypertension in children (Flynn et al. 2014). ABPM should be considered for the confirmation of the diagnosis of HTN (and exclusion of white coat HTN), evaluation for the presence of masked HTN, assessing BP variability, determining nocturnal dipping status, and evaluation of the severity and persistence of chronic diseases associated with HTN.

Evaluation of Target Organ Damage

Recent developments in the field of pediatric HTN include an improved ability to identify target organ damage. The use of echocardiography to evaluate for the presence of left ventricular hypertrophy is routine in clinical practice, and

the detection of a left ventricular mass index (LVMI) >95% is considered an indication for initiation of antihypertensive pharmacological therapy (Garin and Araya 2009; Daniels et al. 1998). However, the complex relationship between heart and body growth during development requires normalization of LV mass to body size, which led to the development and recent proposal of new reference centiles (Foster et al. 2016). Other advances, predominantly used in research settings, include pulse wave velocity to measure central arterial stiffness, augmentation index to measure peripheral arterial stiffness, and radial artery applanation tonometry which measures central vascular pressures and has been shown to be a more accurate predictor of cardiovascular disease outcomes than peripheral blood pressure (O'Rourke and Adji 2010).

Treatment

For most patients with essential hypertension, a 6–12 month trial of nonpharmacological interventions should be recommended which include the DASH diet (Dietary Approaches to Stop Hypertension, a low sodium plant-based diet with whole grains, low-fat dairy and lean meats), moderate to vigorous exercise most days of the week, achievement and maintenance of normal body mass index, and limited screen time (Expert Panel on Integrated Guidelines for Cardiovascular H, Risk Reduction in C, Adolescents, National Heart L, Blood I 2011). Pharmacological therapy is indicated for hypertension that persists despite lifestyle changes, secondary hypertension, hypertension associated with end-organ damage such as left ventricular hypertrophy, and hypertension associated with chronic diseases such as diabetes or chronic kidney disease. In part due to the Best Pharmaceuticals for Children Act, enacted by the FDA in 2002, the number of antihypertensive medications with pediatric-specific indications has increased considerably over the past decade, and includes angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers, beta blockers, calcium channel blockers, and diuretics (Welch et al. 2012).

Genetics and the Kidney

Introduction

The genetics of renal diseases have seen groundbreaking changes over the last two decades with direct effects on diagnosis and clinic practice. Ever since the gene for Autosomal Dominant Polycystic Kidney Disease (ADPKD) was mapped to the short arm of chromosome 16 in 1985 (Reeders et al. 1985), the number of genes associated with renal disease has increased exponentially. Such progress has led to a clearer understanding of the pathophysiology of pediatric kidney disease, transformed the diagnostic workup and in some cases offers the possibility of a diagnosis without the need for a kidney biopsy, and enhanced the ability to provide prognostic information for patients and their families. Although only a tantalizing promise at present, the identification of specific gene mutations holds the possibility of curative treatment through gene therapy.

Glomerular Diseases

Glucocorticoid (steroid)-resistant nephrotic syndrome is a challenging disease in childhood. Histologically, patients with glucocorticoid-resistant nephrotic syndrome often demonstrate focal segmental glomerulosclerosis (FSGS); FSGS is the 2nd common cause of ESRD in the pediatric age group. Principally, glucocorticoid resistant nephrotic syndrome can be divided into (1) congenital forms, the majority of which manifest during the first 3 months of life, (2) FSGS in childhood with identifiable genetic mutations, (3) FSGS without identifiable mutation, but presence of a circulating FSGS factor, and (4) adult onset/familial forms of FSGS. Up to 85% of cases presenting in the first 3 months and 66% of those presenting in the first year of life have identifiable, disease-causing mutations in one of the following four loci: *NPHS1* (encoding nephrin, in the podocyte slit diaphragm), *NPHS2* (podocin), *LAMB2* (laminin beta 2 in the glomerular basement membrane), or *WT1* (Wilms tumor 1, a

transcription factor) (Hinkes et al. 2007). Systematic screening of all putative disease-causing genes by next-generation sequencing can now identify single gene defects in up to 30% of cases of glucocorticoid-resistant nephrotic syndrome (Sadowski et al. 2015). Importantly, 1% of these mutations lead to defects in the mitochondrial coenzyme Q10 biosynthesis pathway (*COQ2*, *COQ6*, *ADCK4*) and are thought to compromise podocyte energy metabolism. Early clinical evidence indicates that proteinuria may be at least partially responsive to treatment with coenzyme Q₁₀ (Montini et al. 2008b; Heeringa et al. 2011), a widely available nutritional supplement. Early identification of children with a monogenic glomerulopathy is vital, not only because patients may be spared exposure to immunosuppressive medications, which are unlikely to have any benefit, but also is also important for prognostic information;” genetic” forms of nephrotic syndrome are unlikely to recur after kidney transplantation.

Known or suspected ethnic disparities in the epidemiology of CKD and ESRD have been linked to genetic factors that contribute to disease susceptibility and increased risk of accelerated disease progression. *APOLI* polymorphisms are found almost exclusively among individuals of African descent and are believed to confer resistance to disease-causing trypanosomes. The *APOLI* risk variant confers tenfold higher risk of ESRD due to FSGS and sevenfold higher risk of ESRD due to hypertension in adults (Parsa et al. 2013); the lifetime risk of kidney disease due to dual-risk *APOLI* risk alleles is estimated at least 15% (Dummer et al. 2015). Two pediatric cohorts of children with CKD, the CKiD cohort and NEPTUNE cohort, have also identified high-risk *APOLI* risk variants to be associated with faster CKD progression and more aggressive glomerular disease (Ng et al. 2017).

Progress has also been made in the last decade in the pathophysiology and treatment of atypical hemolytic uremic syndrome (aHUS). Discovery of multiple genes involved in the alternative pathway of complement activation has led to the emergence of aHUS largely as a disease of complement dysregulation. About 60% of patients

with aHUS carry currently identifiable mutations in complement genes (*CFH*, *CFI*, *MCP*, *C3*, *CFB*, *THBD*, and *DGKE*) or anti-CFH antibodies, and clinical genetic testing is available in several laboratories, by direct or next generation sequencing (Loirat et al. 2016; Bajracharya et al. 2016). Until recently, plasma therapy (preferably plasma exchange) was considered the therapy of choice for presumed aHUS (Ariceta et al. 2009). However, long-term outcomes were generally poor, particularly for HUS due to CFH mutations, with mortality in excess of 8%, frequent relapses with a risk of 50–80% progression to ESRD within a year, and almost universal risk of recurrence in renal allografts (Sellier-Leclerc et al. 2007). The publication of a pair of articles in 2009 (Nurnberger et al. 2009; Gruppo and Rother 2009) demonstrating the remarkable success in treatment of aHUS with blockade of the terminal complement cascade by eculizumab has revolutionized the treatment of this disease. Eculizumab is a humanized monoclonal antibody that binds C5 and blocks the terminal pathway of complement activation by preventing the generation of the cytotoxic membrane attack complex C5b-9 as well as the chemokine C5a. In 2015 consensus clinical practice recommendations on the management of aHUS in children were published, stressing the importance of eculizumab as first-line therapy, and initiating treatment within the first 24–48 h (Loirat et al. 2016). Although eculizumab has transformed the outlook of aHUS from a dismal prognosis to a now treatable condition, this comes at a high financial cost, with an estimated annual price for eculizumab in 2015 of nearly \$400,000 USD (Blackwell 2015).

Ciliopathies

Hereditary renal cystic disease is a broad term encompassing a diverse array of disease processes including autosomal dominant (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD), nephronophthisis, medullary cystic kidney disease, and a variety of syndromic conditions including Bardet-Biedl, Joubert, and Meckel syndrome; to date more than 95 genes

affecting cilia functions or downstream effect have been identified (Table 15.4) (Vivante and Hildebrandt 2016). A unifying paradigm to cystic kidney disease was developed after the discovery that the gene products of many of the mutated genes are expressed at the primary cilia and centrosome complex (Hildebrandt and Otto 2005). Centrosomes play an important role in maintaining polarity in the cell-cycle regulation of sensory cilia and cell-matrix signaling. This has led to much interest in novel therapeutics targeted at the cell signaling process, and in particular the relationship between vasopressin and cyclic AMP in the development of cyst growth. In 2014, Japan was the first country to approve tolvaptan, a vasopressin 2 receptor antagonist for the treatment of ADPKD which showed significant ability to retard cyst growth in the TEMPO 3:4 trial (Torres et al. 2012). This was followed closely by Europe and Canada in 2015, although approval in the U.S. was denied due to concerns over potential hepatotoxicity.

Renal Tubular Disorders

Renal tubules govern the homeostasis of solute and water regulation by modifying the quantity and composition of the glomerular filtrate. Many tubulopathies are now recognized as single-gene disorders. In most instances, the primary genetic defect causes a loss or gain of function of a specific renal tubular transport protein, often a component of a complex channel or a signaling molecule. Because many transport systems are preferentially expressed in specific tubule segments, such defects can result in recognizable clinical syndromes with characteristic diagnostic features. Genetically determined proximal tubular abnormalities can result in glucosuria, phosphaturia, aminoaciduria, and/or proximal renal tubular acidosis. Generalized proximal tubular dysfunction is known as renal Fanconi syndrome and a feature of several genetic disorders, generally with multisystemic (extrarenal) involvement. Examples are cystinosis (caused by autosomal recessive mutations of *CTNS* that encodes cystinosin), and the X-linked disorders,

Table 15.4 Hereditary cystic kidney disease

| Disease | Gene/protein | MOI | Comment |
|---------------------------------|---|-----|---|
| ADPKD | | | |
| Type 1 | <i>PKD1</i> /polycystin 2 | AD | Polycystic kidneys with large cysts, liver cysts, brain aneurysms, CKD |
| Type 2 | <i>PKD2</i> , polycystin 2 | AD | |
| ARPKD | <i>PKHD1</i> /fibrocystin and polyductin | AR | Polycystic kidney disease, liver fibrosis, CKD |
| Nephronophthisis | <i>NPHP1</i> to <i>NPHP9</i> /nephrocystin types 1–9 | AR | Polyuria, polydipsia, anemia, CKD Senior-Loken syndrome associated with retinal lesions (retinal dystrophy, retinitis pigmentosa) |
| Medullary cystic kidney disease | <i>UMOD</i> /Tamm-Horsfall protein (uromodulin) | AD | CKD (adult-onset), familial juvenile hyperuricemic nephropathy |
| Orofacial digital syndrome | <i>OFD1</i> /OFD1 | XLD | Bilateral kidney cysts, CNS malformations (agenesis of corpus callosum, cerebellar agenesis), micrognathia, malformations of digits of hand |
| Meckel-Gruber syndrome | <i>MKS1</i> ; <i>MKS3</i> /meckelin | AR | Polycystic kidneys, multiple-organ dysplasia, perinatal lethal |
| Bardet-Biedel syndrome 1–12 | <i>BBS1</i> to <i>BBS12</i> /Bardet-Biedel's syndrome proteins | AR | Retinitis pigmentosa, polydactyly, mental retardation, hypogonadism, obesity |
| Jeune Syndrome | <i>IFD80</i> /intraflagellar transport protein 80 homolog <i>DYNC2H1</i> /dynein | AR | Bilateral cystic kidneys, skeletal abnormalities including narrow chest, brachydactyly, short stature |
| Tuberous sclerosis | <i>TSC1</i> /hamartin <i>TSC2</i> /tuberin | AD | Renal angiomyolipomas, seizures, cardiac rhabdomyomas, skin lesions, ADPKD (contiguous gene syndrome) |
| von-Hippel-Lindau | <i>VHL</i> /tumor suppressor gene (G7 protein) | AD | Increased risk for tumors: retinal angiomas, pheochromocytoma, hemangioblastoma, renal cell carcinoma, pancreatic cysts |
| WAGR complex | <i>WT1</i> /WT suppressor gene 1 | AD | Wilm tumor, aniridia, genitourinary anomalies, growth retardation |
| Papillary renal cell carcinoma | <i>MET</i> /hepatocyte growth factor receptor | AD | Papillary renal cell carcinoma (subtype of renal cell carcinoma) |

MOI mode of inheritance, AD autosomal dominant, AR autosomal recessive, XLD X-linked dominant

oculocerebrorenal (or Lowe) syndrome (caused by mutations of *OCRL1* that encodes an inositol polyphosphate-5-phosphatase) and Dent's disease (caused by mutations of *CLCN5* that encodes a renal-specific chloride/proton antiporter (Dent 1), or—infrequently—by mutations in the *OCRL1* gene (Dent 2), the same gene that is responsible for Lowe syndrome. Other forms are being identified. Dysfunctional solute reabsorption in the thick ascending limb of the loop of Henle results in Bartter syndrome and its variants and secondary hypokalemic metabolic alkalosis, caused by mutations in *SLC12A2* that encodes the renal-specific Na-K-Cl cotransporter

(NKCC2) (neonatal Bartter type 1), or physiologically related proteins, including the potassium channel *ROMK/KCNJ1* (neonatal Bartter type 2), and other channels or their subunits. Defects of the distal convoluted tubule cause Gitelman syndrome—due to mutations of the sodium-chloride symporter *SLC12A3* (*NCCT*)—and other forms of hypomagnesemia. Defects in the collecting duct impair reabsorption of water, sodium, potassium, and hydrogen ions resulting in type IV renal tubular acidosis. Nephrogenic diabetes insipidus is caused by mutations in the aquaporin-2 water channel (Deen et al. 1994) or the vasopressin-2-receptor (Rosenthal et al. 1992).

Congenital Anomalies of the Kidney and Urinary Tract (CAKUT)

These congenital anomalies are due to a disturbance of nephrogenesis. They may be the consequence of single gene mutations or copy number variations (CNV). Various transcription factors and signaling molecules including but not limited to *WT1*, *RET*, *EYA1*, *FOXC1*, *PAX2*, and *PAX8* that are critical to reciprocal interactions between the metanephric mesenchyme and the ureteric epithelium, have been identified underlying forms of CAKUT. Genomic imbalances using microarray techniques to identify CNVs were reported in 7.4% of the CKiD cohort, and were highest in the participants with underlying renal hypodysplasia (Verbitsky et al. 2015). Monogenic causes of CAKUT are currently estimated at 17% of cases (Vivante and Hildebrandt 2016), and the list is only expected to grow longer.

Nephrolithiasis

Currently >14 genes have been identified in association with nephrolithiasis, estimated at >21% of cases of pediatric nephrolithiasis/nephrocalcinosis and 12% with onset >18 years old (Vivante and Hildebrandt 2016). Mutations in two genes have been causally implicated in cystinuria, *SLC3A1* and *SLC7A9* that are inherited in an autosomal recessive pattern. Mutated or defective transporters interfere with tubular reabsorption of the positively charged amino acids cysteine, lysine, ornithine, and arginine. *AGXT* and *GRHPR* are both associated with primary hyperoxaluria, an autosomal recessive condition resulting in massively increased urinary oxalate excretion, recalcitrant oxalate stones, CKD leading to ESRD often in adolescence or early childhood, and ultimately systemic oxalate deposition. The standard treatment for nephrolithiasis which typically includes increasing fluid intake, minimizing sodium intake, and the use of thiazide diuretics and potassium citrate, which is effective in the majority of calcium-containing stone forming patients, does not address the underlying pathophysiological mechanisms of the described molecular disorders.

References

- Aggarwal A, Kumar P, Chowdhary G, Majumdar S, Narang A. Evaluation of renal functions in asphyxiated newborns. *J Trop Pediatr*. 2005;51(5):295–9.
- Akcan-Arikan A, Zappitelli M, Loftis LL, Washburn KK, Jefferson LS, Goldstein SL. Modified RIFLE criteria in critically ill children with acute kidney injury. *Kidney Int*. 2007;71(10):1028–35.
- Andrassy KM. Comments on 'KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease'. *Kidney Int*. 2013;84(3):622–3.
- Ariceta G, Besbas N, Johnson S, Karpman D, Landau D, Licht C, et al. Guideline for the investigation and initial therapy of diarrhea-negative hemolytic uremic syndrome. *Pediatr Nephrol*. 2009;24(4):687–96.
- Bailey D, Phan V, Litalien C, Ducruet T, Merouani A, Lacroix J, et al. Risk factors of acute renal failure in critically ill children: a prospective descriptive epidemiological study. *Pediatr Crit Care Med*. 2007;8(1):29–35.
- Bajracharya P, Jain A, Baracco R, Mattoo TK, Kapur G. Atypical hemolytic uremic syndrome: a clinical conundrum. *Pediatr Nephrol*. 2016;31(10):1615–24.
- Basu RK, Devarajan P, Wong H, Wheeler DS. An update and review of acute kidney injury in pediatrics. *Pediatr Crit Care Med*. 2011;12(3):339–47.
- Basu RK, Kaddourah A, Terrell T, Mottes T, Arnold P, Jacobs J, et al. Assessment of worldwide acute kidney injury, renal angina and epidemiology in critically ill children (AWARE): study protocol for a prospective observational study. *BMC Nephrol*. 2015;16:24.
- Bell LE, Mattoo TK. Update on childhood urinary tract infection and vesicoureteral reflux. *Semin Nephrol*. 2009;29(4):349–59.
- Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute dialysis quality initiative w. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care*. 2004;8(4):R204–12.
- Blackwell T. World's most expensive drug—which costs up to \$700,000 per year—too expensive. *Can Natl Post*. 2015;3:2015.
- Brandstrom P, Esbjorner E, Herthelius M, Swerkersson S, Jodal U, Hansson S. The Swedish reflux trial in children: III. Urinary tract infection pattern. *J Urol*. 2010;184(1):286–91.
- Brandstrom P, Jodal U, Sillen U, Hansson S. The Swedish reflux trial: review of a randomized, controlled trial in children with dilating vesicoureteral reflux. *J Pediatr Urol*. 2011;7(6):594–600.
- Bucholz EM, Whitlock RP, Zappitelli M, Devarajan P, Eikelboom J, Garg AX, et al. Cardiac biomarkers and acute kidney injury after cardiac surgery. *Pediatrics*. 2015;135(4):e945–56.

- Cachofeiro V, Goicochea M, de Vinuesa SG, Oubina P, Lahera V, Luno J. Oxidative stress and inflammation, a link between chronic kidney disease and cardiovascular disease. *Kidney Int Suppl.* 2008;111:S4–9.
- Carapetis JR, Steer AC, Mulholland EK, Weber M. The global burden of group A streptococcal diseases. *Lancet Infect Dis.* 2005;5(11):685–94.
- Carmody JB, Charlton JR. Short-term gestation, long-term risk: prematurity and chronic kidney disease. *Pediatrics.* 2013;131(6):1168–79.
- Chand DH, Rhoades T, Poe SA, Kraus S, Strife CF. Incidence and severity of vesicoureteral reflux in children related to age, gender, race and diagnosis. *J Urol.* 2003;170(4 Pt 2):1548–50.
- Chesney RW. The development of pediatric nephrology. *Pediatr Res.* 2002;52(5):770–8.
- Chou HH, Chiou YY, Hung PH, Chiang PC, Wang ST. Omega-3 fatty acids ameliorate proteinuria but not renal function in IgA nephropathy: a meta-analysis of randomized controlled trials. *Nephron Clin Pract.* 2012;121(1–2):c30–5.
- Clark JA, Lieh-Lai MW, Sarnaik A, Mattoo TK. Discrepancies between direct and indirect blood pressure measurements using various recommendations for arm cuff selection. *Pediatrics.* 2002;110(5):920–3.
- Conway PH, Cnaan A, Zaoutis T, Henry BV, Grundmeier RW, Keren R. Recurrent urinary tract infections in children: risk factors and association with prophylactic antimicrobials. *JAMA.* 2007;298(2):179–86.
- Coulthard MG. Vesicoureteric reflux is not a benign condition. *Pediatr Nephrol.* 2009;24(2):227–32.
- Craig JC, Simpson JM, Williams GJ, Lowe A, Reynolds GJ, McTaggart SJ, et al. Antibiotic prophylaxis and recurrent urinary tract infection in children. *N Engl J Med.* 2009;361(18):1748–59.
- Daniels SR, Loggie JM, Khoury P, Kimball TR. Left ventricular geometry and severe left ventricular hypertrophy in children and adolescents with essential hypertension. *Circulation.* 1998;97(19):1907–11.
- Davin JC, Coppo R. Henoch-Schonlein purpura nephritis in children. *Nat Rev Nephrol.* 2014;10(10):563–73.
- Deen PM, Verdijk MA, Knoers NV, Wieringa B, Monnens LA, van Os CH, et al. Requirement of human renal water channel aquaporin-2 for vasopressin-dependent concentration of urine. *Science.* 1994;264(5155):92–5.
- Din-Dzietham R, Liu Y, Bielo MV, Shamsa F. High blood pressure trends in children and adolescents in national surveys, 1963 to 2002. *Circulation.* 2007;116(13):1488–96.
- Dummer PD, Limou S, Rosenberg AZ, Heymann J, Nelson G, Winkler CA, et al. APOL1 kidney disease risk variants: an evolving landscape. *Semin Nephrol.* 2015;35(3):222–36.
- Elder JS. Guidelines for consideration for surgical repair of vesicoureteral reflux. *Curr Opin Urol.* 2000;10(6):579–85.
- Expert Panel on Integrated Guidelines for Cardiovascular H, Risk Reduction in C, Adolescents, National Heart L, Blood I. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics.* 2011;128(Suppl 5):S213–56.
- Fassett RG, Venuthurupalli SK, Gobe GC, Coombes JS, Cooper MA, Hoy WE. Biomarkers in chronic kidney disease: a review. *Kidney Int.* 2011;80(8):806–21.
- Fernbach SK, Maizels M, Conway JJ. Ultrasound grading of hydronephrosis: introduction to the system used by the society for fetal urology. *Pediatr Radiol.* 1993;23(6):478–80.
- Flores FX, Brophy PD, Symons JM, Fortenberry JD, Chua AN, Alexander SR, et al. Continuous renal replacement therapy (CRRT) after stem cell transplantation. A report from the prospective pediatric CRRT Registry Group. *Pediatr Nephrol.* 2008;23(4):625–30.
- Flynn J. The changing face of pediatric hypertension in the era of the childhood obesity epidemic. *Pediatr Nephrol.* 2013;28(7):1059–66.
- Flynn JT, Mitsnefes M, Pierce C, Cole SR, Parekh RS, Furth SL, et al. Blood pressure in children with chronic kidney disease: a report from the chronic kidney disease in children study. *Hypertension.* 2008;52(4):631–7.
- Flynn JT, Daniels SR, Hayman LL, Maahs DM, McCrindle BW, Mitsnefes M, et al. Update: ambulatory blood pressure monitoring in children and adolescents: a scientific statement from the American Heart Association. *Hypertension.* 2014;63(5):1116–35.
- Fonseca FF, Tanno FY, Nguyen HT. Current options in the management of primary vesicoureteral reflux in children. *Pediatr Clin N Am.* 2012;59(4):819–34.
- Foster BJ, Khoury PR, Kimball TR, Mackie AS, Mitsnefes M. New reference centiles for left ventricular mass relative to lean body mass in children. *J Am Soc Echocardiogr.* 2016;29(5):441–7. e2
- Gardner-Medwin JM, Dolezalova P, Cummins C, Southwood TR. Incidence of Henoch-Schonlein purpura, Kawasaki disease, and rare vasculitides in children of different ethnic origins. *Lancet.* 2002;360(9341):1197–202.
- Garin EH, Araya CE. Treatment of systemic hypertension in children and adolescents. *Curr Opin Pediatr.* 2009;21(5):600–4.
- Garin EH, Olavarria F, Garcia Nieto V, Valenciano B, Campos A, Young L. Clinical significance of primary vesicoureteral reflux and urinary antibiotic prophylaxis after acute pyelonephritis: a multicenter, randomized, controlled study. *Pediatrics.* 2006;117(3):626–32.
- Gauthier M, Gouin S, Phan V, Gravel J. Association of malodorous urine with urinary tract infection in children aged 1 to 36 months. *Pediatrics.* 2012;129(5):885–90.
- Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med.* 2000;342(20):1478–83.
- Graves JW, Althaf MM. Utility of ambulatory blood pressure monitoring in children and adolescents. *Pediatr Nephrol.* 2006;21(11):1640–52.

- Grignon A, Filion R, Filiatrault D, Robitaille P, Homsy Y, Boutin H, et al. Urinary tract dilatation in utero: classification and clinical applications. *Radiology*. 1986;160(3):645–7.
- Groothoff J, Gruppen M, de Groot E, Offringa M. Cardiovascular disease as a late complication of end-stage renal disease in children. *Perit Dial Int*. 2005;25(Suppl 3):S123–6.
- Group ET, Wuhl E, Trivelli A, Picca S, Litwin M, Peco-Antic A, et al. Strict blood-pressure control and progression of renal failure in children. *N Engl J Med*. 2009;361(17):1639–50.
- Gruppo RA, Rother RP. Eculizumab for congenital atypical hemolytic-uremic syndrome. *N Engl J Med*. 2009;360(5):544–6.
- Hanna MH, Dalla Gassa A, Mayer G, Zaza G, Brophy PD, Gesualdo L, et al. The nephrologist of tomorrow: towards a kidney-omic future. *Pediatr Nephrol*. 2016;32(3):393–404.
- Hannula A, Venhola M, Perhomaa M, Pokka T, Renko M, Uhari M. Imaging the urinary tract in children with urinary tract infection. *Acta Paediatr*. 2011;100(12):e253–9.
- Harambat J, van Stralen KJ, Kim JJ, Tizard EJ. Epidemiology of chronic kidney disease in children. *Pediatr Nephrol*. 2012;27(3):363–73.
- Heeringa SF, Chernin G, Chaki M, Zhou W, Sloan AJ, Ji Z, et al. COQ6 mutations in human patients produce nephrotic syndrome with sensorineural deafness. *J Clin Invest*. 2011;121(5):2013–24.
- Hildebrandt F, Otto E. Cilia and centrosomes: a unifying pathogenic concept for cystic kidney disease? *Nat Rev Genet*. 2005;6(12):928–40.
- Hinks BG, Mucha B, Vlangos CN, Gbadegesin R, Liu J, Hasselbacher K, et al. Nephrotic syndrome in the first year of life: two thirds of cases are caused by mutations in 4 genes (NPHS1, NPHS2, WT1, and LAMB2). *Pediatrics*. 2007;119(4):e907–19.
- Hiraki LT, Feldman CH, Liu J, Alarcon GS, Fischer MA, Winkelmayer WC, et al. Prevalence, incidence, and demographics of systemic lupus erythematosus and lupus nephritis from 2000 to 2004 among children in the US Medicaid beneficiary population. *Arthritis Rheum*. 2012;64(8):2669–76.
- Hoberman A, Wald ER, Hickey RW, Baskin M, Charron M, Majd M, et al. Oral versus initial intravenous therapy for urinary tract infections in young febrile children. *Pediatrics*. 1999;104(1 Pt 1):79–86.
- Hoberman A, Charron M, Hickey RW, Baskin M, Kearney DH, Wald ER. Imaging studies after a first febrile urinary tract infection in young children. *N Engl J Med*. 2003;348(3):195–202.
- Hogg RJ. IgA nephropathy: clinical features and natural history—a pediatric perspective. *Am J Kidney Dis*. 1988;12(5):358–61.
- Hogg RJ, Furth S, Lemley KV, Portman R, Schwartz GJ, Coresh J, et al. National kidney foundation's kidney disease outcomes quality initiative clinical practice guidelines for chronic kidney disease in children and adolescents: evaluation, classification, and stratification. *Pediatrics*. 2003;111(6 Pt 1):1416–21.
- Hui-Stickle S, Brewer ED, Goldstein SL. Pediatric ARF epidemiology at a tertiary care center from 1999 to 2001. *Am J Kidney Dis*. 2005;45(1):96–101.
- Investigators RT, Hoberman A, Greenfield SP, Mattoo TK, Keren R, Mathews R, et al. Antimicrobial prophylaxis for children with vesicoureteral reflux. *N Engl J Med*. 2014;370(25):2367–76.
- Ismaili K, Avni FE, Hall M, Brussels Free University Perinatal Nephrology Study G. Results of systematic voiding cystourethrography in infants with antenatally diagnosed renal pelvis dilation. *J Pediatr*. 2002;141(1):21–4.
- Kamei K, Ogura M, Sato M, Ito S, Ishikura K. Evolution of IgA nephropathy into anaphylactoid purpura in six cases—further evidence that IgA nephropathy and Henoch-Schönlein purpura nephritis share common pathogenesis. *Pediatr Nephrol*. 2016;31(5):779–85.
- Kist-van Holthe JE, van Zwet JM, Brand R, van Weel MH, Vossen JM, van der Heijden AJ. Bone marrow transplantation in children: consequences for renal function shortly after and 1 year post-BMT. *Bone Marrow Transplant*. 1998;22(6):559–64.
- La Scola C, De Mutiis C, Hewitt IK, Puccio G, Toffolo A, Zucchetto P, et al. Different guidelines for imaging after first UTI in febrile infants: yield, cost, and radiation. *Pediatrics*. 2013;131(3):e665–71.
- Lafrance JP, Levin A. Defining AKI: closer to getting the math right. *Nephrol Dial Transplant*. 2013;28(6):1340–2.
- Lameire N, Van Biesen W, Vanholder R. Epidemiology of acute kidney injury in children worldwide, including developing countries. *Pediatr Nephrol*. 2016;32(8):1301–14.
- Lebowitz RL, Olbing H, Parkkulainen KV, Smellie JM, Tamminen-Mobius TE. International system of radiographic grading of vesicoureteric reflux. International reflux study in children. *Pediatr Radiol*. 1985;15(2):105–9.
- Lee RS, Cendron M, Kinnamon DD, Nguyen HT. Antenatal hydronephrosis as a predictor of postnatal outcome: a meta-analysis. *Pediatrics*. 2006;118(2):586–93.
- Lendvay TS, Sorensen M, Cowan CA, Joyner BD, Mitchell MM, Grady RW. The evolution of vesicoureteral reflux management in the era of dextranomer/hyaluronic acid copolymer: a pediatric health information system database study. *J Urol*. 2006;176(4 Pt 2):1864–7.
- Loirat C, Fakhouri F, Ariceta G, Besbas N, Bitzan M, Bjerre A, et al. An international consensus approach to the management of atypical hemolytic uremic syndrome in children. *Pediatr Nephrol*. 2016;31(1):15–39.
- Lurbe E, Alvarez J, Redon J. Diagnosis and treatment of hypertension in children. *Curr Hypertens Rep*. 2010;12(6):480–6.
- Lv J, Xu D, Perkovic V, Ma X, Johnson DW, Woodward M, et al. Corticosteroid therapy in IgA nephropathy. *J Am Soc Nephrol*. 2012;23(6):1108–16.
- MacNeily AE, Afshar K. Screening asymptomatic siblings for vesicoureteral reflux: sound science or religious rhetoric? *Can J Urol*. 2006;13(6):3309–16.

- Mammen C, Al Abbas A, Skippen P, Nadel H, Levine D, Collet JP, et al. Long-term risk of CKD in children surviving episodes of acute kidney injury in the intensive care unit: a prospective cohort study. *Am J Kidney Dis.* 2012;59(4):523–30.
- May AL, Kuklina EV, Yoon PW. Prevalence of cardiovascular disease risk factors among US adolescents, 1999–2008. *Pediatrics.* 2012;129(6):1035–41.
- McDonald SP, Craig JC. Australian, New Zealand Paediatric Nephrology A. Long-term survival of children with end-stage renal disease. *N Engl J Med.* 2004;350(26):2654–62.
- McLorie GA, McKenna PH, Jumper BM, Churchill BM, Gilmour RF, Khoury AE. High grade vesicoureteral reflux: analysis of observational therapy. *J Urol.* 1990;144(2 Pt 2):537–40. discussion 45
- Mehta RL, Pascual MT, Soroko S, Savage BR, Himmelfarb J, Ikizler TA, et al. Spectrum of acute renal failure in the intensive care unit: the PICARD experience. *Kidney Int.* 2004;66(4):1613–21.
- Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute kidney injury network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care.* 2007;11(2):R31.
- Metoki H, Ohkubo T, Kikuya M, Asayama K, Obara T, Hara A, et al. Prognostic significance of night-time, early morning, and daytime blood pressures on the risk of cerebrovascular and cardiovascular mortality: the Ohasama Study. *J Hypertens.* 2006;24(9):1841–8.
- Mishra J, Dent C, Tarabishi R, Mitsnefes MM, Ma Q, Kelly C, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. *Lancet.* 2005;365(9466):1231–8.
- Mitsnefes M, Flynn J, Cohn S, Samuels J, Blydt-Hansen T, Saland J, et al. Masked hypertension associates with left ventricular hypertrophy in children with CKD. *J Am Soc Nephrol.* 2010;21(1):137–44.
- Montini G, Rigon L, Zucchetto P, Fregonese F, Toffolo A, Gobber D, et al. Prophylaxis after first febrile urinary tract infection in children? A multicenter, randomized, controlled, noninferiority trial. *Pediatrics.* 2008a;122(5):1064–71.
- Montini G, Malaventura C, Salviati L. Early coenzyme Q10 supplementation in primary coenzyme Q10 deficiency. *N Engl J Med.* 2008b;358(26):2849–50.
- Montini G, Tullus K, Hewitt I. Febrile urinary tract infections in children. *N Engl J Med.* 2011;365(3):239–50.
- Mori R, Lakhanpaul M, Verrier-Jones K. Diagnosis and management of urinary tract infection in children: summary of NICE guidance. *BMJ.* 2007;335(7616):395–7.
- Muntner P, He J, Cutler JA, Wildman RP, Whelton PK. Trends in blood pressure among children and adolescents. *JAMA.* 2004;291(17):2107–13.
- Nagler EV, Williams G, Hodson EM, Craig JC. Interventions for primary vesicoureteric reflux. *Cochrane Database Syst Rev.* 2011;6:CD001532.
- Narchi H. Risk of long term renal impairment and duration of follow up recommended for Henoch-Schonlein purpura with normal or minimal urinary findings: a systematic review. *Arch Dis Child.* 2005;90(9):916–20.
- National High Blood Pressure Education Program Working Group on High Blood Pressure in C, Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics.* 2004;114(2 Suppl 4th Report):555–76.
- Ng DK, Robertson CC, Woroniecki RP, Limou S, Gillies CE, Reidy KJ, et al. APOL1-associated glomerular disease among African-American children: a collaboration of the chronic kidney disease in children (CKiD) and nephrotic syndrome study network (NEPTUNE) cohorts. *Nephrol Dial Transplant.* 2017;32(6):983–90.
- Nguyen HT, Benson CB, Bromley B, Campbell JB, Chow J, Coleman B, et al. Multidisciplinary consensus on the classification of prenatal and postnatal urinary tract dilation (UTD classification system). *J Pediatr Urol.* 2014;10(6):982–98.
- Nurnberger J, Philipp T, Witzke O, Opazo Saez A, Vester U, Baba HA, et al. Eculizumab for atypical hemolytic-uremic syndrome. *N Engl J Med.* 2009;360(5):542–4.
- Oh J, Wunsch R, Turzer M, Bahner M, Raggi P, Querfeld U, et al. Advanced coronary and carotid arteriopathy in young adults with childhood-onset chronic renal failure. *Circulation.* 2002;106(1):100–5.
- Omoloja A, Jerry-Fluker J, Ng DK, Abraham AG, Furth S, Warady BA, et al. Secondhand smoke exposure is associated with proteinuria in children with chronic kidney disease. *Pediatr Nephrol.* 2013;28(8):1243–51.
- O'Rourke MF, Adji A. Clinical use of applanation tonometry: hope remains in Pandora's box. *J Hypertens.* 2010;28(2):229–33.
- Parekh RS, Carroll CE, Wolfe RA, Port FK. Cardiovascular mortality in children and young adults with end-stage kidney disease. *J Pediatr.* 2002;141(2):191–7.
- Parsa A, Kao WH, Xie D, Astor BC, Li M, Hsu CY, et al. APOL1 risk variants, race, and progression of chronic kidney disease. *N Engl J Med.* 2013;369(23):2183–96.
- Passerotti CC, Kalish LA, Chow J, Passerotti AM, Recabal P, Cendron M, et al. The predictive value of the first postnatal ultrasound in children with antenatal hydronephrosis. *J Pediatr Urol.* 2011;7(2):128–36.
- Pennesi M, Travan L, Peratoner L, Bordugo A, Cattaneo A, Ronfani L, et al. Is antibiotic prophylaxis in children with vesicoureteral reflux effective in preventing pyelonephritis and renal scars? A randomized, controlled trial. *Pediatrics.* 2008;121(6):e1489–94.
- Peters CA, Skoog SJ, Arant BS Jr, Copp HL, Elder JS, Hudson RG, et al. Summary of the AUA guideline on management of primary vesicoureteral reflux in children. *J Urol.* 2010;184(3):1134–44.
- Prelog M, Schieffcker D, Fille M, Wurzner R, Brunner A, Zimmerhackl LB. Febrile urinary tract infection in children: ampicillin and trimethoprim insufficient as empirical mono-therapy. *Pediatr Nephrol.* 2008;23(4):597–602.
- Reeders ST, Breuning MH, Davies KE, Nicholls RD, Jarman AP, Higgs DR, et al. A highly polymorphic DNA marker linked to adult polycystic kidney disease on chromosome 16. *Nature.* 1985;317(6037):542–4.

- Reid S, Cawthon PM, Craig JC, Samuels JA, Molony DA, Strippoli GF. Non-immunosuppressive treatment for IgA nephropathy. *Cochrane Database Syst Rev.* 2011;3:CD003962.
- Ricci Z, Cruz D, Ronco C. The RIFLE criteria and mortality in acute kidney injury: a systematic review. *Kidney Int.* 2008;73(5):538–46.
- Roberts KB, Finnell SM, Downs SM. Response to the AAP section on urology concerns about the AAP urinary tract infection guideline. *Pediatrics.* 2012;129(4):e1054–6.
- Rodenbach KE, Schneider MF, Furth SL, Moxey-Mims MM, Mitsnefes MM, Weaver DJ, et al. Hyperuricemia and progression of CKD in children and adolescents: the chronic kidney disease in children (CKiD) cohort study. *Am J Kidney Dis.* 2015;66(6):984–92.
- Ronkainen J, Koskimies O, Ala-Houhala M, Antikainen M, Merenmies J, Rajantie J, et al. Early prednisone therapy in Henoch-Schonlein purpura: a randomized, double-blind, placebo-controlled trial. *J Pediatr.* 2006;149(2):241–7.
- Rosenthal W, Seibold A, Antaramian A, Lonergan M, Arthus MF, Hendy GN, et al. Molecular identification of the gene responsible for congenital nephrogenic diabetes insipidus. *Nature.* 1992;359(6392):233–5.
- Sadowski CE, Lovric S, Ashraf S, Pabst WL, Gee HY, Kohl S, et al. A single-gene cause in 29.5% of cases of steroid-resistant nephrotic syndrome. *J Am Soc Nephrol.* 2015;26(6):1279–89.
- Samuels J, Ng D, Flynn JT, Mitsnefes M, Poffenbarger T, Warady BA, et al. Ambulatory blood pressure patterns in children with chronic kidney disease. *Hypertension.* 2012;60(1):43–50.
- Saran R, Li Y, Robinson B, Ayanian J, Balkrishnan R, Bragg-Gresham J, et al. US renal data system 2014 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis.* 2015;65(6 Suppl 1):A7.
- Saran R, Li Y, Robinson B, Abbott KC, Agodoa LY, Ayanian J, et al. US renal data system 2015 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis.* 2016;67(3 Suppl 1):A7–8.
- Schiff H, Lang SM. Update on biomarkers of acute kidney injury: moving closer to clinical impact? *Mol Diagn Ther.* 2012;16(4):199–207.
- Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol.* 2009;20(3):629–37.
- Selewski DT, Symons JM. Acute kidney injury. *Pediatr Rev.* 2014;35(1):30–41.
- Selewski DT, Cornell TT, Heung M, Troost JP, Ehrmann BJ, Lombel RM, et al. Validation of the KDIGO acute kidney injury criteria in a pediatric critical care population. *Intensive Care Med.* 2014;40(10):1481–8.
- Sellier-Leclerc AL, Fremaux-Bacchi V, Dragon-Durey MA, Macher MA, Niaudet P, Guest G, et al. Differential impact of complement mutations on clinical characteristics in atypical hemolytic uremic syndrome. *J Am Soc Nephrol.* 2007;18(8):2392–400.
- Shaikh N, Morone NE, Lopez J, Chianese J, Sangvai S, D'Amico F, et al. Does this child have a urinary tract infection? *JAMA.* 2007;298(24):2895–904.
- Shaikh N, Morone NE, Bost JE, Farrell MH. Prevalence of urinary tract infection in childhood: a meta-analysis. *Pediatr Infect Dis J.* 2008;27(4):302–8.
- Shaikh N, Ewing AL, Bhatnagar S, Hoberman A. Risk of renal scarring in children with a first urinary tract infection: a systematic review. *Pediatrics.* 2010;126(6):1084–91.
- Shaikh N, Hoberman A, Keren R, Gotman N, Docimo SG, Mathews R, et al. Recurrent urinary tract infections in children with bladder and bowel dysfunction. *Pediatrics.* 2016;137(1):26647376.
- Shima Y, Nakanishi K, Hama T, Mukaiyama H, Togawa H, Sako M, et al. Spontaneous remission in children with IgA nephropathy. *Pediatr Nephrol.* 2013;28(1):71–6.
- Sims Sanyahumbi A, Colquhoun S, Wyber R, Carapetis JR. Global disease burden of group A Streptococcus. In: Ferretti JJ, Stevens DL, Fischetti VA, editors. *Streptococcus pyogenes: basic biology to clinical manifestations.* Oklahoma City, OK: NCBI Shelf; 2016.
- Singh-Grewal D, Macdessi J, Craig J. Circumcision for the prevention of urinary tract infection in boys: a systematic review of randomised trials and observational studies. *Arch Dis Child.* 2005;90(8):853–8.
- Skoog SJ, Peters CA, Arant BS Jr, Copp HL, Elder JS, Hudson RG, et al. Pediatric vesicoureteral reflux guidelines panel summary report: clinical practice guidelines for screening siblings of children with vesicoureteral reflux and neonates/infants with prenatal hydronephrosis. *J Urol.* 2010;184(3):1145–51.
- Smellie JM, Poulton A, Prescod NP. Retrospective study of children with renal scarring associated with reflux and urinary infection. *BMJ.* 1994;308(6938):1193–6.
- Staples A, LeBlond R, Watkins S, Wong C, Brandt J. Validation of the revised Schwartz estimating equation in a predominantly non-CKD population. *Pediatr Nephrol.* 2010;25(11):2321–6.
- Subcommittee on Urinary Tract Infection SCoQI, Management, Roberts KB. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics.* 2011;128(3):595–610.
- Sutherland SM, Zappitelli M, Alexander SR, Chua AN, Brophy PD, Bunchman TE, et al. Fluid overload and mortality in children receiving continuous renal replacement therapy: the prospective pediatric continuous renal replacement therapy registry. *Am J Kidney Dis.* 2010;55(2):316–25.
- Sutherland SM, Ji J, Sheikhi FH, Widen E, Tian L, Alexander SR, et al. AKI in hospitalized children: epidemiology and clinical associations in a national cohort. *Clin J Am Soc Nephrol.* 2013;8(10):1661–9.
- Sutherland SM, Byrnes JJ, Kothari M, Longhurst CA, Dutta S, Garcia P, et al. AKI in hospitalized children: comparing the pRIFLE, AKIN, and KDIGO definitions. *Clin J Am Soc Nephrol.* 2015;10(4):554–61.

- Symons JM, Chua AN, Somers MJ, Baum MA, Bunchman TE, Benfield MR, et al. Demographic characteristics of pediatric continuous renal replacement therapy: a report of the prospective pediatric continuous renal replacement therapy registry. *Clin J Am Soc Nephrol*. 2007;2(4):732–8.
- Thomas ME, Blaine C, Dawnay A, Devonald MA, Ftouh S, Laing C, et al. The definition of acute kidney injury and its use in practice. *Kidney Int*. 2015;87(1):62–73.
- Torres VE, Chapman AB, Devuyt O, Gansevoort RT, Grantham JJ, Higashihara E, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med*. 2012;367(25):2407–18.
- Tullus K. Vesicoureteric reflux in children. *Lancet*. 2015;385(9965):371–9.
- Vanmassenhove J, Vanholder R, Nagler E, Van Biesen W. Urinary and serum biomarkers for the diagnosis of acute kidney injury: an in-depth review of the literature. *Nephrol Dial Transplant*. 2013;28(2):254–73.
- Verbitsky M, Sanna-Cherchi S, Fasel DA, Levy B, Kiryluk K, Wuttke M, et al. Genomic imbalances in pediatric patients with chronic kidney disease. *J Clin Invest*. 2015;125(5):2171–8.
- Vivante A, Hildebrandt F. Exploring the genetic basis of early-onset chronic kidney disease. *Nat Rev Nephrol*. 2016;12(3):133–46.
- Walters S, Porter C, Brophy PD. Dialysis and pediatric acute kidney injury: choice of renal support modality. *Pediatr Nephrol*. 2009;24(1):37–48.
- Wan J, Skoog SJ, Hulbert WC, Casale AJ, Greenfield SP, Cheng EY, et al. Section on Urology response to new guidelines for the diagnosis and management of UTI. *Pediatrics*. 2012;129(4):e1051–3.
- Warady BA, Abraham AG, Schwartz GJ, Wong CS, Munoz A, Betoko A, et al. Predictors of rapid progression of glomerular and nonglomerular kidney disease in children and adolescents: the chronic kidney disease in children (CKiD) cohort. *Am J Kidney Dis*. 2015;65(6):878–88.
- Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol*. 2004;15(2):241–50.
- Weiss PF, Feinstein JA, Luan X, Burnham JM, Feudtner C. Effects of corticosteroid on Henoch-Schonlein purpura: a systematic review. *Pediatrics*. 2007;120(5):1079–87.
- Welch WP, Yang W, Taylor-Zapata P, Flynn JT. Antihypertensive drug use by children: are the drugs labeled and indicated? *J Clin Hypertens (Greenwich)*. 2012;14(6):388–95.
- Workgroup KA. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl*. 2012;2(1):1–138.
- Working Group of the International Ig ANN, the Renal Pathology S, Roberts IS, Cook HT, Troyanov S, Alpers CE, et al. The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility. *Kidney Int*. 2009;76(5):546–56.
- Wyatt RJ, Julian BA. IgA nephropathy. *N Engl J Med*. 2013;368(25):2402–14.
- Zhanel GG, Hisanaga TL, Laing NM, DeCorby MR, Nichol KA, Palatnik LP, et al. Antibiotic resistance in outpatient urinary isolates: final results from the North American Urinary Tract Infection Collaborative Alliance (NAUTICA). *Int J Antimicrob Agents*. 2005;26(5):380–8.
- Zorc JJ, Levine DA, Platt SL, Dayan PS, Macias CG, Krief W, et al. Clinical and demographic factors associated with urinary tract infection in young febrile infants. *Pediatrics*. 2005;116(3):644–8.



Background

The field of neonatology or neonatal-perinatal medicine is a pediatric subspecialty where the practitioner manages medically sick infants during early postnatal life. The most common patients are newborns who are premature, low birth weight, or who suffer from sepsis, hypoxic ischemic encephalopathy (HIE), congenital malformations or respiratory distress. It is a hospital-based specialty, commonly practiced in Neonatal Intensive Care Units (NICUs). However, the spectrum of care is not limited to sick infants and includes routine immediate care of a healthy newborn.

Distinct care for the newborns first appeared during the early 1920s. As J.W. Ballantyne (1923) wrote: “There is a need for specialization in neonatal medicine, this applies to doctors and nurses as well as teaching and construction of hospitals” (Philip 2005).

However, it took another half century for the specialty to achieve formal recognition. The first meeting of the American Academy of Pediatrics (AAP), including a perinatal section was planned in 1975 and the first neonatal board exam was conducted in same year (Hodge et al. 2006). Since

then the practice has made rapid progress. One example is the survival of extremely premature infants and the age of viability. In 1960s, a pre-term infant was defined as an infant born at 30 weeks’ gestation. Now, the threshold of viability has reached to be 22- to 25-week gestation, depending upon the region of the world. This progress was initially supported by fluid and electrolyte regulation, total parenteral nutrition, mechanical ventilation and minimizing blood sampling. During the early 1990s, the use of antenatal steroids and surfactant for respiratory distress syndrome were a breakthrough in decreasing the mortality of preterm infants. During the same period, the importance of regionalization of care was realized. NICUs were distinguished as primary (Level 1) to tertiary (level 3) units, and trained transport teams were developed to transfer babies from one hospital to another depending upon the care required. Some other successful recent advancements are the use of the therapeutic hypothermia in infants born with hypoxic ischemic encephalopathy, the use of extracorporeal membrane oxygenation (ECMO) in newborns with respiratory failure, non-invasive ventilation for preterm infants, the use of donor breast milk and expanded newborn screening programs.

In parallel to the clinical successes, attitudes towards neonatal care also changed. In the 1960s, parents were only allowed to observe their babies through glass windows (Baker 1999). Now, with the emphasis on family-centered care, parents are involved in decision-making. The infant-parent

F. Khurshid, M.D., F.C.P.S., M.Sc. (H.Q.) (✉)
Department of Pediatrics, Queen’s University,
Kingston, ON, Canada
e-mail: khurshif@kgh.kari.net

I. Ahmad, M.B.B.S., M.Sc.
Department of Biomedical and Molecular Sciences,
Queen’s University, Kingston, ON, Canada
e-mail: imtiaz_dr@hotmail.com

interaction is not limited to visiting at the side of the incubator or bed, but parents are encouraged to touch, hold, engage with their infants and provide expressed breast milk (Ramezani et al. 2014).

The increased survival of NICU patients is also related to progress in the fields of early prenatal detection, minimally invasive fetal surgeries, in utero blood transfusion performed by maternal fetal medicine specialists, the ex utero intrapartum treatment (EXIT) procedure for airway related congenital abnormalities and new surgical techniques for congenital heart disease.

The future of neonatology in the next few years is moving towards whole genome sequencing, artificial placenta, gene therapy and simulated nurseries for teaching and learning.

Normal Newborn Care

Birth is the commonest reason for hospitalization. An adequate transition from intrauterine life to the extra-uterine environment depends on the successful adaptation of the cardiac, hemodynamic, and respiratory systems. Most newborns successfully adapt to this change. However, about 10% of newborns require resuscitative measures just after birth. Once the initial transition is achieved, routine immediate care for healthy infants consists of the establishment of feeding, early bonding cord care, and the prevention of hypothermia, hypoglycemia, hemorrhagic disease of the newborn and eye infection. Family education and assessment of readiness for discharge is also included within routine management.

Neonatal Nutrition

Current evidence has demonstrated that early nutrition plays an important role on later neurodevelopment outcome and adult metabolic health (Robinson and Fall 2012).

Benefits of Breastfeeding

Breastfeeding is now considered the optimal feeding strategy for newborns. However, a few decades ago, breastfeeding was considered as a stigma of lower social class, and the use of for-

mula was prevalent. In the last 20 years, as the benefits of breast milk have become evident, initiatives such as baby friendly hospitals, and organizations such as the World Health Organization (WHO), The Academy of breastfeeding medicine and others are working towards creating awareness of breastfeeding and setting targets to establish exclusive breast feeding in first 6 months of life.

The American Academy of Pediatrics (AAP) and WHO recommend the use of exclusive breast milk for at least 6 months and up to 12 months in a healthy term infant.

Table 16.1 provides a summary of short- and long-term benefits published by WHO and agency of the health care research report, related to breast feeding (Horta and Victora 2013; Horta et al. 2013; Ip et al. 2009). While reading the summarized evidence, it should be kept in mind that the results are synthesized from observational studies as conduction of a trial for breastfeeding would be subjected to ethical justification.

Contraindications to Breastfeeding

Human Immunodeficiency virus (HIV) infection in mothers is a contraindication to breast feeding. However, the Centers of Disease control and Prevention (CDC) suggests that in areas where there is a high prevalence of diarrhea and respiratory illness leading to high infant mortality, exclusive breastfeeding for six months by mothers with HIV may outweigh the risks. Therefore, consideration should be made on an individual basis (CDC 2017). Other contraindications include type I galactosemia in the newborn, maternal infection with human T-cell lymphotropic virus type I or type II, herpes simplex virus with active lesions on the breast, and active tuberculosis not being treated. The use of some illicit drugs and therapeutic medications like antimetabolites, chemotherapeutics and radioisotopes may also preclude breastfeeding (Hauk 2015).

Supplements with Breastfeeding

Although exclusive breast milk provides all necessary nutrients, it is found to be deficient in Vitamin D. Therefore, Vitamin D supplementation of 400 IU/day is required in all breastfeeding babies. It can be started within the first few days

Table 16.1 Benefits of breastfeeding

| <i>Short-term benefits to infant</i> | <i>Short-term benefits to mother</i> |
|---|---|
| <ul style="list-style-type: none"> – Protection against diarrhea and gastroenteritis – Protection against respiratory tract infection and recurrent otitis media – Reduction in asthma, atopic dermatitis – Reduction in sudden infant death syndrome – Reduction in necrotizing enterocolitis – Childhood leukemia | <ul style="list-style-type: none"> – Sustained weight loss – Decreased postpartum depression – Increased infant bonding |
| <i>Long-term benefits to infants</i> | <i>Long-term benefits to mother</i> |
| <ul style="list-style-type: none"> – Reduction of systolic blood pressure (less than 1 mmHg) – Substantial protection against diabetes was noted in the pooled analysis (34% reduction) However randomized trials did not present results of these outcomes – 24% reduction in overweight and/or obesity – An increase in 3.5 points in normalized test scores in the pooled analyses | <ul style="list-style-type: none"> – Decreased risk of Type 2 diabetes – Decreased risk of breast and ovarian cancer – Decreased risk of hypertension, and cardiovascular diseases |
| <ul style="list-style-type: none"> – Breastfeeding does not seem to protect against hyperlipidemia – No effect on diastolic pressure | |

of life and should to be continued until the infant is receiving 1 L/day or 1 quart/day of vitamin D-fortified formula or whole milk. Breastfeeding infants also require iron in a dose of 1 mg/kg/day from 4 months of age which should be continued until the infant consumes adequate oral iron from foods (Kirby and Noel 2007).

Infant Formula

Although the trends towards breastfeeding are encouraging. It will not be possible for every infant and therefore the use of infant formula is still required. Infant formulas are available in different forms including ready to feed, concentrated liquid, and powder. It is essential to guide parents in the proper preparation of the liquid concentrate and powder. The caloric content of

regular standard infant formula is 20 calories per ounce, which is equivalent to the average caloric content of breast milk. However, the nutrient composition of formulas may have subtle differences from breast milk composition. For example, protein contents are higher in formulas, and low and high iron containing formulas are available. Some manufacturers have introduced very long-chain polyunsaturated fatty acids as evidence is promising for its effects on brain development. Some new generation formulas also contain nucleotides, oligosaccharides (prebiotics) and probiotics to promote healthy gut flora. At present, there is no evidence that one formula is better than another (Denne 2015). Soy formula and extensively hydrolyzed protein formula are not recommended for infants except in specific conditions.

Gastroesophageal Reflux (GER) and Gastroesophageal Reflux Disease (GERD)

GER is one of the most common conditions seen in healthy newborns during the first two months of life. Most are ‘happy spitters’ and require no treatment. However, it is necessary to identify the small proportion of infants, suffering from GERD.

An approach suggested by the North American Society for Gastroenterology, Hepatology, and Nutrition describes several steps in managing newborns with GERD (Vandenplas et al. 2009). The first step is to take a good history and perform a physical examination to ascertain adequate caloric intake and to exclude any concerning signs such as bilious vomiting, GI bleeding, etc. As a first step, dietary changes are used to address the concern of milk protein allergy. Breastfeeding mothers are advised to avoid the use of dairy and egg products while formula-fed infants can be given a trial of hydrolyzed formula. Thickened formulas are also available; their use is contraindicated in preterm neonates due to the risk of necrotizing enterocolitis. If no response is achieved than consultation with a pediatric gastroenterologist and the use of acid suppression therapy should be considered. An upper gastrointestinal series can be performed in the presence of any concerning symptoms or signs.

Newborn Skin and Umbilical Cord Care

The skin provides an effective barrier, and a breach of this barrier can create means of introducing bacteria which could potentially lead to systemic infection. Over the last decade, newborn skin care practices, cord care and methods of bathing have changed considerably which has created confusion among health care providers and parents. With emerging evidence of the association of initial skin care with development of atopy in later life, it is necessary to adopt practices for healthier skin (Cork et al. 2006).

Umbilical Cord Care

The umbilical cord is a unique structure present in newborns. It provides a route whereby bacteria may gain direct access to the systemic circulation. Infection of the cord can present as omphalitis, thrombophlebitis, cellulitis or necrotizing fasciitis.

The common risk factor in developed countries include umbilical catheterization, prematurity, chorioamnionitis, prolonged rupture of membrane (PROM) (Mason et al. 1989). The incidence of umbilical cord -related infections is highly variable and is dependent upon the place of delivery (home vs. hospital) and cord care practices. One published study from Canada reported only three cases among 3518 infants (Dore et al. 1998) while in developing countries, this could be as high 17% (Mir et al. 2011).

The controversy over the use of chlorhexidine vs. dry care is long standing. However, in recent years the WHO has released evidence-based guidelines for cord care. Due to the difference in incidence, WHO guidelines suggest dry cord care for infants born within low incidence countries and use of chlorhexidine solution in high incidence setting (WHO 2014).

In a statement released by the AAP, high importance was placed on the promotion of skin to skin with mother to increase colonization with non-pathogenic bacteria and considered dry cord care as another step towards reducing resistant bacterial growth (Stewart and Benitz 2016).

First Newborn Cleaning

The importance of vernix caseosa has finally been recognized as a protective moisturizer (Visscher et al. 2015). Also, an immediate cleaning with water or wet wipe can interfere with the thermoregulation and therefore skin to skin care is preferred (Darmstadt and Dinulos 2000). Newborn babies should be wiped off with a dry towel after birth. The first bath should be considered only when the temperature has stabilized. The use of gloves for the first bath is also required in hospital settings (Blume-Peytavi et al. 2016).

Routine Bathing

The European group (Blume-Peytavi et al. 2016) have clarified some controversial issues related to routine bathing. Based on available data, newborn infants should be bathed for 5–10 min at least 2–3 times a week; it can be started even when the cord is not yet separated. The benefits include tactile stimulation, infant bonding, and improved sleep (Bryanton et al. 2004; Mindell et al. 2009). However, the benefits of bathing versus sponging is not yet clear. For bathing either water or liquid cleaner with a neutral or slightly acidic pH is preferable (Hachem et al. 2003).

Diaper Care

Diaper dermatitis is one of the common problem seen in the initial months of life. The skin barrier is broken by the occlusive diaper environment, with alkaline urine disrupting the epidermis along with fecal enzymes causing further damage. Several studies have suggested that the diaper area should be cleaned with washcloths dipped in water or if available, particular wipes which maintain a slight acidotic environment (Lavender et al. 2012).

Newborn Screening

Newborn screening is a practice whereby a single test in apparently healthy babies at birth can detect a fatal disorder, which otherwise might not be diagnosed at birth. Newborn screening began in 1960 when Robert Guthrie developed a blood test to detect phenylketonuria (Guthrie and Susi 1963).

This has evolved from a blood or urine test to detect a single disease to a three-part screen. Now, one drop of blood can be used to screen for as many as 50 diseases. Hearing screen at birth and pulse oximetry to detect critical congenital heart disease are also component of newborn screening.

To increase the number of disorders in the screening program, the method of laboratory techniques to carry out screening tests have also changed. The method introduced by Guthrie was a bacterial inhibition assay, while currently, tandem mass spectrometry can allow rapid and accurate analysis for multiple conditions simultaneously (Chace and Naylor 1999).

In most developed countries, screening is a public health service. However, there is a huge variation in the number of diseases available on the screening panel of different countries or even different states/provinces of the same country (Therrell et al. 2015).

It is important to remember that screening cannot confirm the disease. It identifies newborns who require further follow-up testing to confirm the diagnosis. It is always hard to set the threshold level for screening tests. If it is too high, the false negative number will be high, and a certain number of infants who have the disorder will go undetected. If it is set too low, the false positivity rate will be higher.

For instance, data extracted from the National Newborn Screening Information System revealed that 3,364,612 infants were tested for maple syrup urine disease (MSUD) in the United States during 2007. The initial reports were positive for 1249 among all tested, but after further testing, only 18 newborns were eventually confirmed as having the disease (The President's Council on Bioethics 2017).

Newborn Blood Spot Screening

Typically, blood is taken from a heel stick to be absorbed on a special filter paper and sent to designated laboratories. Most countries have developed a central laboratory system where tests are performed.

The conditions that could be screened for newborns include inborn errors of metabolism, endocrine disorders, hemoglobinopathies, immu-

nodeficiencies and cystic fibrosis. A list is provided in Table 16.2.

The Secretary of Health and Human Services' Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) in the United States of America (USA) is the organization which oversees regulations regarding newborn screening program across the country. This centralization has helped to develop a Recommended Uniform Screening Panel (RUSP) in the USA. Initially, RUSP had 29 core condition. In 2015 four additional conditions were included on the panel list. [severe combined immunodeficiency disease (SCID), Pompe disease, and Mucopolysaccharidosis type I (MPS I)] along with 1 secondary target, T-cell lymphocyte deficiencies.

Hearing Screening Program

Hearing loss is another common disorder with the prevalence being as high as 1–3/1000 births (Hyde 2005). Hearing loss may be sensorineural, conductive or mixed type. Initially, screening was only offered to high-risk populations (premature, neonates with persistent pulmonary hypertension, hyperbilirubinemia, newborns requiring mechanical ventilation or ECMO, congenital infections, meningitis, family history of hearing impairment). However, as risk factors are only present in 50% of infants who develop hearing impairment during infancy, the practice of universal hearing screening for every newborn has been adopted in many countries (Patel and Feldman 2011). The two methods used in screening programs are the auditory brainstem response (ABR) and Otoacoustic emissions (OAEs).

The effectiveness of universal screening programs has been demonstrated in systematic reviews. A recent meta-analysis based on 17 studies concluded that studies comparing screening versus no screening showed an improvement in speech development in the screening group (Wolff et al. 2010).

The effectiveness of prompt interventions based on early detection is also well studied. There is a clear evidence that infants who receive intervention before 6 months of age score higher on school-related measure (Korver et al. 2010).

Table 16.2 Diseases available on screening panels for newborn screening program

| Metabolic disorder | Lysosomal disorder | Endocrine disorder | Hemoglobinopathies/hematology related | Miscellaneous | Infections |
|--|--------------------|--------------------------------|--|---------------------------------------|------------------------------------|
| Six core amino acid disorders | Krabbe | Hypothyroidism | Beta thalassemia | SCID | Toxoplasmosis |
| Eight secondary amino acid disorders | Pompe | Congenital adrenal hyperplasia | Hemoglobin S-C disease | X-Linked Adrenoleukodystrophy (X-ALD) | Human immunodeficiency virus (HIV) |
| Five core fatty acid oxidation disorders | Fabry | | Sickle cell disease | Cystic fibrosis | |
| Eight secondary fatty acid disorders | Gaucher | | Glucose-6-phosphate dehydrogenase deficiency (G6PD) deficiency | | |
| Nine core organic acid disorders | Niemann pick | | Other Hb variant | | |
| Six secondary organic acid disorders | MPS-I | | | | |
| Biotinidase deficiency | MPS-II | | | | |
| Galactosemia | | | | | |

Congenital Cardiac Disease

Critical congenital heart defects (CCHD) are serious congenital conditions that require treatment right after birth or need surgery within the first year of life. These conditions include hypoplastic left heart syndrome, pulmonary atresia, tetralogy of Fallot, total anomalous pulmonary venous return, transposition of the great arteries, tricuspid atresia, and truncus arteriosus. The reported incidence of these conditions in the United States is approximately 7200 babies per year (Oster et al. 2013). Pulse oximetry screening at 24 h of age or later could detect these seven critical diseases. Pulse oximetry is widely available as an accurate method of measuring oxygen saturation. The sensitivity of this screening method has been shown to range from 60% to 100% specificity being $\geq 94\%$ in most studies (Narayan et al. 2016). In 2011, the Secretary of Health and Human Services recommended adding screening for CCHD using pulse oximetry before hospital discharge to RUSP (Mahle et al. 2012). The screening has also been adopted in most of the European countries and USA.

Future Perspective

In upcoming years, newborn screening programs are expected to expand.

Research is ongoing to include fragile X syndrome, spinal muscular atrophy, Wilsons disease, guanidinoacetate methyl transferase deficiency (Therrell et al. 2015). DNA-based testing to confirm results when newborn tests are positive for a disorder, the use of nanotechnology (a lab on a chip) to save and screen mass samples are examples of work in progress.

Neonatal Resuscitation

Although the risk of requiring resuscitation at birth is small with only 1–3 per 1000 term newborns requiring chest compressions or emergency medications, it is strongly advised that even in the absence of anticipated risk factors, at least one qualified individual, skilled in the initial steps of newborn care and positive-pressure ven-

tilation (PPV) should be present at each delivery (Wyckoff et al. 2015).

The international Liaison Committee on Resuscitation (ILCOR) is responsible for developing recommendations based on currently available evidence.

These recommendations are then adapted by regional organizations with some subtle differences. (Neo-Resus in Australia and New Zealand, Newborn Life support in Europe, Neonatal Resuscitation Provider (NRP) in North America). Recent updates were published in 2015 introducing some significant changes from the previous 2010 edition (Perlman et al. 2015). Since then, local organizations have released their updated version with provisions of timeline within which to start new practices.

The basic principle of neonatal resuscitation has remained unchanged. This includes emphasis on the establishment of effective ventilation, synchronized chest compression with a ratio of three compression per one breath (3:1), and the use of blended oxygen to target oxygen saturation.

Below is a summary of significant changes suggested by ILCOR.

1. Management of meconium

The long-standing practice of routine tracheal intubation and suction of non-vigorous infants born through meconium stained amniotic fluid is no longer recommended. There was insufficient published human evidence to suggest any benefit of intubation for suctioning. As ventilation is the most important aspect of newborn resuscitation, tracheal suction can delay the establishment of effective ventilation.

2. Cord clamping

In recent publications, delayed cord clamping has demonstrated a decreased incidence of intraventricular hemorrhage in preterm infants and anemia in later infancy. Based on this evidence, it is suggested that cord clamping be delayed for at least 1 min after birth in uncompromised term and preterm infants. The evidence is not clear to guide timing of cord clamping in non-vigorous infants who require resuscitation. Another similar approach is cord milking. At this time, ILCOR recommendations

do not support this practice in the infants born at or less than 28 weeks' gestation.

3. Assessment of heart rate

The traditional approach to assess heart rate was the use of umbilical cord palpation as well as auscultation. Now ILCOR suggests that electrocardiographic monitoring (ECG) should be used to provide a rapid, accurate estimation of heart rate in newborns requiring resuscitation.

4. Temperature control

ILCOR recommends that an infant should be maintained between 36.5 and 37.5 °C after birth and during stabilization. A combination of interventions including the use of plastic wrap, warming mattresses, hats and raising of the environmental temperature to 23.0–25.0 °C should be used to achieve target temperatures.

5. Oxygen concentration for preterm infants

In the previous ILCOR version, the use of room air during the resuscitation of full-term infants was recommended. In the current update, ILCOR recommends against initiating resuscitation of preterm newborns <35 weeks' gestation with high concentrations of oxygen (65–100%). This change was translated in the new edition of NRP as a recommendation to initiate resuscitation of newborns <35 weeks' gestation at 21–30% oxygen.

ILCOR found insufficient human evidence to inform the practice of oxygen concentration during CPR (cardiac compressions), suggesting, if supplementary oxygen is used, should be weaned as soon as the heart rate has recovered.

The AAP and American Heart Association (AHA) released a new NRP publication in the spring of 2016. Along with clinical changes as suggested by ILCOR, emphasis was placed on preparation for resuscitation and teamwork including identification of role and debriefings.

Common Neonatal Problems

Prevention and Management of Procedural Pain in Neonates

Alleviation of pain is a fundamental right and ethical principal in medicine. It is not uncom-

mon for a newborn to undergo painful procedures. Until the early 1990s, a common belief was that infants do not feel pain. Now it is well known that premature infants as young as this age and repeated noxious stimulus can cause increased excitability in nociceptive neurons, resulting in sensitization and future hyperintense response to pain (Ingram et al. 2008). Repeated painful procedures or even routine heel puncture or tape removal can affect future pain perception (Bellieni et al. 2009). Pain and stress in neonatal life also impact long-term neurodevelopment.

It is widely recommended by the AAP (Keels et al. 2016) and Canadian Pediatric Society (CPS) (Batton et al. 2006) that every facility involved in newborn care should develop a standard to evaluate/assess pain as well as a pain prevention program. Since these recommendations were published there has been a significant drop in the number of procedures and increased use of pain management strategies to control pain. In a recent report from the USA, the number of painful procedures declined from 14.3 procedure per infant per day in 2001 to 11.4 in 2014. Similarly, use of analgesia increased from 36.6% to 60.3% during the same period (Roofthoof et al. 2014).

Scoring System

The biggest challenge is to find an efficient scoring system for assessment. The pain assessment scores usually combine behavior and physiological responses. There are many published scoring system, but only a few have undergone psychometric testing to prove validity (MEDICINE COFANA SOAAP et al. 2016). The most common score systems in use are the PIPP (premature infant pain profile (Stevens et al. 1996), neonatal facial coding system (Grunau et al. 1998), and Behavior Indicators of Infant Pain (Holsti and Grunau 2007).

Pain Management

Pain management in neonates consists of environmental changes, nonpharmacological maneuvers and pharmacological measures. Nonpharmacological maneuvers include breastfeeding, swaddling, rocking, and sensorial

stimulation. A 2012 Cochrane review of 20 studies demonstrated that breastfeeding is effective as compared to other non-pharmacological methods and has similar effectiveness as the administration of glucose solution in reducing pain scores during heel lancet or venipuncture (Shah et al. 2012).

Sensorial stimulation (SS) during painful procedures has recently been introduced as one of the methods to reduce pain in newborns. SS could be as simple as looking and talking to an infant and gentle massage of the back. However, it was found to be more effective when used along with sucrose as an analgesia (Bellieni et al. 2012).

The most well studied pharmacological analgesia in newborns is oral sucrose. The effect is generated through the release of possible endogenous opiates (Shide and Blass 1989). It's effect is well described when used as a single dose in moderate painful procedures. Longer procedure may need repeated doses (Stevens et al. 2013). Topical analgesia can be used to relieve pain from local painful procedures. They are usually applied 30 min prior to the procedure. The other commonly used analgesic agents are morphine, fentanyl, and acetaminophen (Table. 16.3). Continuous use of opiate analgesia for pain relief during prolonged intubation and ventilation is not recommended (Canadian Pediatric Society 2017a).

Table 16.3 Use of analgesia in procedural pain

| Name of procedure | NNS | Sucrose | Topical anesthesia | Acetaminophen | Systemic/opiate based analgesia | Regional block |
|---|-----|---------|-------------------------|--------------------|---------------------------------|--|
| Heel puncture | Y | Y | N | | | |
| Venipuncture, arterial puncture, percutaneous central venous catheter insertion | Y | Y | ± (EMLA) | | | |
| Intramuscular Or subcutaneous injection | | | Y(EMLA) | | | |
| Central venous catheter insertion by surgical cut-down | Y | Y | Y (EMLA) | | Y | |
| Tracheal intubation | | | | | Y | |
| Lumbar puncture | Y | Y | Y (EMLA) | | ± | |
| Chest tube insertion | | | Y LIDOCAINE | | Y | |
| Chest tube removal | | | Y | | Y | |
| Screening for ROP | Y | Y | Y Local anesthetic drop | | | |
| Laser therapy for ROP | | | | | Y | |
| Circumcision | | Y | Y (EMLA) | Y (post procedure) | | Y (Dorsal penile nerve block, Subcutaneous ring block) |
| Post-operative | Y | | | Y | Y | ± |

Adapted from (Lago et al. 2009; Pediatrics and FaN 2006)

NNS non-nutritive sucking, Y recommended, N no recommendation, ± suggested

Neonatal Sepsis

Early-onset sepsis (EOS) is defined as sepsis occurring within first seven days of life. Vertical transmission of pathogens is considered as an important etiology, and Group B streptococcus (GBS) is the most common bacteria causing sepsis in full-term infants. In 2002, CDC recommended routine intrapartum screening of GBS for all expectant mothers at 35–37 weeks of gestation and intrapartum antibiotics prophylaxis (IAP) for women with GBS vaginal colonization, GBS bacteriuria, and previous child with invasive GBS disease (Di Renzo et al. 2015). A guide to manage newborn at risk of sepsis due to perinatal factors was also implemented at same time. The reported prevalence of Early onset GBS sepsis in USA decreased from 1.7 cases per 1000 live births to 0.45/1000 cases after implementation of screening guidelines i.e. an approximate 70% reduction (Schrag et al. 2002). Although these guidelines were effective to decrease the neonatal disease burden due to EOS, they raised other controversies like increased incidence of infection due to organisms other than GBS like EColi, excessive use of antibiotics, and increase in invasive testing in newborns.

Diagnosis of Sepsis

Suspected sepsis is one of the commonest diagnoses in NICUs. Sepsis is diagnosed using a combination of strategies including perinatal risk factors, infants' signs and symptoms, and laboratory testing. It is challenging for physicians to decide when to perform invasive tests and start antibiotics in a healthy-looking newborn based on risk factors only and, when to stop antibiotics in a low likelihood of infection before discharging the baby home (Polin 2012). The major risk factors for sepsis include chorioamnionitis, rupture of membranes >18 h, maternal GBS colonization with inadequate prophylaxis, and prematurity (Schuchat et al. 2000).

At present, there is not a single test which could safely confirm or rule out early onset sepsis. Blood culture is the gold standard to diagnose EOS but use of maternal antibiotics and volume of blood obtained to grow on culture media can affect the sensitivity of the results (Schelonka

et al. 1996). Total white blood cell (WBC) count is the most common test in clinical practice as it is low cost and readily available but the predictive value of WBC for diagnosis of EOS is poor. Few recent studies reported a high likelihood of confirmed sepsis if the WBC count is performed at 4–6 h of life or the absolute neutrophil count is low (Newman et al. 2010). The acute phase reactant C-reactive protein is a marker of tissue injury or an infectious process. A single value of CRP should not be used to diagnose sepsis; however, serial levels of CRP could help in determination of length of antibiotic therapy in cases of suspected sepsis (Lacaze-Masmonteil et al. 2014).

Management of Newborns >35-Weeks of Gestation at Risk for Sepsis

There are published practice guidelines available to manage full term infants born at risk for sepsis. The recommendations to treat a newborn are based on the presence of risk factors at delivery and clinical signs in the newborn. Table 16.4 presents a brief comparison of three commonly used guidelines in the North America (CDC (CDC 2017), APA (Polin 2012), CPS (Canadian Pediatric Society 2017b) and National Institute for health care and Excellence (NICE) from the United Kingdom (NICE 2012).

Puopolo and colleagues developed a calculator to predict the incidence of sepsis in a newborn based on a dose-dependent relationship of risk factors rather than on a dichotomous relation as in previous studies. Authors of the study demonstrated a significant decrease in the number of invasive tests and antibiotic usage without any missed cases with the use of their proposed calculator (Puopolo et al. 2011).

Hypoxic Ischemic Encephalopathy

Neonatal encephalopathy is characterized by disturbed neurological function resulting in reduced level of consciousness with or without seizures (Pediatrics AAO 2014). Hypoxia, ischemia or birth asphyxia, is the commonest cause of encephalopathy in early days of life. In this instance, it is often accompanied with multisystem

Table 16.4 Managements of term newborn with risk of early onset sepsis

| | Routine care | Observation only | Limited evaluation and observation | Full evaluation with antibiotics |
|------|--|---|---|---|
| CPS | <ul style="list-style-type: none"> – GBS + ve with adequate IAP – GBS –ve/ GBS unknown with one risk factor and adequate IAP | <ul style="list-style-type: none"> GBS + ve with adequate IAP and no risk factors – GBS –ve/GBS unknown with one risk factor and inadequate IAP | <ul style="list-style-type: none"> Chorioamnionitis or multiple risk factors – <i>Observation for 24 h</i> – <i>Consider CBC at 4–6 h of age</i> | Unwell/symptomatic infant at birth |
| AAP | | | <ul style="list-style-type: none"> – GBS +ve with inadequate IAP or risk factors – <i>CBC with differential and CRP at 6–12 h of age</i> – <i>Observation 48 h</i> | <ul style="list-style-type: none"> Chorioamnionitis – Unwell/symptomatic infant at birth |
| CDC | <ul style="list-style-type: none"> GBS –ve with no risk factors | <ul style="list-style-type: none"> – GBS +ve with adequate prophylaxis – GBS +ve with inadequate prophylaxis but >37 week and ROM <18 h | <ul style="list-style-type: none"> GBS + ve with Inadequate IAP and risk factors – <i>CBC</i> – <i>Observation for 48 h</i> | <ul style="list-style-type: none"> Chorioamnionitis – Unwell/symptomatic infant at birth |
| NICE | | <ul style="list-style-type: none"> Babies with one risk factor^a – <i>monitor for 12 h</i> | | <ul style="list-style-type: none"> – Maternal confirmed bacterial infection – confirmed infection in second twin – Two or more risk factors^a – Unwell babies |

CPS Canadian Pediatric Society, AAP American Academy of Pediatrics, CDC Centers of disease control and prevention, NICE National Institute for health care and Excellence, CBC Complete blood count, CRP C reactive protein, GBS Group B streptococcus, IAP Intrapartum prophylaxis

Full evaluation = (CBC, blood Culture) chest x-ray and lumbar puncture if indicated

Risk factor in CPS statement = Rupture of membrane >18 h, Maternal temperature > 38.0 °C

RISK factor * in NICE guidelines (Maternal GBS + ve in current pregnancy, invasive disease in previous baby, GBS bacteriuria, pre-labor rupture of membranes, Intrapartum fever or confirmed Chorioamnionitis)

organ failure including difficulty in maintaining respiration, myocardial depression, liver and acute kidney injury, and disseminated intravascular coagulation.

Hypoxic Ischemic Encephalopathy (HIE) is historically associated with high mortality and morbidity. The incidence ranges from 1 in 8/1000 live births in developed countries to 26/1000 live birth in other parts of world (Kurinczuk et al. 2010).

Pathophysiology of HIE

Adequate blood supply is needed to provide oxygen and nutrient to the brain. Disruption of pla-

cental blood flow results in compromised blood supply to the fetal heart and brain leading to the initiation of a hypoxic cascade. Hypoxic injury to the brain is a staged process. Initially, neurons suffer with energy failure and anaerobic metabolism is used to generate energy. This primary phase enters into latent and secondary phases characterized by inflammation, cytotoxic edema, and continuation of the apoptotic cascade (Douglas-Escobar and Weiss 2015) (Fig. 16.1).

Diagnosis of HIE

The diagnosis of HIE is based on the presence of abnormal neurological signs and sentinel events

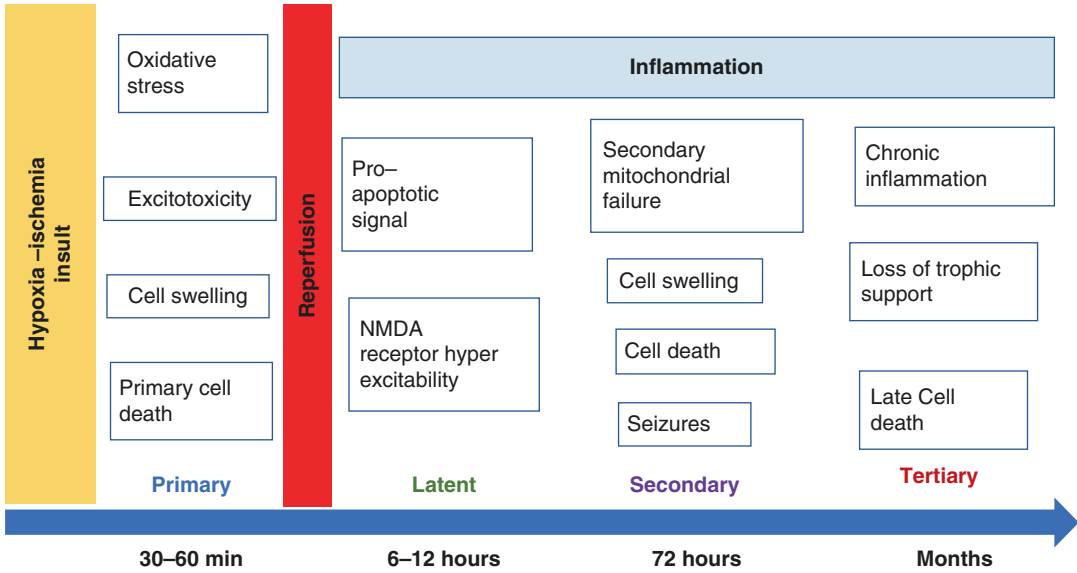


Fig. 16.1 Pathophysiological features of hypoxic ischemic encephalopathy (adapted from Davidson (Davidson et al. 2014))

in proximity to labor and delivery. The sentinel hypoxic events are ruptured uterus, placental abruption, umbilical cord prolapse, maternal cardiovascular collapse, and massive fetal blood loss. Perinatal hypoxia is recognized before birth with characteristic fetal heart rate patterns (category III pattern, tachycardia with recurrent deceleration, and persistent minimal variability with recurrent deceleration). After birth, umbilical artery acidemia, poor Apgar scores, and resuscitation at birth will identify newborn at risk of developing HIE (Nelson et al. 2012). The Sarnat scoring staging system assesses the severity of encephalopathy. It is a bedside clinical tool based on the following: level of consciousness, motor tone, reflexes, and autonomic dysfunction. It grades neurological dysfunction into mild, moderate, and severe encephalopathy (Sarnat and Sarnat 1976).

Besides the clinical examination and a history of perinatal risk factors, neuroradiology findings are diagnostic in cases of HIE. Magnetic resonance imaging (MRI) and Magnetic spectroscopy (MS) provide characteristic features of timing and type of hypoxic brain injury. Deep grey nuclear matter (basal ganglia) injury is a feature of an acute severe asphyxiated insult.

Other areas involved in hypoxic injury are the watershed cortex and the posterior limb of the internal capsule, while global injury affecting both grey and white matter is seen in cases of persistent severe hypoxia (Rutherford et al. 2010). The diffusion-weighted images (DWI) performed as early as 48–72 h of life have shown predictive value in cases of neonatal HIE. These findings help the physician in decision-making for continuing management and the counseling of parents. However, a word of caution should be used while predicting prognosis with a normal MRI. Rollins and colleagues have shown that as many as 26% who receive hypothermia could have a normal MRI with later abnormal development (Rollins et al. 2014).

Electroencephalogram (EEG) is another common investigation used for HIE infants. It is used in the diagnosis of neurological abnormalities and the management of associated seizures. Also, pattern and recovery time of amplitude-integrated EEG (aEEG) has a predictive value for later prognosis (van Laerhoven et al. 2013).

Management

Previously, only supportive management was offered to newborns with HIE. After successful

clinical trials of therapeutic hypothermia within the last year, it has been adopted as the treatment of choice in HIE.

1. Supportive management

- Maintenance of adequate ventilation. Newborns with a moderate to severe brain injury require ventilatory support. A critical approach to prevent hypocapnia and hyperoxia, to maintain normal cerebral perfusion, and to reduce oxidative stress should be adopted to minimize secondary brain injury (Lingappan et al. 2016; Klingler et al. 2005).
- Maintenance of organ perfusion. Cardiac dysfunction is common in newborns with HIE as documented by elevated troponin levels. Normal systemic blood pressure is required to maintain cerebral blood perfusion. New advances in functional echocardiography, and organ-specific regional oximetry will help guide treatment in the future (Howlett et al. 2013).
- Maintenance of normal metabolic status (glucose, calcium, magnesium, pH).
- Maintenance of fluid and electrolyte balance. Acute kidney injury is often accompanied with HIE, and fluid overload can worsen brain edema.
- Control of seizures. Seizures are common in moderate to severe encephalopathy. Timely control of seizures is necessary to prevent further brain injury.

2. Therapeutic hypothermia

Moderate hypothermia (33.5–34.5 °C) for 72 h started within 6 h of birth is the only effective neuroprotective therapy available to infants with HIE. Currently, it is offered only in regional tertiary care centers to eligible patients (Takenouchi et al. 2012).

The eligibility criteria are based on major published trials and generally include the following criteria: Infants >36 weeks of gestation and less than 6 hours of age with moderate to severe encephalopathy. The presence of intrapartum hypoxia is demonstrated by a pH of ≤ 7.0 or a base deficit of ≥ 16 mmol/L in a sample of umbilical cord blood or any blood

obtained within the first hour after birth, in addition to any one of following: Apgar score <5 at 10 min, and the need for resuscitation after 10 min of life. In some centers, aEEG changes have also been included within eligibility criteria (Papile et al. 2014).

3. Emerging therapies

Although therapeutic hypothermia has significantly improved the prognosis in HIE patients. There is still a search underway to develop therapies that can act synergistically with hypothermia to improve outcomes. Some of these agents include Xenon, allopurinol, erythropoietin and stem cell therapy.

Prognosis

Neurological sequelae depend upon brain damage and the degree of encephalopathy. Most infants with mild HIE will have normal developmental outcomes. Children with moderate to severe encephalopathy are likely to develop permanent neurological outcomes later. These can range from mild learning difficulties to severe cerebral palsy (Van Handel et al. 2007).

Neonatal Hypoglycemia

During normal physiological transition to extra-uterine life, blood glucose concentrations fall after delivery. It can take two hours to overcome the lowest nadir of glucose levels and to reach normal physiological levels. However, some high-risk newborns will not be able to maintain normal glucose levels, which will result in persistent or recurrent hypoglycemia. A study showed that almost 50% of high risk infants can develop hypoglycemia in first 24 h of life and within this group 20% had blood glucose levels less than 2 mmol/L (Harris et al. 2012). Adequate treatment of hypoglycemia is required to prevent neurological injury and developmental sequelae. Currently, infants born at risk for hypoglycemia are offered frequent feedings and blood glucose checks. High risk infants include those who are born preterm, small for gestational age (SGA), large for gestational age (LGA), and infants of the diabetic mothers. If frequent feeding is unable

to maintain sugar levels than an intravenous infusion is offered (Aziz and Dancy 2004). In the case of symptomatic hypoglycemia, or when frequent feeding cannot maintain normal glycemic levels, a bolus of 200 mg/kg dextrose water is required before starting a continuous infusion of glucose. This results in painful intravenous insertion, admission in neonatal intensive care, and interruption to normal breastfeeding and skin to skin care.

Definition of Hypoglycemia

A threshold level of blood glucose requiring treatment and when neuroglycopenia will occur is controversial. However, a plasma glucose level of 47 mg/dL (2.6 mmol/L) was used in multiple studies and management guidelines as the cut off value (Rozance and Hay 2016). In 2015, the Pediatric Endocrine Society released a new guideline with the goal to identify newborns at risk for developing pathological and persistent hypoglycemia. The guideline suggests 50 mg/dL (2.8 mmol/L) as a target threshold of treatment in newborns. Further, the guideline advises to set different blood glucose targets in a subset of patients with different risk factors. For high risk newborns, maintaining plasma glucose level >50 mg/dL (2.8 mmol/L) at less than 48 h of age and more than >60 mg/dL (>3.3 mmol/L) after 48 h of age is recommended. In contrast, the suggested target goals are higher >70 mg/dL (3.9 mmol/L) in newborns with a suspected congenital hypoglycemia disorder (Thornton et al. 2015).

Use of Dextrose Gel

Harris et al. introduced a new intervention to treat asymptomatic newborns at risk of hypoglycemia. In the Sugar Babies Study, 40% Dextrose gel (200 mg/kg) was rubbed into the baby's buccal mucosa followed by breast feeding. The results were significant for reducing treatment failure in comparison to placebo without any serious side effects (Harris et al. 2014). A recently published Cochrane systematic review also supported safety of dextrose gel in high-risk newborns; the number of newborns needed to treat were eight to prevent one admission to the NICU for hypoglycemia (Weston et al. 2016). Dextrose gel offers a

promising way to prevent separation of mother and baby; however, a potential delay in definitive treatment might occur. It is necessary to establish long-term safety of this new treatment. The Sugar Babies Study group recently published two-year outcomes of the study cohort with no difference between placebo and the gel group (Harris et al. 2016). However, before adopting the practice of glucose gel, it is important to note the following limitations in this study: this was a single center study with a high rate of breast feeding, definition and screening procedures can be different from other practice groups, and only asymptomatic neonates were eligible to enroll for intervention. Protocols using dextrose gel should be created as per current practices in that respective center. The reports after implementation of the new protocol are very promising (Bennett et al. 2016).

Continuous Glucose Monitoring

Point of care whole blood analyzers and laboratory plasma levels are current standards to monitor glucose levels. The use of the bedside glucometer provides rapid and easy access for measuring glucose levels; however, sensitivity in relation to lab values is variable. Once hypoglycemia is detected on a point of care testing device, confirmation from the laboratory could take time and can cause treatment delays. Notwithstanding, low glucose levels can cause neuroglycopenia and require urgent treatment, thus showing the need to develop an accurate bedside tool for timely detection and management of low glucose levels. So far, the role of continuous interstitial monitoring is limited to research studies. Continuous interstitial monitoring was well tolerated in newborns during research trials. The results indicated that almost 80% of the time, low interstitial glucose values on continuous monitoring were not detected with a spot blood glucose measurement (Harris et al. 2010).

Neonatal Abstinence Syndrome

Maternal use of opioids during pregnancy can cause drug withdrawal in exposed newborns after

birth. The clinical presentation is referred as neonatal abstinence syndrome (NAS). In addition to this specific group, newborns who are treated with long-term opioids used as analgesia or sedation can also develop similar signs and symptoms. Although NAS is generally related to the use of opioids, use of other substances like nicotine, cigarettes, benzodiazepines, and selective serotonin reuptake inhibitors (SSRI) can also manifest with similar symptoms.

A sudden rise of NAS has been observed in last 20 years which is attributed to increased maternal use of opioid as pain medication. The NICU admission rate across the USA for newborns diagnosed as NAS has climbed from 7 to 27 cases per 1000 admissions from 2004 to 2013. There is also an observed increase in the length of hospital stays from 13 to 19 days in the same population (Tolia et al. 2015).

Pathophysiology of NAS

NAS is a complex and ill-defined spectrum of behaviour dysregulation which is not completely understood yet. Changes in the levels of different neurotransmitters like dopamine, serotonin, and norepinephrine are thought to be responsible for most of the clinical manifestations (Kocherlakota 2014). The new discovery of genetic influences on the need for pharmacotherapy and length of stay in patients exposed to opioids has opened new doors that may change the future management of these infants. The two genes currently under research are mu-opioid receptor and catechol-o-methyltransferase (Wachman et al. 2013).

Clinical Manifestation

NAS is diagnosed based on the clinical presentation and a positive prenatal history of drug exposure. The characteristic signs of NAS include high-pitched cry/irritability, sleep and wake disturbances, alteration in the tone usually hypertonicity and tremors, and gastrointestinal symptoms including vomiting, diarrhea, and difficulty in feeding. Overall, these symptoms reflect dysfunction of the nervous system related to motor, autonomic, attention, and sensory integration. Seizures have been reported in 2–11% infants

(Herzlinger et al. 1977). The time to manifest clinical symptoms is variable. Timing depends upon the type, dose, and pharmacokinetics of the drug in use. Heroin withdrawal symptoms presents within 24 h due to its short half-life, while long-acting methadone withdrawal might not appear until 5 days of age (Hudak and Tan 2012).

Management

The mother-infant dyad is cared for by a multi-disciplinary team, which includes a health care provider and a social worker. The goal is to allow the successful integration of the infant into the environment, and the establishment of weight gain and adequate sleep. Both supportive non-pharmacological and pharmacological therapies play an important role. Supportive care should be offered to all exposed infants regardless of the presence of clinical symptoms. Although it is not an alternative to drug therapy, it can avoid and reduce the need for drugs. Breastfeeding is encouraged in women whereby the urine toxicology at delivery is negative except for prescribed medications, and there is no other contraindication to breastfeeding (e.g., HIV status). Appropriate skin care is necessary to prevent excoriation. Routine skin care includes keeping the skin dry, clean, and open to the air, and the application of barrier creams if necessary. Non-pharmacological support of infants is individualized based upon behavioral observation. Swaddling, vertical rocking, and side lying in the C position reduce motor hyperactivity. Reduction in tactile, auditory, and visual stimuli helps to down regulate sensory disintegration. The need to start pharmacological therapy is based upon assessment using the NAS scoring system. The Finnegan neonatal abstinence scoring system is most commonly used in clinical practice (Finnegan et al. 1974). The Lipsitz tool and the neonatal withdrawal inventory are other scoring systems to name.

Opioids are used as first-line pharmacological therapy. Oral morphine is the most common drug used for NAS. Buprenorphine has been used in small cohort studies but there is no randomized control trial available to compare efficacy (Kraft et al. 2011). The addition of a second drug is

required as an adjunct when symptoms are not controlled with a single agent. Oral clonidine is currently used as the drug of choice as second line agent (Agthe et al. 2009). Phenobarbitone has also been used in resistant cases.

Long-Term Management

Available data about developmental outcomes is conflicting. A systematic review based on case-control studies found trends toward a poor outcome, but the difference was not significant among exposed and non-exposed groups (Baldacchino et al. 2014). A recent longitudinal study showed lower intelligence quotient (IQ) scores in exposed neonates (Nygaard et al. 2015).

Other Drugs

Fetal and neonatal exposure to marijuana usually does not result in any withdrawal symptoms in neonates, but it can effect long-term neurobehavioral outcome (Campolongo et al. 2009). CNS stimulants like cocaine and amphetamine exposure cause symptoms similar to opioid withdrawal, but reports are controversial. Fetal exposure to cocaine and methamphetamine leads to increased risk of prematurity and intrauterine growth restriction.

SSRIs are frequently used antidepressant drugs. Exposure to SSRIs during pregnancy, especially in the third trimester, results in neonatal symptoms. The manifestation can be due to either serotonin syndrome (increased serotonin concentration in the inter-synaptic cleft) or withdrawal effects of drug. The current recommendation is to continue SSRIs on lowest effective dose during pregnancy. However neonatal practitioners should be aware of the possibility of toxicity/withdrawal symptoms, and should ensure close follow up for neonates exposed to SSRIs in pregnancy.

NAS in Preterm Infants

Preterm infants manifest fewer symptoms as compared to their term peers. The lower gestational age decreases the severity of withdrawal. This relates to immaturity of the brain and lower fat depots of the drug. It is also more difficult to identify symptoms in preterm infants; dedicated

scoring system for this population are not available (Liu et al. 2010).

Acquired Opioid or Benzodiazepam Dependency in Infants

Physical dependency results when sick neonates require analgesia and sedation, which cannot be stopped within few days. Cumulative exposure and development of drug tolerance also contributes towards drug withdrawal. Infants with long-term exposure should be weaned by a defined protocol. Signs and symptoms of withdrawal should be observed in these patients. If withdrawal signs and symptoms develop during the tapering opioids, methadone can be used as a rescue approach. For midazolam withdrawal, the infusion can be substituted with enteral Lorazepam (Hudak and Tan 2012).

Prematurity

A birth prior to 37 completed weeks (less than 259 days) is defined as premature birth. Premature infants are further divided into three categories per gestational age at birth.

Extremely preterm infants (EPT) are newborns born at or below 28 weeks of gestation, very Preterm infant (VPT) are born at or below 32 weeks of gestation, and late preterm infants are born between 34 weeks and 36 weeks and 6 days of gestation (Blencowe et al. 2013).

Another method to classify babies who are born small is based on birth weight. Newborns are categorized as extremely low birth weight (ELBW) when birthweight is less than 1000 g. Similarly, very low birth infants (VLBW) are below 1500 g and low birth weight (LBW) are below 2500 g at birth (Fig. 16.2).

Incidence and Risk Factors of Prematurity

In 2010, a total of 14.9 million babies were born before 37 week of gestation. The true incidence is variable in different parts of world; it ranges from 5% in some European countries to

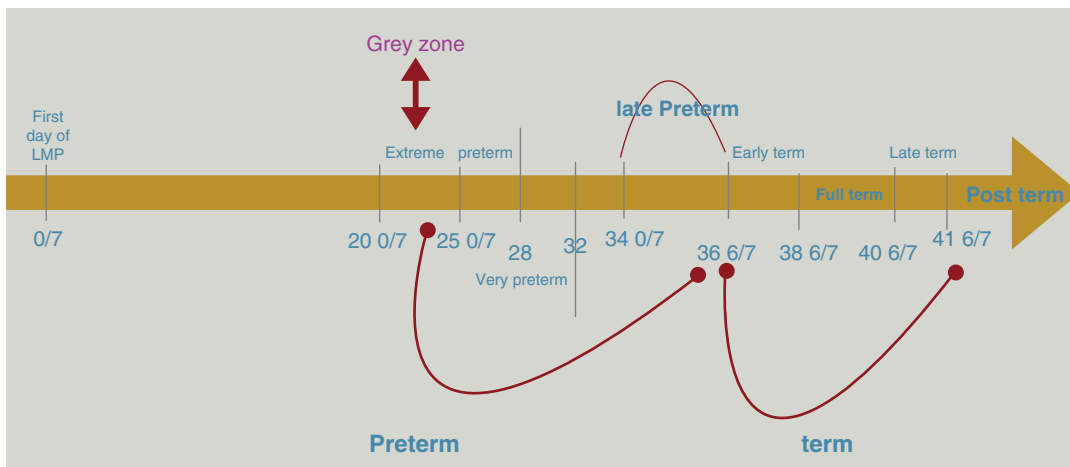


Fig. 16.2 Classification of newborns at different gestation

18% in Africa (Blencowe et al. 2012). In the North America, it is estimated around 11% (Hamilton et al. 2013). The burden of disease can be estimated from the fact that prematurity is a direct cause of 50% neonatal deaths worldwide.

Spontaneous onset of preterm labor or premature rupture of membranes accounts for 80% of premature births. Factors associated with the spontaneous onset of preterm labor include infection, pathological uterine distension, hypothalamic–pituitary adrenal axis activation, and decidual hemorrhage. The remaining 20% are medically indicated preterm births due to various maternal or fetal conditions. Fetal indications of early delivery are congenital abnormalities, infection, growth restriction and fetal distress. Maternal indications of early delivery include antepartum hemorrhage (placenta previa, placenta accreta), hypertensive disorder of pregnancy (preeclampsia), and maternal chronic health conditions.

The advancement in assisted reproductive techniques (ART) is considered to be an important factor in the increased incidence of premature babies; ART is related to an increase in multiparity and infants of multiple gestation are prone to deliver as preterm. Many socioeconomic factors have been identified as risk factors for preterm births. These factors include maternal age (<16 and >35 years), non-Hispanic

black ethnicity, previous history of preterm birth, and life style issues like stress, substance abuse, smoking, diet, and weight (Behrman and Butler 2007).

Grey Zone or Limit of Viability

Viability is defined as a gestational age (GA) when a fetus reaches an anatomical threshold that critical organs, such as the lungs and kidneys, can sustain life' (Seri and Evans 2008). With increased survival and decreased morbidities of extremely premature infants, the age of viability where neonatal resuscitation is offered has been pushed back in last 20 years. In the 1960s, a newborn at 30 weeks of gestation was considered to have a 50% chance of survival. In 2000, perinatal guidelines suggested management and resuscitation at 24 weeks of gestation. Currently in some countries, resuscitation is offered as low as 22 weeks of gestation. In a meta-analysis review for perinatal guidelines at the threshold of viability, authors reported a summary of 34 guidelines from 23 countries and four international groups. Sixty-eight percent of the guidelines supported comfort care at 22-week gestation. However, variation was observed for 23 and 24 weeks GA, with the majority recommending parental involvement in decision making for active care at that gestation (Guillén et al. 2015).

Initial Stabilization and Short-Term Morbidities

The initial stabilization is very important for preterm infants and proper management can reduce the risk of later complications. Perinatal care of an anticipated delivery includes maternal transport to a high-risk center, antenatal steroids, tocolytics to enhance latency for potential benefit from steroids, magnesium sulfate (Mg So₄) for neuroprotection, antibiotics for premature rupture of membranes, and continuous fetal monitoring. Delivery room management comprises establishment and maintenance of respiratory support, hemodynamic stability, prevention of hypothermia, avoidance of hypoglycemia, early start of parenteral nutrition and minimal handling strategies to prevent neurological injury.

Short-term complications observed within the neonatal period are linked to a high rate of mortality and long-term sequelae, which occur in patients who survive and are discharged home from NICU. The risk of complications increases with decreasing gestational age.

The Neonatal Research Network published data for common complications in a cohort of 9575 infants born at an extremely low gestational age between 2003 and 2007. The common problems observed in decreasing order were respiratory distress syndrome (93%), retinopathy of prematurity (59%), Patent ductus arteriosus (46%), late onset sepsis (36%), severe intraventricular hemorrhage (16%), and necrotizing enterocolitis (11%). The rate of survival to discharge in this cohort was 6% at 22 weeks and 92% at 28 weeks (Stoll et al. 2010). The rates of complications and morbidities are highly variable among centers and regions of the world, ultimately reflecting practice variation in the management of these infants.

Post-discharge Care of NICU Graduate

With the increase in survival rates of premature infants, the number of NICU graduates being discharged home is increasing. Although most of

these preterm babies will be discharged around their term gestational age, the medical needs are higher in this group than healthy term infants and require special attention. Effective communication between the neonatologist and primary care provider is required for continuity of care in the community after discharge from the NICU.

Outpatient care of this high-risk population includes evaluation of growth and neurodevelopment, hearing and vision assessments, and immunization. Some prematurity related complications like bronchopulmonary dysplasia, anemia of prematurity, metabolic bone disease, apnea of prematurity, gastroesophageal reflux, and hernias might be present at discharge and require continuous monitoring and care. Depending upon their medical need, the initial visit should be scheduled within first week following hospital discharge to ensure safe transition to home and the provision of social supports to the parents. Following the initial visit, subsequent visits should occur every month in first 6–9 months (Andrews et al. 2014).

Preterm infants should receive all recommended childhood vaccinations as per chronological age with the same schedules and doses recommended for term infants (Saari 2003). Prophylactic administration of Palivizumab (respiratory syncytial virus {RSV} antibody) during RSV season is recommended especially in infants with chronic lung disease. The risk of readmission in ex-preterm infants is twice as high in comparison to term infants during first year of life. Re-admissions are usually related to infections, respiratory problems, surgery, and gastrointestinal issues (Houweling et al. 2013).

Extrauterine growth failure is very common among preterm infants. During the NICU stay, fortification of milk helps to maintain growth, but the risk of a faltering growth pattern remains high after discharge. In part, this is attributed to by an increased caloric requirement for catch up growth in preterm babies and in patients with bronchopulmonary dysplasia. However, feeding problems associated with prematurity also play an important role, such as oral aversion, GERD, oral motor dysfunction, and hypersensitivity. These feeding issues require special attention and the

collaboration of various specialties including occupational therapy and feeding experts for management (Samara et al. 2010). Premature infants who are below the 10th centile at discharge should continue to use nutrient enriched formulas or preterm discharge formulas to maintain optimal growth. Iron and vit. D should also be continued until foods enriched with both are consumed in adequate quantities (Gauer et al. 2014).

Neurodevelopmental follow up for preterm infants is carried out in specialized clinics. These clinics are equipped with specialized screening tools for developmental evaluation. Until two years of age, developmental milestones should be plotted against post-menstrual age rather than chronological age. The purpose of regular monitoring is to identify and start early intervention if required. The developmental issues in ex-preterm infants are not limited to motor abnormalities; learning and language delays are very common. In recent years, an increased incidence of autism spectrum disorder (ASD) has also been linked to prematurity; accordingly, the use of appropriate screening tools like the Modified Checklist for Autism in Toddlers, Revised with Follow-Up (m-CHAT-R/F) should be part of developmental screening programs.

Preterm infants who develop retinopathy of prematurity are at high risk of other ophthalmological issues like visual field problems, cataract, strabismus, amblyopia, and refractory errors. Ophthalmological referral and follow up is recommended after discharge from the NICU (Holmström et al. 1999).

Dental eruption is delayed in preterm infants with an increase rate of dental caries, enamel hypoplasia, and palatal groove. Regular dental follow up with fluoride treatment is recommended by the AAP (Creighton 1998).

As survival of premature infants has improved, and preterm babies now survive into their adulthood, studies have started to explore the long-standing impact of this early post-natal alteration on developmental programming of metabolic problems that are observed later in life. Data suggests that individuals born preterm have an increased risk of metabolic syndrome (increased blood

pressure, insulin sensitivity, and increased adiposity), chronic kidney conditions, asthma and pulmonary abnormalities, psychological disorders, and poor social adaptation. Due to the life-long impact of prematurity, it is now considered as a chronic disease condition (Raju et al. 2016).

References

- Agthe AG, Kim GR, Mathias KB, Hendrix CW, Chavez-Valdez R, Jansson L, et al. Clonidine as an adjunct therapy to opioids for neonatal abstinence syndrome: a randomized, controlled trial. *Pediatrics*. 2009;123(5):e849–e56.
- Andrews B, Pellerite M, Myers P, Hageman JR. NICU follow-up: medical and developmental management age 0 to 3 years. *NeoReviews*. 2014;15(4):e123–e32.
- Aziz K, Dancey P. Screening guidelines for newborns at risk for low blood glucose. *Paediatr Child Health*. 2004;9(10):723–40.
- Baker JP. *Newborn Medicine and Society: European background and American practice (1750–1975)* (review). *Bull Hist Med*. 1999;73(4):743–4.
- Baldacchino A, Arbuckle K, Petrie DJ, McCowan C. Neurobehavioral consequences of chronic intra-uterine opioid exposure in infants and preschool children: a systematic review and meta-analysis. *BMC Psychiatry*. 2014;14(1):104.
- Batton D, Barrington K, Wallman C. American Academy of Pediatrics Committee on Fetus and Newborn; American Academy of Pediatrics Section on Surgery; Canadian Paediatric Society Fetus and Newborn Committee. Prevention and management of pain in the neonate: an update. *Pediatrics*. 2006;118(5):2231–41.
- Behrman R, Butler A. Institute of Medicine (US) Committee on understanding premature birth and assuring healthy outcomes. *Preterm Birth: Causes, Consequences, and Prevention*. Washington, DC: National Academies Press; 2007.
- Belliemi C, Iantorno L, Perrone S, Rodriguez A, Longini M, Capitani S, et al. Even routine painful procedures can be harmful for the newborn. *Pain*. 2009;147(1):128–31.
- Belliemi CV, Tei M, Coccina F, Buonocore G. Sensorial saturation for infants' pain. *J Matern Fetal Neonatal Med*. 2012;25(Suppl 1):79–81.
- Bennett C, Fagan E, Chaharbakshi E, Zamfirova I, Flicker J. Implementing a protocol using glucose Gel to treat neonatal hypoglycemia. *Nurs Womens Health*. 2016;20(1):64–74.
- Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller A-B, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *Lancet*. 2012;379(9832):2162–72.

- Blencowe H, Cousens S, Chou D, Oestergaard M, Say L, Moller A-B, et al. Born too soon: the global epidemiology of 15 million preterm births. *Reprod Health*. 2013;10(1):S2.
- Blume-Peytavi U, Lavender T, Jenerowicz D, Ryumina I, Stalder JF, Torrelo A, et al. Recommendations from a European roundtable meeting on best practice healthy infant skin care. *Pediatr Dermatol*. 2016;33(3):311–21.
- Bryanton J, Walsh D, Barrett M, Gaudet D. Tub bathing versus traditional sponge bathing for the newborn. *J Obstet Gynecol Neonatal Nurs*. 2004;33(6):704–12.
- Campolongo P, Trezza V, Palmery M, Trabace L, Cuomo V. Developmental exposure to cannabinoids causes subtle and enduring neurofunctional alterations. *Int Rev Neurobiol*. 2009;85:117–33.
- Canadian Pediatric Society. Prevention and management of pain in the neonate: an update. Position statements and practice points. Ottawa, ON: Canadian Paediatric Society; 2017a.
- Canadian Pediatric Society. Management of term infants at increased risk for early onset bacterial sepsis. Position statements and practice points. Ottawa, ON: Canadian Paediatric Society; 2017b.
- CDC. GBS. Perinatal prevention guidelines. Group B Strep. Atlanta, GA: CDC; 2017.
- Centers for Disease Control and Prevention. Pregnant women, infants, and children. Gender. HIV by group. HIV/AIDS. Atlanta, GA: Centers for Disease Control and Prevention; 2017. <https://www.cdc.gov/hiv/group/gender/pregnantwomen/>
- Chace DH, Naylor EW. Expansion of newborn screening programs using automated tandem mass spectrometry. *Dev Disabil Res Rev*. 1999;5(2):150–4.
- Cork MJ, Robinson DA, Vasilopoulos Y, Ferguson A, Moustafa M, MacGowan A, et al. New perspectives on epidermal barrier dysfunction in atopic dermatitis: gene–environment interactions. *J Allergy Clin Immunol*. 2006;118(1):3–21.
- Creighton PR. Common pediatric dental problems. *Pediatr Clin North Am*. 1998;45(6):1579–600.
- Darmstadt GL, Dinulos JG. Neonatal skin care. *Pediatr Clin North Am*. 2000;47(4):757–82.
- Davidson JO, Wassink G, van den Heuvel LG, Bennet L, Gunn AJ. Therapeutic hypothermia for neonatal hypoxic-ischemic encephalopathy—where to from here? *Front Neurol*. 2014;6:198.
- Denne SC. Neonatal nutrition. *Pediatr Clin North Am*. 2015;62(2):427–38.
- Di Renzo GC, Melin P, Berardi A, Blennow M, Carbonell-Estrany X, Donzelli G, et al. Intrapartum GBS screening and antibiotic prophylaxis: a European consensus conference. *J Matern Fetal Neonatal Med*. 2015;28(7):766–82.
- Dore S, Buchan D, Coulas S, Hamber L, Stewart M, Cowan D, et al. Alcohol versus natural drying for newborn cord care. *J Obstet Gynecol Neonatal Nurs*. 1998;27(6):621–7.
- Douglas-Escobar M, Weiss MD. Hypoxic-ischemic encephalopathy: a review for the clinician. *JAMA Pediatr*. 2015;169(4):397–403.
- Finnegan L, Connaughton J Jr, Kron R, Emich J. Neonatal abstinence syndrome: assessment and management. *Addict Dis*. 1974;2(1–2):141–58.
- Gauer RL, Burket J, Horowitz E. Common questions about outpatient care of premature infants. *Am Fam Physician*. 2014;90(4):244–51.
- Grunau RE, Oberlander T, Holsti L, Whitfield MF. Bedside application of the neonatal facial coding system in pain assessment of premature infants. *Pain*. 1998;76(3):277–86.
- Guillén Ú, Weiss EM, Munson D, Maton P, Jefferies A, Norman M, et al. Guidelines for the management of extremely premature deliveries: a systematic review. *Pediatrics*. 2015;136(2):343–50.
- Guthrie R, Susi A. A simple phenylalanine method for detecting phenylketonuria in large populations of newborn infants. *Pediatrics*. 1963;32(3):338–43.
- Hachem J-P, Crumrine D, Fluhr J, Brown BE, Feingold KR, Elias PM. pH directly regulates epidermal permeability barrier homeostasis, and stratum corneum integrity/cohesion. *J Invest Dermatol*. 2003;121(2):345–53.
- Hamilton BE, Hoyert DL, Martin JA, Strobino DM, Guyer B. Annual summary of vital statistics: 2010–2011. *Pediatrics*. 2013;2012:3769.
- Harris DL, Battin MR, Weston PJ, Harding JE. Continuous glucose monitoring in newborn babies at risk of hypoglycemia. *J Pediatr*. 2010;157(2):198–202. e1.
- Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. *J Pediatr*. 2012;161(5):787–91.
- Harris DL, Weston PJ, Signal M, Chase JG, Harding JE. Dextrose gel for neonatal hypoglycaemia (the sugar babies study): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2014;382(9910):2077–83.
- Harris DL, Alsweiler JM, Ansell JM, Gamble GD, Thompson B, Wouldes TA, et al. Outcome at 2 years after dextrose gel treatment for neonatal hypoglycemia: follow-up of a randomized trial. *J Pediatr*. 2016;170:54–9. e2.
- Hauk L. AAFP releases position paper on breastfeeding. *Am Fam Physician*. 2015;91(1):56–7.
- Herzlinger RA, Kandall SR, Vaughan HG. Neonatal seizures associated with narcotic withdrawal. *J Pediatr*. 1977;91(4):638–41.
- Hodge JW, Greiner JW, Tsang KY, Sabzevari H, Kudo-Saito C, Grosenbach DW, et al. Costimulatory molecules as adjuvants for immunotherapy. *Front Biosci*. 2006;11:788–803.
- Holmström G, El Azazi M, Kugelberg U. Ophthalmological follow up of preterm infants: a population based, prospective study of visual acuity and strabismus. *Br J Ophthalmol*. 1999;83(2):143–50.
- Holsti L, Grunau RE. Initial validation of the behavioral indicators of infant pain (BIIP). *Pain*. 2007;132(3):264–72.
- Horta BL, Victora CG. Long-term effects of breastfeeding—a systematic review. Geneva: World Health Organization; 2013.

- Horta BL, Victora CG, Organization WH. Short-term effects of breastfeeding: a systematic review on the benefits of breastfeeding on diarrhoea and pneumonia mortality. Geneva: World Health Organization; 2013.
- Houweling LM, Bezemer ID, Penning-van Beest FJ, Meijer WM, van Lingen RA, Herings RM. First year of life medication use and hospital admission rates: premature compared with term infants. *J Pediatr*. 2013;163(1):61–6. e1.
- Howlett JA, Northington FJ, Gilmore MM, Tekes A, Huisman TA, Parkinson C, et al. Cerebrovascular autoregulation and neurologic injury in neonatal hypoxic-ischemic encephalopathy. *Pediatr Res*. 2013;74(5):525–35.
- Hudak ML, Tan RC. Neonatal drug withdrawal. *Pediatrics*. 2012;129(2):e540–e60.
- Hyde ML. Newborn hearing screening programs: Overview. *J Otolaryngol*. 2005;34(2):S70.
- Ingram RA, Fitzgerald M, Baccei ML. Developmental changes in the fidelity and short-term plasticity of GABAergic synapses in the neonatal rat dorsal horn. *J Neurophysiol*. 2008;99(6):3144–50.
- Ip S, Chung M, Raman G, Trikalinos TA, Lau J. A summary of the Agency for Healthcare Research and Quality's evidence report on breastfeeding in developed countries. *Breastfeed Med*. 2009;4(S1):S-17–30.
- Keels E, Sethna N, Watterberg KL, Cummings JJ, Benitz WE, Eichenwald EC, et al. Prevention and management of procedural pain in the neonate: an update. *Pediatrics*. 2016;137(2):1–13.
- Kirby M, Noel RJ, editors. Nutrition and gastrointestinal tract assessment and management of children with dysphagia. Seminars in speech and language. New York, NY: Thieme Medical Publishers Inc.; 2007.
- Klinger G, Beyene J, Shah P, Perlman M. Do hyperoxaemia and hypocapnia add to the risk of brain injury after intrapartum asphyxia? *Arch Dis Child Fetal Neonatal Ed*. 2005;90(1):F49–52.
- Kocherlakota P. Neonatal abstinence syndrome. *Pediatrics*. 2014;134(2):e547–e61.
- Korver AM, Konings S, Dekker FW, Beers M, Wever CC, Frijns JH, et al. Newborn hearing screening vs later hearing screening and developmental outcomes in children with permanent childhood hearing impairment. *JAMA*. 2010;304(15):1701–8.
- Kraft WK, Dysart K, Greenspan JS, Gibson E, Kaltenbach K, Ehrlich ME. Revised dose schema of sublingual buprenorphine in the treatment of the neonatal opioid abstinence syndrome. *Addiction*. 2011;106(3):574–80.
- Kurinczuk JJ, White-Koning M, Badawi N. Epidemiology of neonatal encephalopathy and hypoxic-ischaemic encephalopathy. *Early Hum Dev*. 2010;86(6):329–38.
- Lacaze-Masmonteil T, Rosychuk RJ, Robinson JL. Value of a single C-reactive protein measurement at 18 h of age. *Arch Dis Child Fetal Neonatal Ed*. 2014;99(1):F76–F9.
- van Laerhoven H, de Haan TR, Offringa M, Post B, van der Lee JH. Prognostic tests in term neonates with hypoxic-ischemic encephalopathy: a systematic review. *Pediatrics*. 2013;2012:1297.
- Lago P, Garetti E, Merazzi D, Pieragostini L, Ancora G, Pirelli A, et al. Guidelines for procedural pain in the newborn. *Acta Paediatr*. 2009;98(6):932–9.
- Lavender T, Furber C, Campbell M, Victor S, Roberts I, Bedwell C, et al. Effect on skin hydration of using baby wipes to clean the napkin area of newborn babies: assessor-blinded randomised controlled equivalence trial. *BMC Pediatr*. 2012;12(1):59.
- Lingappan K, Kaiser JR, Srinivasan C, Gunn AJ, Group CS. Relationship between PCO2 and unfavorable outcome in infants with moderate-to-severe hypoxic ischemic encephalopathy. *Pediatr Res*. 2016;
- Liu AJ, Jones MP, Murray H, COOK CM, Nanan R. Perinatal risk factors for the neonatal abstinence syndrome in infants born to women on methadone maintenance therapy. *Aust N Z J Obstet Gynaecol*. 2010;50(3):253–8.
- Mahle W, Martin G, Beekman R III, Morrow W. Section on Cardiology and Cardiac Surgery Executive Committee. Endorsement of health and human services recommendation for pulse oximetry screening for critical congenital heart disease. *Pediatrics*. 2012;129(1):190–2.
- Mason WH, Andrews R, Ross LA, WRIGHT JR HT. Omphalitis in the newborn infant. *Pediatr Infect Dis J*. 1989;8(8):521–5.
- MEDICINE COFANA SOAAP, Keels E, Sethna N, Watterberg KL, Cummings JJ, Benitz WE, et al. prevention and management of procedural pain in the neonate: an update. *Pediatrics*. 2016;137(2):e20154271.
- Mindell JA, Telofski LS, Wiegand B, Kurtz ES. A nightly bedtime routine: impact on sleep in young children and maternal mood. *Sleep*. 2009;32(5):599–606.
- Mir F, Tikmani SS, Shakoor S, Warraich HJ, Sultana S, Ali SA, et al. Incidence and etiology of omphalitis in Pakistan: a community-based cohort study. *J Infect Dev Countr*. 2011;5(12):828–33.
- Narayan IC, Blom NA, Ewer AK, Vento M, Manzoni P, te Pas AB. Aspects of pulse oximetry screening for critical congenital heart defects: when, how and why? *Arch Dis Child Fetal Neonatal Ed*. 2016;101(2):F162–7.
- Nelson KB, Bingham P, Edwards EM, Horbar JD, Kenny MJ, Inder T, et al. Antecedents of neonatal encephalopathy in the vermont oxford network encephalopathy registry. *Pediatrics*. 2012;2012:0714.
- Newman TB, Puopolo KM, Wi S, Draper D, Escobar GJ. Interpreting complete blood counts soon after birth in newborns at risk for sepsis. *Pediatrics*. 2010;126(5):903–9.
- NICE (2012) Early-onset neonatal infection overview - NICE Pathways: sNICE guidance and other sources used to create this interactive flowchart. Neonatal infection (early onset): antibiotics for prevention and treatment NICE guideline CG149 Neonatal infection (2014) NICE quality standard 75Xpert GBS test for the intrapartum detection of group B streptococcus (2015) NICE medtech innovation briefing 28; 2017 [Available from: <https://pathways.nice.org.uk/pathways/early-onset-neonatal-infection>].

- Nygaard E, Slinning K, Moe V, Walhovd KB. Cognitive function of youths born to mothers with opioid and poly-substance abuse problems during pregnancy. *Child Neuropsychol*. 2015;159–87.
- Oster ME, Lee KA, Honein MA, Riehle-Colarusso T, Shin M, Correa A. Temporal trends in survival among infants with critical congenital heart defects. *Pediatrics*. 2013;2012:3435.
- Papile L-A, Baley JE, Benitz W, Cummings J, Carlo WA, Eichenwald E, et al. Hypothermia and neonatal encephalopathy. *Pediatrics*. 2014;133(6):1146–50.
- Patel H, Feldman M. Universal newborn hearing screening. *Paediatr Child Health*. 2011;16(5):301.
- Pediatrics AAo. Neonatal encephalopathy and neurologic outcome, second edition. Report of the American College of Obstetricians and Gynecologists' Task Force on Neonatal Encephalopathy. *Pediatrics*. 2014;133(5):e1482–e8.
- Pediatrics AA, FaN C. Prevention and management of pain in the neonate: an update. *Pediatrics*. 2006;118(5):2231–41.
- Perlman JM, Wyllie J, Kattwinkel J, Wyckoff MH, Aziz K, Guinsburg R, et al. Part 7: neonatal resuscitation. *Circulation*. 2015;132(16 suppl 1):S204–S41.
- Philip AG. The evolution of neonatology. *Pediatr Res*. 2005;58(4):799–815.
- Polin RA. Management of neonates with suspected or proven early-onset bacterial sepsis. *Pediatrics*. 2012;129(5):1006–15.
- Puopolo KM, Draper D, Wi S, Newman TB, Zupancic J, Lieberman E, et al. Estimating the probability of neonatal early-onset infection on the basis of maternal risk factors. *Pediatrics*. 2011;2010:3464.
- Raju TN, Pemberton VL, Saigal S, Blaisdell CJ, Moxey-Mims M, Buist S. Long-term healthcare outcomes of preterm birth: an executive summary of a conference sponsored by the National Institutes of Health. *J Pediatr*. 2016;181:309–318.e1.
- Ramezani T, Shirazi ZH, Sarvestani RS, Moattari M. Family-centered care in neonatal intensive care unit: a concept analysis. *Int J Commun Nurs Midwif*. 2014;2(4):268.
- Robinson S, Fall C. Infant nutrition and later health: a review of current evidence. *Forum Nutr*. 2012;4(8):859–74.
- Rollins N, Booth T, Morriss MC, Sanchez P, Heyne R, Chalak L. Predictive value of neonatal MRI showing no or minor degrees of brain injury after hypothermia. *Pediatr Neurol*. 2014;50(5):447–51.
- Roofthoof DW, Simons SH, Anand KJ, Tibboel D, van Dijk M. Eight years later, are we still hurting newborn infants? *Neonatology*. 2014;105(3):218–26.
- Rozance PJ, Hay WW. New approaches to management of neonatal hypoglycemia. *Mat Health Neonatol Perinatol*. 2016;2(1):3.
- Rutherford M, Biarge MM, Allsop J, Counsell S, Cowan F. MRI of perinatal brain injury. *Pediatr Radiol*. 2010;40(6):819–33.
- Saari TN. Immunization of preterm and low birth weight infants. *Pediatrics*. 2003;112(1):193–8.
- Samara M, Johnson S, Lamberts K, Marlow N, Wolke D. Eating problems at age 6 years in a whole population sample of extremely preterm children. *Dev Med Child Neurol*. 2010;52(2):e16–22.
- Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress: a clinical and electroencephalographic study. *Arch Neurol*. 1976;33(10):696–705.
- Scheltonka RL, Chai MK, Yoder BA, Hensley D, Brockett RM, Ascher DP. Volume of blood required to detect common neonatal pathogens. *J Pediatr*. 1996;129(2):275–8.
- Schrag SJ, Zell ER, Lynfield R, Roome A, Arnold KE, Craig AS, et al. A population-based comparison of strategies to prevent early-onset group B streptococcal disease in neonates. *N Engl J Med*. 2002;347(4):233–9.
- Schuchat A, Zywicki SS, Dinsmoor MJ, Mercer B, Romaguera J, O'sullivan MJ, et al. Risk factors and opportunities for prevention of early-onset neonatal sepsis: a multicenter case-control study. *Pediatrics*. 2000;105(1):21–6.
- Seri I, Evans J. Limits of viability: definition of the gray zone. *J Perinatol*. 2008;28:S4–8.
- Shah PS, Herbozo C, Aliwalas LL, Shah VS. Breastfeeding or breast milk for procedural pain in neonates. *Cochrane Database Syst Rev*. 2012;12:CD004950.
- Shide DJ, Blass EM. Opioidlike effects of intraoral infusions of corn oil and polycoxe on stress reactions in 10-day-old rats. *Behav Neurosci*. 1989;103(6):1168.
- Stevens B, Johnston C, Petryshen P, Taddio A. Premature infant pain profile: development and initial validation. *Clin J Pain*. 1996;12(1):13–22.
- Stevens B, Yamada J, Lee GY, Ohlsson A. Sucrose for analgesia in newborn infants undergoing painful procedures. *Cochrane Database Syst Rev*. 2013;1:CD001069.
- Stewart D, Benitz W. Umbilical Cord Care in the Newborn Infant. *Pediatrics*. 2016;138(3):e20162149.
- Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. *Pediatrics*. 2010;126(3):443–56.
- Takenouchi T, Iwata O, Nabetani M, Tamura M. Therapeutic hypothermia for neonatal encephalopathy: JSPNM & MHLW Japan Working Group practice guidelines: consensus statement from the Working Group on therapeutic hypothermia for neonatal encephalopathy, Ministry of Health, Labor and Welfare (MHLW), Japan, and Japan Society for Perinatal and Neonatal Medicine (JSPNM). *Brain Dev*. 2012;34(2):165–70.
- The President's Council on Bioethics. The President's Council on Bioethics: The changing moral focus of newborn screening: an ethical analysis by the president's council on bioethics (Table of Contents); 2017. https://bioethicsarchive.georgetown.edu/pbce/reports/newborn_screening/.
- Therrell BL, Padilla CD, Loeber JG, Kneisser I, Saadallah A, Borrajo GJ, et al., editors. Current status of newborn screening worldwide: 2015. *Semin Perinatol*. 2015;39(3):171–87.

- Thornton PS, Stanley CA, De Leon DD, Harris D, Haymond MW, Hussain K, et al. Recommendations from the pediatric endocrine society for evaluation and management of persistent hypoglycemia in neonates, infants, and children. *J Pediatr*. 2015;167(2):238–45.
- Tolia VN, Patrick SW, Bennett MM, Murthy K, Sousa J, Smith PB, et al. Increasing incidence of the neonatal abstinence syndrome in US neonatal ICUs. *N Engl J Med*. 2015;372(22):2118–26.
- Van Handel M, Swaab H, De Vries LS, Jongmans MJ. Long-term cognitive and behavioral consequences of neonatal encephalopathy following perinatal asphyxia: a review. *Eur J Pediatr*. 2007;166(7):645–54.
- Vandenplas Y, Rudolph CD, Di Lorenzo C, Hassall E, Liptak G, Mazur L, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr*. 2009;49(4):498–547.
- Visser MO, Adam R, Brink S, Odio M. Newborn infant skin: physiology, development, and care. *Clin Dermatol*. 2015;33(3):271–80.
- Wachman EM, Hayes MJ, Brown MS, Paul J, Harvey-Wilkes K, Terrin N, et al. Association of OPRM1 and COMT single-nucleotide polymorphisms with hospital length of stay and treatment of neonatal abstinence syndrome. *JAMA*. 2013;309(17):1821–7.
- Weston PJ, Harris DL, Battin M, Brown J, Hegarty JE, Harding JE. Oral dextrose gel for the treatment of hypoglycaemia in newborn infants. *Cochrane Database Syst Rev*. 2016;5:CD011027.
- WHO. Compilation of WHO recommendations on maternal, newborn, child and adolescent health. Geneva: World Health Organization; 2014. http://www.who.int/maternal_child_adolescent/documents/mnca-recommendations/en/
- Wolff R, Hommerich J, Riemsma R, Antes G, Lange S, Kleijnen J. Hearing screening in newborns: systematic review of accuracy, effectiveness, and effects of interventions after screening. *Arch Dis Child*. 2010;95(2):130–5.
- Wyckoff MH, Aziz K, Escobedo MB, Kapadia VS, Kattwinkel J, Perlman JM, et al. Part 13: neonatal resuscitation. *Circulation*. 2015;132(18 suppl 2):S543–S60.



Andrea Andrade and Asuri N. Prasad

Introduction

Repetitive, stereotyped paroxysmal events account for a significant number of pediatric consultations and pediatric ER visits. These events can affect children of all ages. Paroxysmal events that affect young infants are different from those affecting older children and adolescents. Variability in clinical features and age-dependent expression pose a diagnostic challenge. Accurate and early recognition of these events is important for the implementation of appropriate therapeutic measures and for the provision of reassurance to families.

Paroxysmal events in children can be divided in two major groups: epileptic and non-epileptic events. In the following sections, we will review the classification, differential diagnosis, and treatment of paroxysmal events in children, with a focus on events most frequently encountered by the pediatrician.

Definitions and Classifications

Pediatric paroxysmal events can be divided in two major groups:

A. Andrade (✉) • A.N. Prasad
Department of Pediatrics, Schulich School of
Medicine and Dentistry, Neurology Division LHSC,
London, Ontario Canada
e-mail: Andrea.Andrade@lhsc.on.ca;
narayan.prasad@lhsc.on.ca

1. Epileptic seizures—when the clinical paroxysmal event is the result of abnormal hypersynchronized electrical activity in the brain cortex, and is commonly associated with electroencephalogram (EEG) abnormalities. These usually respond to anticonvulsant medications. Epileptic seizures represent the principal symptom of epilepsy.
2. Non epileptic—these events are divided into psychogenic (conversion disorder) and non-psychogenic or physiologic events that are caused by the following etiologies: cardiac, autonomic, behavioral, and movement disorders.

Epileptic Seizures and Epilepsy: Definitions and Current Concepts

Seizures—Seizures are paroxysmal, episodic events that result from underlying neuronal dysfunction. Seizures cause a sudden and transient occurrence in behavioral, somatosensory, motor, or visual signs and/or symptoms depending on the location in the cerebral cortex where the seizure is generated (Fig. 17.1). Seizures can be *provoked* by certain triggers (i.e. trauma, infection, a brain hemorrhage, metabolic abnormalities, or a drug exposure) or *unprovoked* if there is no an identifiable or reversible trigger (Berg et al. 2010).

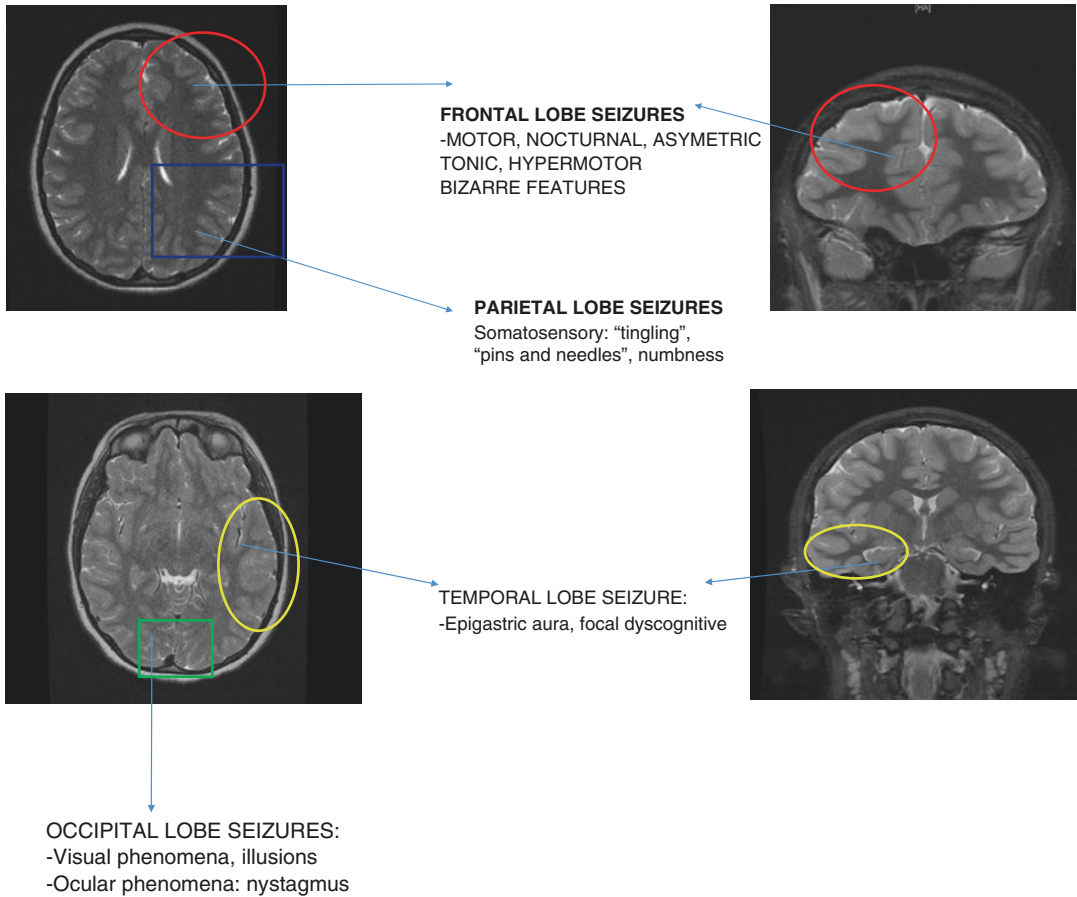


Fig. 17.1 Seizure semiology and anatomical correlation: red circle = frontal lobe, blue square = parietal lobe, yellow oval = temporal lobe, green circle = occipital lobe

Epilepsy—The current ILAE (International League Against Epilepsy) definition of epilepsy refers to epilepsy as either a disease characterized by one or more seizures with a relatively high risk of recurrence (60% risk or more, given clinical, EEG and/or MRI findings) or recurrent unprovoked seizures (two or more unprovoked seizures occurring at least 24 h apart). The implication of this definition is that antiepileptic therapy can be initiated following the first seizure in certain situations (Berg et al. 2010).

Epilepsy affects an estimated 50 million people worldwide. The prevalence of epilepsy in childhood is approximately 0.5%. In developed countries, an average of about 50 per 100,000 children

newly develop epilepsy each year (Berg et al. 2010; St Louis and Cascino 2016).

The principal clinical symptoms of epilepsy can be divided in: *ictal*—during the seizure; *post-ictal*—immediately following seizure termination; and *interictal*—in between seizure episodes (St Louis and Cascino 2016).

The constellation of ictal phenomena can range from subjective symptoms reported by the patient to objectively witnessed events of involuntary motor activity, behavioral arrest, etc.

The prognosis and management of epilepsy are directed by the diagnosis of a specific epilepsy syndrome. Seizure type and epilepsy syndrome diagnoses are based on a description of the ictal phenomena in addition to the EEG findings;

neuroimaging and genetic studies can be complementary findings (Berg et al. 2010).

The classification of epileptic seizures has changed over time, which is also the result of further advances in genetics and neuroimaging technology.

The revised classification by the ILAE in 2010 proposed that seizures should be divided into focal (formerly partial) and generalized seizures. Focal seizures are subdivided into focal dyscognitive seizures (formerly complex partial) and focal seizures with loss of awareness. Although the terminology refers to the same seizures, the reader should be familiar with the different terms used to define and classify seizures (Berg et al. 2010).

Focal Epilepsies in Children

Approximately 50% of childhood epilepsies have a focal onset. Focal epilepsies originate in the neuronal network confined to a regional or hemispheric distribution. The seizure type will depend on the area of the brain that is affected, the age of the child, and the presence of a cerebral structural lesion. Pediatric patients with focal epilepsies usually present a bigger challenge due to their unpredictable age of onset, the presence of subtle and under recognized phenomena with or without dyscognitive symptoms. The evolution in seizure semiology as children get older and access challenges to appropriate high resolution neuroimaging techniques and epilepsy protocols for infants and young children are added challenges (Moosa and Wyllie 2013). These factors often lead to a delay in the diagnosis and treatment in childhood epilepsies.

A very accurate and detailed description of the seizure sequence is key to the diagnosis of focal epilepsies in infants and children. It is important to elicit historical details of the following focal features: forced eye deviation, asymmetric or unilateral motor activity, head deviation, focal dyscognitive seizures (presence of ictal speech/recollection of the seizure), asymmetric tonic posturing, and hypermotor nocturnal seizures.

Other clues to the diagnosis include the presence of an aura (such as epigastric sensation), sensory phenomena, visual disturbances, and psychic and experiential phenomena (“deja-vu” and “jamais vu”). During the post-ictal state, deficits (motor, sensory, visual, etc.) are highly suggestive of focal epilepsy and should direct the clinician to consider early neuroimaging.

Focal epilepsy should be suspected in children with seizures and pre-existing focal neurological deficits on history (early hand preference or gaze preference) and neurological exam (hemiparesis, monoparesis, even subtle asymmetries on rapid alternating movements and tests of coordination). Stressed gait manoeuvres can be clues to the presence of a structural abnormality.

In Fig. 17.1 we describe different seizure semiologies and their anatomical correlates.

Epileptogenic lesions refer to structural brain abnormalities that are responsible for causing epileptic seizures. These can be very diverse and include the following: focal encephalomalacia secondary to remote brain lesions (such as perinatal or neonatal stroke), cerebral infections, malformations of cortical development that can affect the entire hemisphere (hemimegalencephaly), focal cortical dysplasia, low grade CNS tumors, mesial temporal sclerosis, Rasmussen encephalitis, and Sturge Weber Syndrome. In Fig. 17.2 we present examples of common epileptogenic lesions in children (Moosa and Wyllie 2013).

The diagnosis of epilepsy should be made on the basis of the history, physical exam, neurological electroencephalogram, and MRI of the brain. Added investigations are dependent on the nature of the epilepsy and the suspected etiology.

Initial treatment with antiepileptic medications targeting focal seizures such as carbamazepine is warranted. When a patient continues having seizures despite an appropriate dose of an anticonvulsant and subsequently fails to respond to two anticonvulsants in monotherapy or in combination (Kwan et al. 2010), an early referral to a paediatric epilepsy center should be made. Such a referral will help facilitate the evaluation for other therapeutic strategies, such as epilepsy surgery.

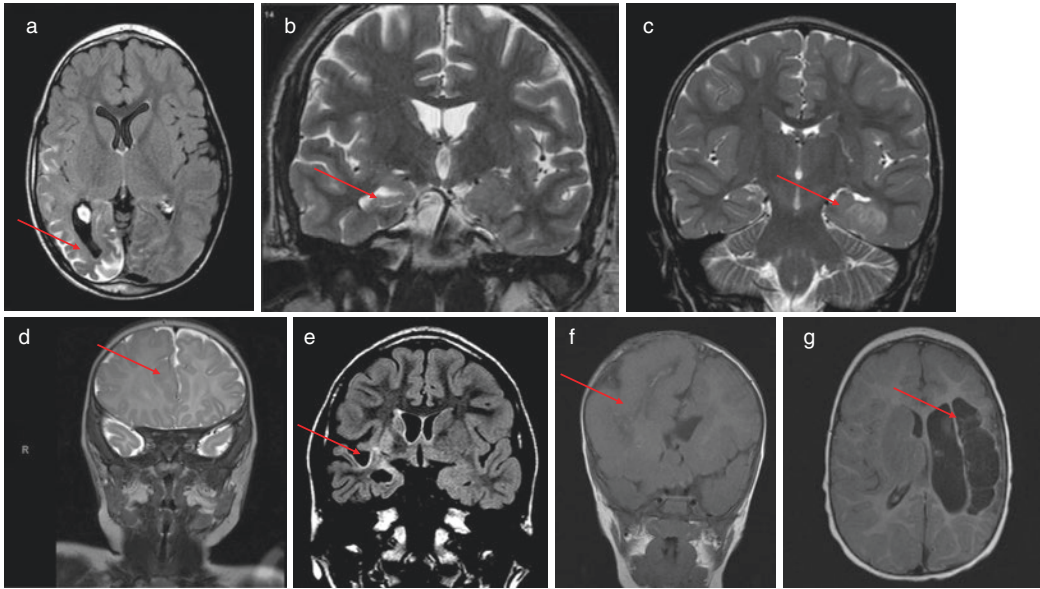


Fig. 17.2 Examples of focal epileptogenic lesions commonly seen in children: (a) Sturge Weber, right hemisphere leptomeningeal angioma (b) Right mesial temporal sclerosis (c) Left mesial temporal low grade tumor (d)

Right focal cortical dysplasia (e) Right hemisphere Rasmussen's encephalitis, (f) Right hemimegalencephaly, (g) Left remote MCA stroke

Epilepsy Syndromes in the Neonatal Period and in Infancy

Epilepsy syndromes in children can be divided into focal epilepsy syndromes and generalized epilepsy syndromes. In this section we will review the most common benign epilepsy syndromes encountered by the general pediatrician.

In this section, we discuss several types of early onset epilepsies beginning in the neonatal stage or in infancy. Three following familial focal epilepsy syndromes are most notable: benign familial neonatal seizures (BFNS), benign familial neonatal-infantile seizures (BFNIS), and benign familial infantile seizures (BFIS).

Inheritance

All three syndromes show autosomal dominant inheritance with variable penetrance.

Seizure Semiology and Evolution

1. Focal motor phenomena that can evolve into generalized seizures, with apnea, cyanosis and staring.

2. Typically, these seizures remit spontaneously after a few weeks to months, and respond well to conventional antiepileptic drugs.
3. These infants are neurologically normal on examination, and tend to have normal developmental outcomes for the most part (Cross 2013).

Benign Familial Neonatal Seizures

Benign familial neonatal seizures (BFNS) are caused by dominant mutations in the potassium voltage-gated channel KQT-like subfamily genes: *KCNQ2* and *KCNQ3*. There is a higher incidence of patients carrying *KCNQ2* mutations. These genes code for corresponding subunits of the potassium channel. Fixed genetic deficits in channel structure lead only to intermittent seizures in early life that tend to remit over time. The reason for this may be related to time locked changes in the expression of different channel genes and their component subunits and physiological changes in gating effects of channel dependent currents during brain development. Rarely, *KCNQ2* mutations have also been

reported in association with early life seizures and an epileptic encephalopathy eventually leading to intellectual disability (Cross 2013). The remaining two entities less frequently encountered are listed below.

Benign Familial Neonatal-Infantile Seizures (BFNIS)

Among families described with benign familial neonatal convulsions, there exist families with an age of onset intermediate between classic BFNS and BFIS (i.e. onset predominantly after 1 month). The seizures are partial onset with secondary generalization beginning between 2 and 7 months and carry a good prognosis. A missense mutation in the alpha2 subunit of the voltage-gated sodium channel (*SCN2A*) has been identified (Cross 2013).

Benign Familial Infantile Seizures (BFIS)

A less commonly encountered syndrome, with age of onset between 3 and 8 months and spontaneous remission by age 3 years, has been described in some families. This condition, benign familial infantile seizures, has been described to cosegregate with a movement disorder (choreoathetosis) as well as hemiplegic migraine. The condition is genetically heterogeneous (Cross 2013).

Epileptic Encephalopathy

In 2001, the international league against epilepsy (ILAE) identified *epileptic encephalopathy* as a distinct group encompassing disorders in which a progressive disturbance in cerebral function was the result of a combination of frequent and severe seizures and continuous unremitting interictal paroxysmal epileptiform activity. Epileptic encephalopathy can be further divided into two main categories: (1) Epileptic encephalopathy syndromes in infancy and (2) Epileptic encephalopathy syndromes in childhood (Berg et al. 2010).

Several epileptic encephalopathies have been described in infancy based on their electroclinical features (age of onset, seizure type, and EEG pattern). Epileptic encephalopathy syndromes in infancy can be further classified into:

1. Early infantile epileptic encephalopathy (EIEE or Ohtahara syndrome)
2. Early myoclonic encephalopathy (EME)
3. Infantile spasms (West syndrome)
4. Malignant epilepsy with migrating partial seizures in infancy (MMPS)
5. Severe myoclonic epilepsy in infancy (SMEI)

The etiologies of epileptic encephalopathies are heterogeneous and a significant proportion of cases are attributable to structural brain defects and inherited metabolic disorders. This is an evolving field, genotype-phenotype correlations are not completely well understood, and there is considerable phenotypic variability within the same genetic defect.

There is recognition of both *locus heterogeneity* and *genetic heterogeneity*. In *locus heterogeneity*, mutations in the sodium channel genes cause Dravet syndrome as well as generalized epilepsy with febrile seizures plus (GEFS+). In *genetic heterogeneity*, a particular electroclinical syndrome may be caused by multiple gene defects. In the latter for example, Ohtahara syndrome may be caused by mutations in syntaxin binding protein-1 (*STXBPI*), potassium channel mutations (*KCNQ2*), Aristaless related homeobox (*ARX*), solute carrier family 25, and member 22 (*SLC25A22*) encoding a mitochondrial glutamate carrier. Currently, as many as 35 different genes have been identified as being associated with an early onset epileptic encephalopathy and it is likely that the list will grow longer each year (Pisani et al. 2015).

Early Infantile Epileptic Encephalopathy

Early infantile epileptic encephalopathy (EIEE), more commonly known as Ohtahara syndrome, was first described by Japanese neurologist Shunsuke Ohtahara in 1976 and is one of the earliest and most severe forms of age-related epileptic encephalopathies.

Seizure Semiology

1. The major seizure type is tonic spasms but can vary to include tonic/clonic, clonic, myoclonic, atonic, absences, partial, complex partial, gelastic seizures, and seizures with Jacksonian features (motor activity that marches along the body mimicking spread across the Rolandic motor strip).
2. Seizure onset is within the first 10 days or up to 3 months of life eventually leading to psychomotor impairment and death.

Inheritance

The majority of cases arise from sporadic *de novo* mutations (no mutational change identified in either parent). However, in rare cases, autosomal and X-linked recessive inheritance patterns have been observed (Pisani et al. 2015; Prasad and Hoffmann 2010).

Early Myoclonic Encephalopathy (EME)

Early myoclonic encephalopathy is a neonatal onset disorder beginning typically within the first month of life.

Seizure Semiology and Evolution

Early myoclonic encephalopathy is characterized clinically by erratic, fragmentary or massive myoclonus, partial seizures, and late tonic spasms. Early myoclonic encephalopathy shares many clinical and pathological features with Ohtahara syndrome. However, the etiology of EME is highly variable and typically associated with an inborn error of metabolism (glycine encephalopathy, organic acidemias, Menke's disease, Zellweger syndrome, and molybdenum cofactor deficiency). The prognosis and outcome are generally poor and dependent on the underlying disorder.

Inheritance

Inborn errors of metabolism are inherited as Mendelian recessive conditions with a few exceptions, where *de-novo* mutations, and/or compound heterozygosity may be responsible for a severe phenotype.(Prasad and Hoffmann 2010; Sharma and Prasad 2013).

Epilepsy of Infancy with Migrating Focal Seizures (Malignant Migrating Partial Seizures of Infancy (MMPSI))

This condition is characterized by normal early development, refractory focal seizures arising independently from either hemisphere, severe psychomotor retardation, and a poor prognosis. While the electroclinical features of this condition are being better recognized owing to typical seizure semiology and EEG findings, the condition appears to be genetically heterogeneous with pathogenic mutations in SCN1A, KCNT1, SCN8 identified.

Inheritance

Mutations of *de novo* origin are mostly considered responsible (Sharma and Prasad 2013).

Infantile Spasms (IS)

Infantile spasms represent a specific syndrome of generalized epileptic seizures associated with a characteristic EEG pattern of hypsarrhythmia (Fig. 17.3). Both genetic (tuberous sclerosis, inborn errors of metabolism, Down syndrome), and non-genetic (perinatal hypoxic ischemic encephalopathy) conditions are associated with this epilepsy syndrome.(Prasad and Hoffmann 2010; Sharma and Prasad 2013).

Seizure Semiology and Evolution

West syndrome is characterized by the occurrence of infantile spasms, the EEG finding of hypsarrhythmia, and developmental delay or regression. Infantile spasms typically occur between 3 and 12 months of age. Spasms usually occur in clusters comprising of tonic contractions of limb and axial muscles, and may be flexor, extensor or mixed. The spasms typically occur in relation to the sleep wake cycle; they occur when the child wakes up from sleep, or is going to sleep. Often the onset of spasms may be preceded by loss of ocular pursuit, and be associated with development arrest.

Etiology

The etiology is diverse and heterogeneous. An insult to the developing brain (intra-uterine

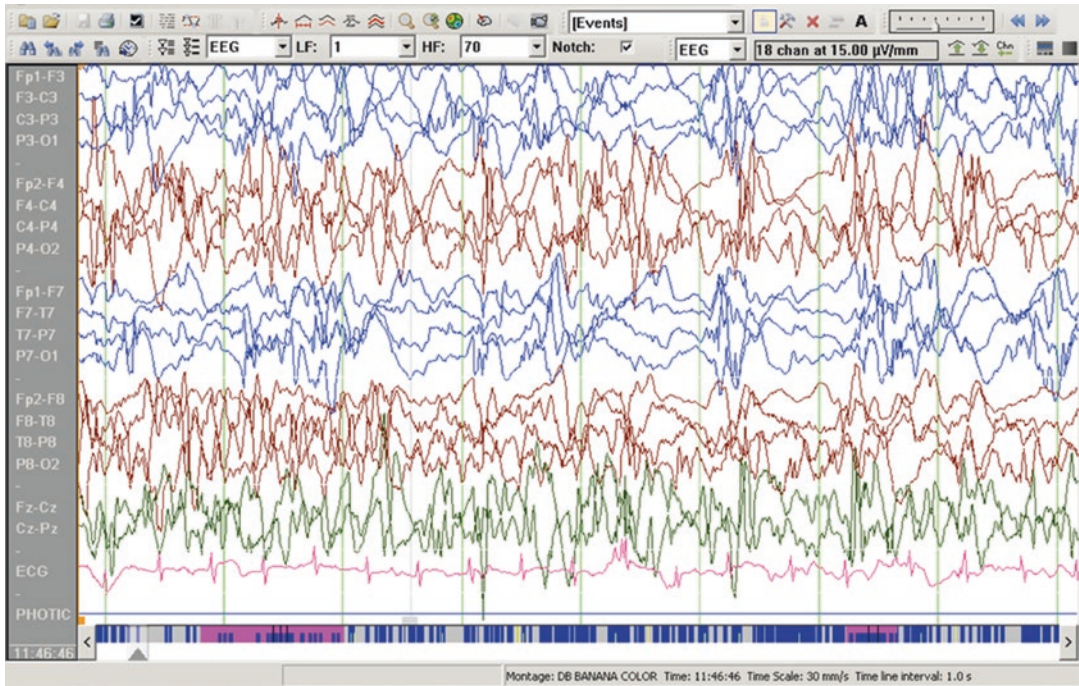


Fig. 17.3 EEG of a 6 month old infant diagnosed with infantile spasms. The EEG epoch shows the typical, chaotic, disorganized interictal pattern of hypsarrhythmia

infections), inherited metabolic disorders, brain malformations, or post-natal acquired brain insults (e.g. meningoencephalitis, hypoxic brain injury) during a critically vulnerable window of time can also lead to West syndrome. In as many as 30% of the affected children, previously no cause could be identified, and in these cases NGS technologies are identifying pathogenic gene mutations that seem to arise de-novo (Sharma and Prasad 2013).

Epilepsies of Early Childhood

Febrile seizures are common and present a different situation and are not dealt with in this discussion.

Generalized Epilepsy with Febrile Seizures Plus (GEFS+)

Scheffer and Berkovic reported on an expanding clinical phenotype of febrile seizures (FS) in an

Australian kindred. A variety of dominantly inherited epilepsy phenotypes occurred in these families, and they proposed a syndrome designated as “generalized epilepsy with FS plus” (GEFS+) (Sharma and Prasad 2013).

Semiology

The most common phenotype, termed “febrile seizures plus” (FSP), consists of multiple FS with onset in infancy and the continued occurrence of afebrile seizures beyond 6 years of age. All seizures remit by adolescence. Other phenotypes identified in this family include FS plus absences, FS plus myoclonic seizures, and FS plus atonic seizures.

Inheritance

The mode of inheritance in GEFS+ remains a matter of debate; in some a dominant pattern is observed. In others, an oligogenic effect accounts for a wide variation in the clinical phenotype. So far, only a single gene defect has been identified in each family with a GEFS+ phenotype. Mutations appear to involve subunits of voltage

gated sodium channels and subunits of the ligand gated GABAergic receptors. An overlap is noted between the clinical features and genetic basis of GEFS+ and SMEI (Dravet syndrome described below), exemplifying the enormous complexity of genotype-phenotype correlations in the epilepsies (McTague et al. 2016).

Severe Myoclonic Epilepsy of Infancy (SMEI, Dravet Syndrome)

This condition can begin in developmentally normal infants with an onset similar to febrile seizures.

Seizure Semiology and Evolution

Dravet syndrome described by Charlotte Dravet, is characterized by the occurrence of generalized or unilateral/hemibody clonic or tonic-clonic seizures, usually triggered by fever, in the first year of life. Later, other types of seizures are reported, including myoclonus, atypical absences and partial seizures. Development slows in the second year of life after the onset of seizures. Cognitive decline and behavioral disturbances are frequently noted.

Neurological signs consisting of hypotonia, ataxia, pyramidal signs, and motor incoordination may also be seen. A positive family history is noted in 25–71% of patients. The interictal EEG is usually normal in the first year of life. Between the second and the fifth years of life, a progressive increase in paroxysmal epileptiform abnormalities with background slowing is evident in more than 50% of the cases on the EEG. Paroxysmal EEG abnormalities are constituted by generalized spike wave and polyspike wave discharges. Focal and multifocal abnormalities such as fast spikes or polyspikes are also described.

Inheritance

Mutations in the *SCN1A* gene encoding the alpha-1 subunit of the sodium channel are detectable in 70–80% of patients with Dravet syndrome. Rarely mutations have been identified in the *GABRG2* and *SCN1B* genes. The most significant aspect of the molecular genetic basis is that

most of these mutations occur de novo, and the absence of a family history or a Mendelian pattern of inheritance is not a necessary prerequisite for testing.

Mutations associated with *PCDH19* encoding Protocadherin 19 have also been associated with a Dravet-like syndrome in girls. Mutations of *PCDH19* were originally described with the disorder called ‘epilepsy with mental retardation limited to females’ (EFMR). This disorder is characterized by seizure onset in infancy or early childhood (6–36 months) and cognitive impairment. The disorder is X-linked with an unusual expression pattern and with the phenotype being restricted to females; carrier males remain apparently unaffected, with normal cognitive function. The *PCDH19* mutation-affected patients however, present with a later mean age of onset (9 months compared with 6 months), fewer absence and myoclonic seizures, and the condition carries a slightly better developmental outcome. Also photosensitivity, which is very common in Dravet syndrome, is unusual in *PCDH19* patients.

The appropriate diagnosis of Dravet syndrome is important as it has therapeutic implications. Lamotrigine, phenytoin, carbamazepine, and vigabatrin may worsen the seizures, and their use should be avoided. Treatments with a beneficial effect include sodium valproate, stiripentol, topiramate, benzodiazepines, and the ketogenic diet (Sharma and Prasad 2013; McTague et al. 2016).

Acquired Epileptic Aphasia

Epileptic aphasias include the following conditions; Landau-Kleffner syndrome (LKS, also known as acquired epileptic aphasia) and epileptic encephalopathy with continuous spike and wave during slow-wave sleep (CSWS).

Semiology

Seizures typically have their origins in the temporal lobe, or rolandic regions around the opercular region of the brain affecting speech and language; therefore, one of the first symptoms of LKS is developmental regression particularly affecting language in otherwise normal chil-

dren. This is initially not coupled with any other neurological abnormalities or cognitive impairment; however, a distinct EEG pattern of nearly continuous generalized spike and wave pattern occupying more than 80% NREM sleep emerges over time. With unremitting electrical changes in sleep, gradual regression occurs in speech (verbal auditory agnosia), leading eventually to complete mutism, behavioral and psychomotor regression. Eventually the epileptiform activity may cease as seizures remit with age; residual neurological deficits are often not reversible.

Treatment

Timely diagnosis and early institution of treatment with nocturnal administration of high dose diazepam, and steroids can be of help in ameliorating the situation. The condition requires expert management under the supervision of a neurologist.

Mutations in the glutamate receptor, ionotropic, N-methyl-D-aspartate, subunit 2A gene (*GRIN2A*), which encodes an N-methyl-D-aspartate (NMDA) receptor subunit, have been linked to LKS. NMDA receptors are postsynaptic glutamate receptors that facilitate sodium and calcium influx to promote transmission of neuronal activity. They also play a crucial role in maintaining synaptic plasticity, which is important for learning and memory (McTague et al. 2016).

Clinical and Laboratory Evaluation of an Infant with Epileptic Encephalopathy

The evaluation begins with a detailed history, which should include details of the pregnancy, delivery, and postnatal factors. History of excessive fetal movements could signify the presence of fetal seizures, which are seen in pyridoxine dependency and in *KCNQ2* epileptic encephalopathy. History of excessive irritability, vomiting, and multisystem symptoms are also frequently reported in pyridoxine dependency. A gender predisposition is seen in epileptic encephalopathies associated with *CDKL5* mutations, and *PCDH19* mutations are reported in females, while the ones associated with *ARX* mutations

are seen in male infants. However, recently mutations in the *CDKL5* gene have been described in epileptic encephalopathy in boys as well. The developmental history prior to the onset of seizures (normal or pre-existing developmental delay) and the parental report of developmental arrest or regression carries added significance. The presence of other neurological problems such as abnormal muscle tone and, vision, and hearing problems must be screened for. A detailed family history and a three-generation pedigree should be constructed. A history of seizures triggered by fever is characteristic in patients with Dravet syndrome and *PCDH19* related mutations.

A general physical examination must be performed to look for craniofacial dysmorphic features (chromosomal abnormalities, peroxisomal disorders, abnormal fat pads in congenital disorders of glycosylation), and neurocutaneous markers such as ash leaf macules, which are characteristic of tuberous sclerosis. Visceromegaly is a feature of metabolic storage disorders. The presence of ambiguous genitalia in a child with infantile spasms is an indication to screen for *ARX* mutations. The neurological examination is conducted to identify abnormalities of muscle tone, and gait abnormalities (ataxia) associated movement disorders such as dystonia, choreoathetosis, and motor stereotypies. The presence of dystonias and progressive spasticity in a child with infantile spasms may be a clue towards an underlying *ARX* mutation. The ocular fundi must be examined for the presence of chorioretinitis and/or changes of a pigmentary retinopathy or optic atrophy, which may point towards the presence of infantile neuronal ceroid lipofuscinosis and mitochondrial disorders (Prasad and Hoffmann 2010; Sharma and Prasad 2013; McTague et al. 2016).

Investigations

Investigations of an infant or child with an epileptic encephalopathy must be conducted in consultation with a pediatric neurologist and a clinical and biochemical geneticist. The investigation process can be complex and time consuming and

a final diagnosis at present may still prove elusive. The role of next generation sequencing technologies is continually expanding and proving indispensable to the diagnostic process.

An EEG and often video EEG to provide clinical and EEG correlation are often the first step. A discussion of the EEG abnormalities encountered is beyond the scope of the present discussion. Suffice it to say that EEG abnormalities, which are often present in waking and sleep, tend to be persistent in the established phase of the condition. A neuroimaging study, preferably an MRI of brain, must be performed in all children with epileptic encephalopathy. MRI is often diagnostic for brain malformations, tuberous sclerosis, perinatal insult sequelae such as asphyxia, while an MR spectroscopy performed simultaneously can be of diagnostic value in patients with inborn errors of metabolism (glycine encephalopathy, creatine deficiency syndromes) and mitochondrial disorders (elevated lactate). In the majority of the genetic epileptic encephalopathies, the MRI is normal or may show non-specific features such as cerebral atrophy or delayed myelination. The presence of a cortical dysgenesis does not however, preclude a genetic or metabolic etiology as the two may coexist.

Chromosomal karyotyping must be performed if dysmorphic features and a genetic syndrome is suspected. Chromosomal microarray (array-CGH) is now recommended as a first-tier test in patients with epilepsy associated with unexplained developmental delay, intellectual disability, autism spectrum disorders, or multiple congenital anomalies. As discussed earlier, there are emerging data on the role of copy number variations in epileptic encephalopathies, which can be detected through microarrays.

When the clinical evaluation and imaging studies are not informative, a metabolic etiology must be excluded, even though the diagnostic yield for inborn errors of metabolism is presently around 5% of total cases in case registries. The initial metabolic investigations in most practice settings should exclude hypoglycemia, hypocalcemia, hypomagnesemia, and elevations of lactate and ammonia. The focus of the investigation should prioritize a search for treatable epileptic encephalopathies. A CSF examination

should be done to look for the following: low glucose levels and a low CSF to serum glucose ratio (glucose transporter defect); elevated lactate (mitochondriopathies); elevated glycine (non-ketotic hyperglycinemia), serine (serine biosynthesis defects), or pipercolic acid (pyridoxine dependency); and neurotransmitters (abnormalities seen in Pyridoxal phosphate dependency, Folic acid transport defects). Again, consultation with a biochemical geneticist should prove invaluable.

Some authorities recommend that a sequential therapeutic trial with vitamin B6, pyridoxal phosphate, and folinic acid should be instituted early in all babies with epileptic encephalopathy and a poor response to antiepileptic treatment. There are numerous other metabolic conditions that are associated with epilepsy and the reader is referred to a recent article on the metabolic evaluation and management of PDE (antiquitin deficiency) for rationale and additional details (Gallager et al. 2009; Sharma and Prasad 2017).

There is a debate as to whether molecular genetic testing should precede screening for metabolic disorders. The costs of molecular diagnostics under current conditions are rapidly changing. Currently, special approval from the provincial ministry of health has to be sought before of out of country testing is sought. Where no definite syndromic diagnosis is evident, genetic heterogeneity is high, and targeted testing excludes the known gene defects, the value of further genetic testing and its diagnostic yield remains unclear (Sharma and Prasad 2013).

The Role of Emerging Genetic Technologies

In addition, the availability of next-generation sequencing methods, via exome-wide sequencing or an epilepsy specific gene panel approach can have clinical utility in the field of epileptic encephalopathies. This field is rapidly evolving and will continue to generate additional susceptibility genes of interest that are hitherto undiscovered in epilepsy research. NGS technologies is a broad umbrella term for technologies that allow for rapid, efficient sequencing of multiple human

genomes by facilitating millions of reactions simultaneously leading to high throughput of data. The advent of NGS technologies has accelerated gene discoveries for both simple and complex epilepsies and has also been widely used in virtually all diseases. There are three main types of NGS applications including (1) whole-genome sequencing (WGS); (2) whole-exome sequencing (WES); and (3) targeted gene panels. (Prasad and Hoffmann 2010; Sharma and Prasad 2013; McTague et al. 2016).

WGS is an indiscriminate approach that decodes the genetic information in an individual's entire genome. In contrast, WES targets only the protein-coding regions or the "exome" of the genome by designing probes that are unique to the exons. Targeting only the protein-coding regions of the genome stems from the trend that nearly 85% of human genetic diseases are caused by non-synonymous mutations in evolutionarily considered protein-coding genes. Moreover, the difference in cost between the two methods (WGS ~\$7000 USD; WES ~\$1000 USD); and the computational power necessary to reassemble the human exome (1–2% of the human genome) is significantly less resource intensive. Notably however, while NGS has led to the discovery of mutations in genes not previously implicated in human diseases, the majority of findings are novel mutations in known disease-causing genes. These trends have consequently led to the development of custom designed NGS gene panels where disease-specific genes are preselected and are screened for without sequencing other regions of the genome. This prioritized approach provides an economical, focused, and rapid diagnostic method without the burden of incidental findings in known disease causing genes not relevant to the disease of interest.

A protocol for targeted and selective genetic testing can be developed based on the clinical characteristics of the epileptic encephalopathy, the seizure phenotype, and a syndromic diagnosis. In this context, the decision and selection of genetic testing is guided by several principles that take into account the many variables of the clinical presentation. These principles have been discussed in the document produced by the ILAE genetics commission. Where a distinct electro-

clinical phenotype is evident and the genetic heterogeneity is low (restricted to a single or a few known genes), a targeted mutation analysis would carry great clinical utility as pointed out in the commission document.

Currently the commercial availability of gene panels has made this task easier. These gene panels screen for known gene mutations and can lead to a rapid molecular diagnosis if the affected individual carries a common or known pathogenic mutation. Thus potentially treatable disorders can be screened for with a rapid turnaround time. A negative test does not however rule out the existence of a genetic etiology. It is conceivable in these situations that the patient may carry an previously unreported pathogenic mutation in a known gene, or in a gene hitherto not known to be associated with a clinical phenotype.

For further information on available genetic testing methods, the reader is directed to www.genetests.org and www.genereviews.org (Prasad and Hoffmann 2010; Sharma and Prasad 2013).

Conclusion

Epileptic encephalopathies in infants and young children are caused by structural brain malformations, acquired brain insults, and inborn errors of metabolism in the majority of the affected patients. However, no cause may be identified in a significant number of children under present conditions. Recent advances in molecular diagnostics have led to the discovery of a number of genetic defects that may be causative in many epileptic encephalopathies. Most of these disorders are relatively rare and it will be a while before sufficient testing and experience will be available to formulate evidence-based guidelines. Identification of the causative mutation is important for prognostication and genetic counseling, and as has been discussed, provides a sound basis of treatment decisions, and symptom management. Knowledge of the clinical profile, seizure types, and EEG features of the disease phenotype associated with the specific mutation help the clinician improve diagnostic precision and management. Over time, large scale studies involving multicenter databases and rare disorder registries may capture the relative prevalence of

these rare disorders in populations to provide evidence based data to make informed decisions.

Epileptic Syndromes in the Pre-school and School Age Child

Benign Epilepsy with Centro Temporal Spikes (BECTS)

Benign epilepsy with centro temporal spikes (BECTS) is the most common childhood idiopathic focal epilepsy. Its benign nature is related to the lack of effect on neurological development, lack of focal neurological deficits, high rates of spontaneous remission in its natural history and good response to first line anticonvulsant medication. BECTS accounts for around 15% of children diagnosed with epilepsy. The typical onset is around 7–9 years and before the age 13.

Seizure Semiology

The classic seizures occur during sleep and involve the oro-facial muscles with rhythmic clonic movements that usually interfere with speech and phonation (dysarthria). During the seizures, children retain awareness and may appear fearful (30%). Other symptoms include oropharyngo-laryngeal paresis (53%), speech arrest (40%) and drooling (30%). Progression to a secondary generalized tonic-clonic seizure occurs in around 50% of affected children. Post-ictal paresis is rare and should be considered an atypical feature for BECTS that might prompt further investigations such as neuroimaging.

Diagnosis

The diagnosis is made on the clinical grounds and supported by a routine EEG, that typically shows bihemispheric, independent, centro-temporal spikes that are exacerbated in sleep. Neuroimaging is typically normal, therefore MRI is not indicated in classic cases.

Rarely, patients with other more complex epilepsies may have similar clinical patterns. When atypical features are present; i.e. post-ictal paresis, status epilepticus, abnormal neurological exam, persistent unilateral centro-temporal

spikes on EEG, the child should be considered for further investigations such as neuroimaging (preferentially MRI) and should be referred to a pediatric neurologist.

Treatment

Treatment with daily anticonvulsants is often not necessary, as seizures are brief and self-limited, occur mainly during sleep and minimally interfere activities of daily living.

Prognosis

The prognosis is usually excellent. Epilepsy remission occurs within 2–4 years from onset and before the age of 16 in the majority of cases (Park et al. 2015; Panayiotopoulos et al. 2008).

Childhood Absence Epilepsy (CAE)

The age of onset is around 5–6 years of age (4–10 years). CAE accounts for 8–15% of all childhood epilepsies.

Seizure Semiology

Typical absence seizures are described as brief (4–20 s), periods of loss of awareness, that can occur frequently through the day (10 to >100 day⁻¹), with an abrupt “onset and offset”. There is no postictal state and the child resumes his/her activity immediately after the absence seizure. Other associated ictal findings include the following: rapid eye blinking; lip smacking and twitching of the eyelids, eyebrows or mouth; simple motor and/or orolimentary automatisms (in up to two-thirds of cases); and incontinence (unusual). At times slumping of posture may be seen due to a reduction in axial muscle tone, but falls associated with atonic seizures do not occur in CAE and if present the patient should be referred to a pediatric neurologist. Around 35% of these children may present with one generalized tonic-clonic seizure.

Diagnosis

In around 80% of cases, absence seizures can be reproduced by hyperventilation. This manoeuvre is part of the routine EEG when CAE is suspected

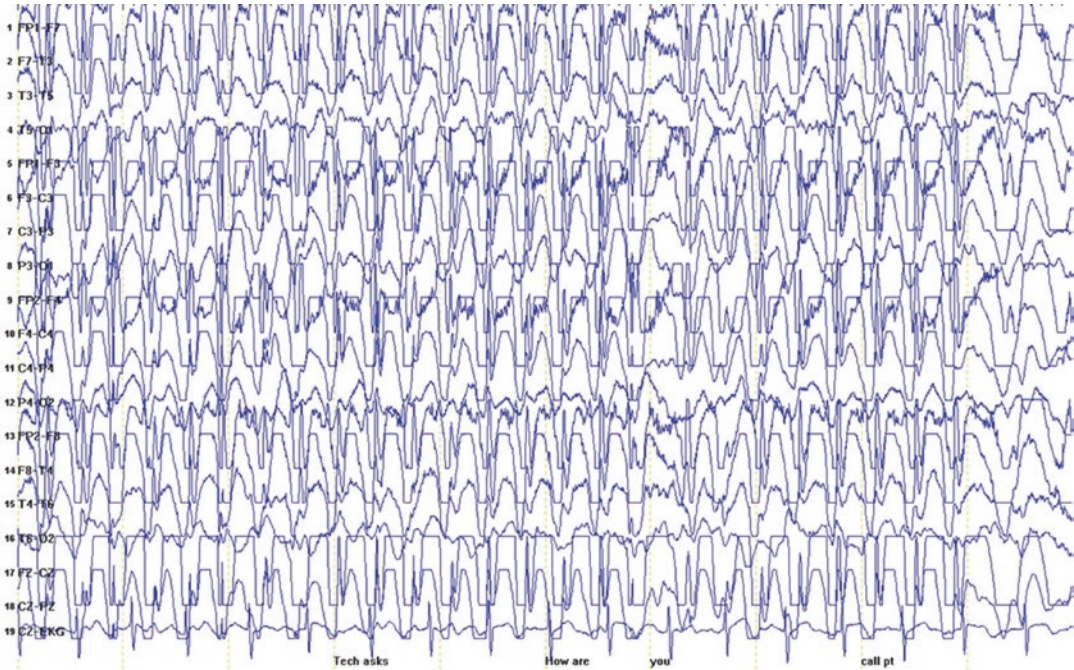


Fig. 17.4 The figure represents one epoch of an EEG in a 5 year old child with typical absence seizures. The EEG demonstrates the typical generalized 3 Hz per second spike and wave discharges

and can be also applied in the office to provoke an absence seizure for anticipation of the diagnosis and management. The findings on EEG are usually diagnostic with monomorphic generalized 3 Hz spike and waves (Fig. 17.4) or fragments of these epileptiform discharges occur in association with absences or on interictal records.

Treatment

Seizures usually respond well to ethosuximide, valproate, and lamotrigine. First line therapy is ethosuximide given its efficacy controlling absence seizures in 70% of cases without significant side effects. Beyond the age of 10 years, children may also develop generalized tonic clonic seizures, and in that instance the choice of lamotrigine, valproic acid or levetiracetam may be considered. Prognosis is excellent with complete remission in 56–84% of cases within 2–5 years from onset (Park et al. 2015; Panayiotopoulos 2008).

Epileptic Encephalopathies in School Age Child

Lennox Gastaut Syndrome

Lennox Gastaut Syndrome is considered an epileptic encephalopathy based on a triad of multiple seizure types, usually refractory to conventional antiepileptic drugs, severe developmental psychomotor retardation, and typical EEG findings.

The usual onset is between 1 and 8 years of life with a peak between 3 and 5 years. Lennox Gastaut syndrome accounts for 3–10% of pediatric epilepsies.

Seizure Semiology

Typically tonic seizures involving different muscle groups such as *axial* (head and trunk muscles), *axorhizomelic* (arms predominantly), and *global* (the whole body) are essential to diagnosis. Tonic seizures can be accompanied by autonomic symptoms including loss of bladder

control, respiratory changes, tachycardia, facial flushing and dilated pupils. Other seizures include the following: atypical absence (which are of longer duration than typical absence seizures and the EEG shows generalized slow spike and wave) and drop attacks (which include myoclonic or atonic seizures).

Up to 60% of children with LGS have a previous diagnosis of epileptic encephalopathy such as infantile spasms.

Diagnosis

LGS can be divided in symptomatic (a clear cause for the epilepsy can be identified) or cryptogenic (a clear cause cannot be established). Among the symptomatic cases are children with severe/diffuse brain injury including hypoxic-ischemic encephalopathy, post-meningitis, tuberculous sclerosis, diffuse malformations of cortical development (lissencephaly), and genetic syndromes (Aicardi syndrome, trisomy 21), etc.

The diagnosis is made on the basis of the seizure description, global developmental delays and classic EEG findings of generalized slow spike and wave and paroxysmal fast activity.

Treatment

Seizure control is difficult to achieve with typical antiepileptic drugs, and at times palliative surgery (corpus callosotomy) for atonic drop seizures, non-pharmacological therapies such as ketogenic diet, placement of a vagal nerve stimulator, and even cannabidiol can be considered to ameliorate the severity of the seizures (Arzimanoglou et al. 2009).

Epileptic Syndromes in the Adolescent Child

Juvenile Myoclonic Epilepsy (JME)

JME accounts for 5–10% of all epilepsy syndromes, and affects mainly adolescents between 13 and 15 years of age.

Seizure Semiology

The main seizure type is myoclonic seizures (97%), but generalized tonic clonic seizures

(79%) and absence seizures (33%) might be present. Seizures appear frequently upon awakening in the morning, and patients find themselves dropping objects or with morning “clumsiness” due myoclonic jerks. Many seizure precipitants were described including sleep deprivation, flashing lights, alcohol consumption, anxiety, stress, and menstruation. JME is considered a genetic epilepsy.

Diagnosis

Made on the basis of clinical history, age of onset and seizure types. The EEG abnormalities are usually supportive for JME, showing generalized 4–6 Hz (fast) polyspike and wave (Fig. 17.5) and a photoparoxysmal response.

Treatment

JME patients respond very well to sodium valproate, rendering at least 80% with seizure freedom. However, sodium valproate may not be the drug of choice for an adolescent girl due to gynaecological (polycystic ovarian syndrome), cosmetic (acne and gain weight) and teratogenic side effects. In female patients, other broad spectrum antiepileptics should be considered, including levetiracetam, topiramate and clobazam. Lamotrigine can be effective at managing children with JME with GTCs, however it can trigger or increase the frequency of the myoclonic jerks.

JME is a lifelong condition and seizure recurrence occurs almost always when a wean-off of AED is attempted (Park et al. 2015; Brodie 2016).

Progressive Myoclonic Epilepsies (PME)

This is a rare group of conditions characterized by myoclonic seizures, progressive developmental regression, and cognitive decline. The differential diagnosis include: Baltic myoclonus, myoclonic epilepsy with red ragged fibers (MERRF), storage disorders such as sialidosis type 1, neuronal ceroid lipofuscinosis and Lafora body disease. Further details on these disorders are beyond the scope of this book chapter (Shahwan et al. 2005).

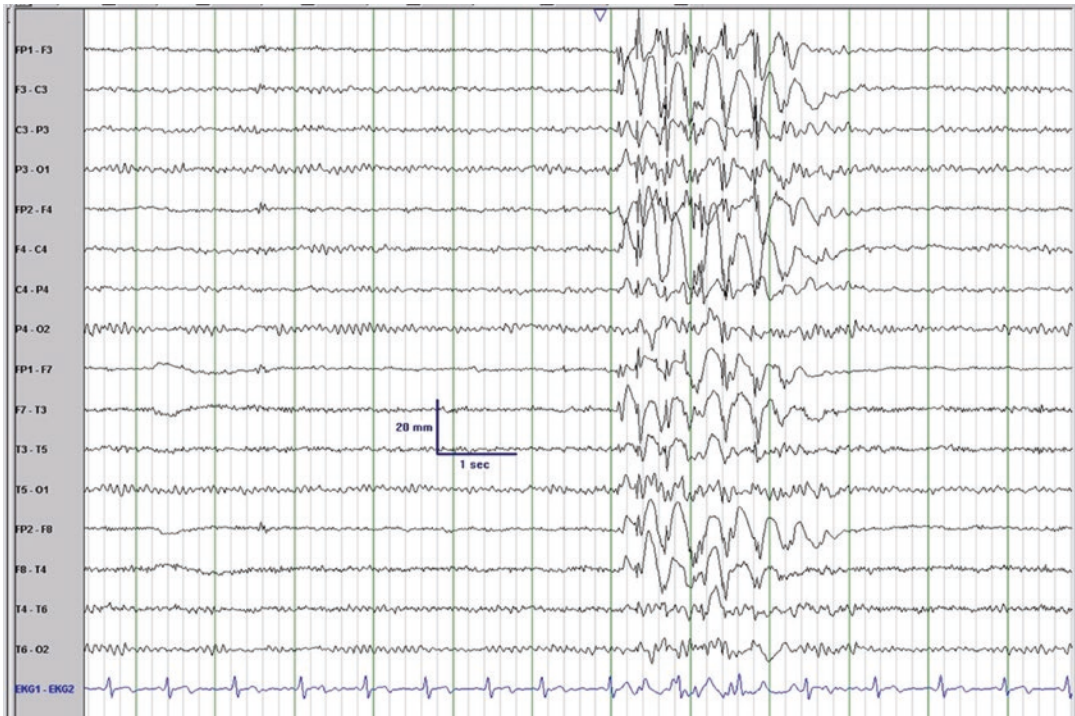


Fig. 17.5 This figure demonstrates an EEG epoch of a 15 year old girl with morning myoclonic seizures and one generalized-tonic-clonic seizure. The EEG findings are consistent of generalized polyspike and wave consistent with Juvenile Myoclonic Epilepsy (JME)

Nonepileptic Paroxysmal Events

Other conditions different to epilepsy can also cause paroxysmal events in children, some of which may involve alteration in level of consciousness and/or involve motor, visual, or sensory phenomena. A list of differential diagnoses of non epileptic events are listed in (Tables 17.3)/ Boxes 17.1 and 17.2.

Syncope

One of the commonest occurrences involving an altered level of consciousness reported at extremes of age (young and old) is a “syncopal” event. These events are the result of a transient reduction of cerebral perfusion below a critical threshold required to maintain consciousness. Typically, a trigger that induces, by direct or indirect pathways, a reduction of heart rate and blood pressure

leading to a drop in cerebral perfusion, is described as a reflexive syncope. Syncope is most frequently reported in the adolescent years and is twice as common in females than males. The incidence of syncope is considered to be around 0.5–3 per 1000 children (Anderson et al. 2016; Yeh 2015).

A description of common types of syncope is provided below.

Vasovagal Syncope

Typically in a vasovagal (cardiogenic, cardiodepressor, neurocardiogenic) syncope, there is peripheral pooling of blood by arterial and/or venous dilatation followed by a bradycardia that is profound and leads to hypotension and reduced cerebral perfusion. Such an occurrence may follow a prolonged period of standing in a warm environment (standing in a church choir, after strenuous exercise on a hot day). At other times

Table 17.3 Clinical features and etiologies of common paroxysmal events in children

| Paroxysmal event | Features | Etiology/comorbidities |
|--------------------|---|---|
| Epileptic seizures | Paroxysmal stereotyped, focal or generalized. With and without loss of awareness. Abnormal EEG and postictal state | Epilepsy, febrile seizures, metabolic disturbances, traumatic brain injury, stroke, CNS infections, CNS tumors, CNS malformations |
| Tics | Sudden, rapid, non-rhythmic, motor or vocalizations, premonitory urge, can be suppressed transiently | Tourette Syndrome, Tic Disorder OCD, oppositional and aggressive behavior, mood disorder |
| Dyskinesias | Involuntary, focal, sudden onset, persistent | Infection, medications reaction, Sydenham chorea, Huntington disease |
| Stereotypies | Repetitive, stereotyped, affecting arms, hands, trunk. Intermittent movements. Usually experienced as pleasant | ASD, Intellectual disability |
| PNES | Variable and bizarre motor features, waxing and waning, long duration (several minutes to hours), eyes closed, disappeared during sleep | Conversion disorder/coexistence with epileptic seizures, mood disorder, PTSD, anxiety disorder |

Box 17.1 Differential Diagnosis of Seizures in Infants and Children

| |
|--|
| 1. Epilepsy/epileptic seizures |
| 2. Syncope |
| 3. Movement disorders |
| (a) Tics |
| (b) Chorea/Dyskinesias |
| • Paroxysmal choreoathetosis |
| (c) Dystonia |
| (d) Ballism |
| (e) Ataxias |
| • Episodic ataxias |
| 4. Transient ischemic attacks |
| 5. Metabolic disturbance-hypoglycemia, hyperammonemia |
| 6. Sleep related disorders-parasomnias-night terrors, REM sleep behavior disorders |
| 7. Narcolepsy |
| 8. Migraine and Migraine equivalents |
| 9. Psychiatric disturbances- Anxiety, panic attacks |
| 10. Psychogenic non epileptic seizures (PNES) |

Box 17.2 Triggers for Syncopal Events

| |
|--|
| 1. Prolonged standing in crowded places, warm environments |
| 2. Emotional events, pain |
| 3. Sleep deprivation, fasting, febrile illness |
| 4. Dehydration |
| 5. Post tussive/coughing paroxysm |
| 6. Straining at bowel movements |
| 7. Sudden change in posture i.e. standing up from a squatting position |
| 8. Post micturition |
| 9. After a period of rapid weight loss i.e. anorexia nervosa |
| 10. Drugs/medications |
| 11. Psychogenic |

the event may follow a specific trigger like vigorous brushing of one's hair or using a toothbrush, or watching or reading about a painful or emotional scene on television. While most events occur in a standing position, events are reported even while sitting or during activities like walking, cycling, etc.

The individual may report prodromal symptoms such as a warm feeling, nausea, dizziness, epigastric discomfort, palpitations, a graying and constriction of the visual field, or the "dropping of the curtain" prior to a loss of consciousness. Observers or caregivers can also report pupillary dilatation and sweating (Yeh 2015).

Orthostatic Hypotension and Postural Orthostatic Tachycardia Syndrome (POTS)

Orthostatic hypotension is a transient sensation of dizziness and visual blurring that may accompany a rapid change in posture from supine or squatting position to standing. This phenomenon occurs in young healthy adolescents, particularly in tall individuals with an asthenic build and poor muscle mass. Typically, there is prompt recovery from symptoms within 30 seconds. The cause of this transient drop is not entirely well understood. Such a drop may not be demonstrable on a tilt table test.

Postural orthostatic tachycardia syndrome (POTS) is a condition characterized by symptoms of cerebral and retinal hypoperfusion that is accompanied by a dramatic rise in heart rate with a relatively normal blood pressure in the upright posture. The symptoms of lightheadedness, fatigue, weakness, and blurring of vision are reported. It must be noted that in older children and adolescents the change in heart rate that accompanies a change in posture must be adjusted for age, as an increase of 20 beats or more is not uncommon in this age group. An increase of >35 beats/min and a heart rate above 135 beats/min, two min after standing in an average adolescent, can be considered abnormal.

The pathophysiology underlying POTS is attributable to a number of central and periph-

eral regulatory mechanisms that maintain heart rate and blood pressure becoming discordant. Inappropriate cerebral vasoconstriction in the face of normal blood pressure, excess venous pooling, enhanced cardiac sympathetic responsiveness, reduced peripheral sympathetic responsiveness, and reflex sympathetic activation are some of the involved variables. The diagnostic confirmation of this condition can only be carried out in a specialized laboratory investigating autonomic dysfunction (Anderson et al. 2016).

Stretch Syncope

In stretch syncope, some teenagers show a tendency to faint when they stretch themselves, a movement associated with hyperextension of the neck. There is often a family history of fainting in these individuals. A combination of valsalva induced peripheral pooling, and reduction in cerebral blood flow due to compression of blood vessels in the neck may be involved (Anderson et al. 2016; Yeh 2015).

Self-Induced Syncope

Some children may be able to induce syncope almost at will. They have taught themselves to hyperventilate while squatting, rapidly stand up and straining that through a valsalva maneuver, ultimately producing a combination of venous pooling and cerebral vasoconstriction sufficient to induce loss of consciousness. This may be used as an entertainment or has been reported as an avoidance measure to miss out unpleasant situations like a school examination (fainting lark) (Anderson et al. 2016; Yeh 2015).

Reflex Anoxic Seizure

Towards the end of a syncopal episode, there may be enough hypoxia associated with cerebral hypoperfusion to induce a brief "reflex anoxic" seizure. Reflex anoxic seizures may take the

form of tonic posturing, clonic movements, and myoclonic jerks. Typically, the seizure is self-limited and often terminates with recovery of consciousness. In a reflex anoxic seizure, the loss of consciousness is brief, urinary incontinence is uncommon, and post event confusion is short lived while fatigue can be prolonged. On the other, in an epileptic seizure, the events are longer, and they are often associated with incontinence and a prolonged postictal state of confusion. Reflex anoxic seizures are also noted in the context of breathholding spells described below (Anderson et al. 2016; Yeh 2015).

Breathholding Spells

This condition is extremely common in toddlers, and is often a dramatic event causing alarm and anxiety for parents. Two types of spells are recognized; the “pallid” and “cyanotic” type. The events begin around 6 months to 2 years of age begin to remit spontaneously by school entry. Both types are triggered following relatively minor trauma or pain following which, the child begins a cry that may be short in the pallid type, and prolonged in the cyanotic variety. The child goes pale or becomes cyanosed and then loses posture; subsequently, the child may develop clonic and or myoclonic movements that are self-limited, followed by recovery of consciousness. The pathophysiology involved may invoke mechanistic factors that are operative in other kinds of syncopal events discussed above. For instance, the pallid attack may have a component of severe bradycardia and even transient asystole. On the other hand, the cyanotic type may depend on hyperventilation associated with crying and resulting vasoconstriction and valsalva induced venous pooling (Anderson et al. 2016; Yeh 2015).

Pseudosyncope

Recurrent syncopal events in adolescents for which no explanation is found despite thorough evaluation and investigation should raise the suspicion of psychogenic pseudosyncope (PPS).

Psychogenic pseudosyncope is the appearance of transient loss of consciousness (TLOC) in the absence of a true loss of consciousness. The disorder is under investigated in the unexplained syncope population. Patients are more likely to be adolescent females reporting an increased frequency of episodes over the past 6 months. Affected individuals frequently experience symptoms prior to their episodes including light-headedness, shortness of breath and tingling. The events are prolonged often 10–30 min in duration and tend to continue despite a supine posture. The individual will maintain eyes closed or eyelid fluttering. Unresponsiveness is rarely maintained to painful stimuli. The passive lifting and dropping of the arm and hand onto the face may show an avoidance movement. The diagnosis may require the performance of transcranial doppler studies for blood flow, and a heads up tilt table test which will not show the typical changes in terms of a drop in blood pressure and transcranial blood flow in patients with PPS (Anderson et al. 2016; Yeh 2015) There may be on careful history taking evidence to support psychiatric comorbid features and environmental stressors. This form of conversion disorder is associated with symptomatic chronicity, increased psychiatric and physical impairment, and diminished quality of life.

Approach to the Investigation of Syncope

In all patients presenting with a single or recurrent event suggestive of syncope, a detailed history and physical examination must be performed. The purpose of such an evaluation is to rule out any serious cardiac pathology that may present initially with such events. For instance, an underlying serious brady or tachyarrhythmia that may carry with it the risk of sudden death must be ruled out. Descriptions of the event obtained directly from observers witnessing the event, to identifying the temporal evolution of events, the initiating triggers, and the environmental factors can be helpful. Every effort must be made to directly talk to such individuals and obtain a

written description; a video recording on the cellphone can all be helpful. A family history of any pacemaker placement, sudden death, cardiac rhythm abnormalities, syncope, and/or epilepsy should be carefully sought and documented.

If the description is typical and definite triggers identifiable, then a diagnosis of syncope can be offered with little need for major investigations. If the presentation is atypical, then a careful physical examination looking for any cardiac abnormalities, measurement of vitals, including supine and erect recordings after 2 min of standing for both blood pressure and heart rate can be helpful to detect orthostatic changes. At the minimum, an ECG with a rhythm strip (to exclude a prolonged QTc interval and any other conduction abnormalities), and an EEG to rule out an epileptiform abnormality may be considered in selected cases where there may be a family history of seizures or heightened parental anxiety for their young child. However, the evaluation may not yield clues in which case referral to a cardiologist to rule out structural heart disease, and arrhythmias (echocardiogram and Holter recordings) can be considered. Where the history gives a suspicion of epileptic or non-epileptic events, referral to a neurologist for EEG and/or video EEG recordings can be helpful. In recurrent cases, when the work up does not yield any answers, referral to a specialized centre for a tilt table test can be considered. There are caveats to tilt testing as there is often a high false positive rate in children. However, the test can be helpful when positive to offer reassurance to the patient and family of a relatively benign form of syncope and if negative, provide support to the diagnosis of a psychogenic pseudosyncope. (Anderson et al. 2016; Yeh 2015).

Benign Neonatal Sleep Myoclonus (BNSM)

Benign neonatal sleep myoclonus is a benign and common condition affecting 0.8–3/1000 full term and near-term neonates. BNSM may occur in neurologically normal and healthy infants. It can be mistaken for epilepsy and even

for status epilepticus if prolonged. It is characterized by myoclonic jerks involving the limbs, most frequently generalized and symmetric, but at times affecting only one limb or one side of the body. The paroxysmal movements only occur during sleep, mainly in quiet sleep and they stop on arousal. Rocking or repetitive stimuli may provoke the motor phenomena. The onset of BNSM is usually during the first weeks of life and resolution occurs spontaneously within six months of age. This phenomena may be the result of both immaturity of the networks involved in motor control during sleep and genetic factors. The EEG and psychomotor development of affected newborns are both normal (Facini et al. 2016).

Tic Disorders

Tics are “sudden, rapid, recurrent, but non-rhythmic movements and/or vocalizations, generally preceded by premonitory sensory “urges”. They are experienced as purposeless and only partially suppressible.

The age of onset for tic disorders is between 6 and 7 years of age (3–11 years). In children, motor tics tend to appear a few years earlier than vocal tics. Tics are divided into the following categories: simple (eye blinking, nose twitching, jaw or neck movements, sniffing, grunting, throat clearing, and coughing) or complex (squatting, touching, jumping, uttering words, or sentences). Some vocal tics (clearing throat and snuffing) can be misdiagnosed as upper airway disease, asthma or allergies. Tics usually affect the facial and cephalic body areas and subsequently involve the shoulders and extremities. The severity of tics usually peaks around 12 years of age. Tics could be a transitory condition currently recognized by the DSMV as “provisional tic disorder”. When tics persist longer than 12 months, a “persistent tic disorder” is recognized. Tourette Syndrome is a childhood onset neurodevelopmental disorder characterized by motor and vocal tics lasting more than a year. Only a small proportion of children with tics (5–10%) will continue to have tics in adulthood.

Tics occur in bouts and usually follow a waxing and waning pattern in frequency, intensity, location and complexity. Most patients can suppress their tics for a short period of time, but usually this is followed by a rebound effect and a transitory increase in its intensity and frequency. Some children are able to suppress tics when at school or in the presence of peers, and later relieve the urge for tics at home. Triggers that can exacerbate tics bouts include excitement, frustration, stress, fatigue, or boredom. There are also, situations that can help to suppress tics such as: intense concentration (goal-directed attention) and focused activities, such as playing an instrument or performing certain sports.

Tics are more frequent in boys (4:1). Transient tic disorder affects around 3–20% of school age children. They can be associated with attention deficit and hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD) and less frequently in children with oppositional and aggressive behaviours, depression and parasomnias.

Tics need to be differentiated from other childhood movement disorders such as stereotypies, chorea and dyskinesia. These other type of motor phenomena are more common in children with Autistic Spectrum Disorders (ASD), cerebral palsy (CP) and drug induced psychomotor disorders (Table 3)

The majority of tic disorders respond to cognitive behavioural therapy. Pharmacological treatment is considered for severe and chronic cases. Indications for medication include the following: if tics cause pain, emotional problems, or strong discomfort; or if they lead to social isolation, stigmatization or bullying. In North America first line drugs include alpha-2 agonists such as guanfacine and clonidine. In Europe risperidone is the first line drug (Dooley 2006; Ganos 2016).

Non-epileptic Seizures

A significant minority of children referred because of suspected epileptic seizures may not actually have the condition. Non-epileptic seizures can be present in psychiatric and non-psychogenic disorders. The non-psychogenic conditions in the pedi-

atric population consist of physiologic and organic disorders. The most common of these conditions include inattention/daydreaming/staring, sleep myoclonus, stereotyped movements, hypnic jerks, tonic posture, parasomnias, and movement disorders.

Of those with a psychogenic basis, psychogenic non epileptic seizures (PNES) are the most common non epileptic events. The prevalence increases in older children.

PNES involve observable abrupt paroxysmal changes in consciousness or behaviour that present similarly to epileptic seizures but are not accompanied by EEG changes associated with epilepsy, and there is a strong suspicion of a psychogenic cause.

Some authors have reported that based on video EEG children with PNES could be divided into three groups: patients with prominent motor activity, patients with subtle motor activity, and patients with both types of events. Subtle motor activity was more prominent in those younger than 13 years old, and prominent motor activity was found more consistently in children older than 13 (Sankhyan 2014).

The semiology of the PNES is variable, in children with video EEG recordings, rhythmic motor movements have been commonly described. Complex motor PNES (ie. diverse and bizarre motor activity such as pelvic thrusting, body shaking or bizarre body posturing) has been described in only 13% of the pediatric population and mixed PNES in 4%. Dialectic PNES (i.e. behavioral arrest, staring spells, “absence-like” behavior) were found more frequently in children (29%) than in adults. Children were unresponsive during 34% of the events. The most common motor sign was a tremor (25%) involving the upper limbs more frequently than the lower limbs. Emotional manifestations were observed in approximately 43% of events, and the emotions were negative in almost all children.

When encountering a child or adolescent with suspected PNES, a detail psychosocial history is key in identifying triggers. The main areas of precipitating stressors in children are: school related difficulties (academic difficulties and bullying), family/interpersonal conflict, and physical/sexual

abuse. Studies suggest that a significant proportion of children with PNES have a psychiatric disorder as well as conversion disorder, such as a mood disorder, separation anxiety school phobia, and less frequently reactive psychosis or schizophrenia.

The diagnosis is based on a description of the events plus a history of a significant psychosocial component. Video-recording through smart phones can be helpful to differentiate epileptic vs non epileptic events. The diagnostic gold standard is the video EEG.

Delivering the diagnosis to families and patients is important, and the importance of effective communication of the diagnosis of PNES as a therapeutic measure is clearly established. Most authors emphasize that it is crucial to make it explicit that the attacks are real and the certainty of a psychogenic basis for the events should be clearly conveyed to the child and the family. A proportion of children with PNES will also have epilepsy, and it is important that the manifestations of both events are made clear to the family.

In the pediatric population most authors recommend a prompt intervention by a pediatric mental health professional. Cognitive Behavioral Therapy (CBT) has been shown to be effective in adults with PNES.

The outcome of PNES in pediatric patients is more favorable than the outcome in adults; accordingly, prompt recognition and referral to the appropriate specialist is important (Szabo et al. 2012; Reilly et al. 2013).

Conclusion

Paroxysmal events in children are diverse in presentation, mechanisms and etiology. Familiarity of these phenomena by the pediatrician is important to establish the most accurate diagnosis, treatment, and when necessary early referral to the appropriate specialized medical team.

In summary, paroxysmal events with or without alteration in level of consciousness are some of the most frequently encountered diagnostic challenges in pediatric clinical practice. Developing an approach to diagnosis and man-

agement requires the clinician to adopt a careful and systematic evaluation of the semiology of the event, its evolution, progression and termination. Clinical history taking combined with a complete physical and neurological examination often can provide diagnostic clues that point toward an epileptic or non-epileptic etiology in the majority. If an epilepsy-related diagnosis is suspected, the diagnostic testing will involve electroencephalography, neuroimaging, and further evaluation by a pediatric neurologist. If a non-epileptic condition is suspected, an EEG study may still be part of the investigation. Assessment of cardiac function, if indicated, may necessitate referral for evaluation by a cardiologist in addition to routine studies of ECG, chest xray and Holter studies. By and large, a systematic process of evaluation and elimination of unlikely conditions in the differential diagnosis can establish a diagnosis. It is in the process that the above descriptions will be most helpful.

The clinician is well advised to consult subspecialty services (pediatric neurologist and a cardiologist), where indicated in order to exclude conditions that may require specialised diagnostic and treatment interventions.

References

- Anderson JB, Willis M, Lancaster H, Leonard K, Thomas C. The evaluation and management of pediatric syncope. *Pediatr Neurol.* 2016;55:6–13.
- Arzimanoglou A, French J, Blume WT, Cross JH, Ernst JP, Feucht M, et al. Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology. *Lancet Neurol.* 2009;8(1):82–93.
- Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde BW, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. *Epilepsia.* 2010;51(4):676–85.
- Brodie MJ. Modern management of juvenile myoclonic epilepsy. *Expert Rev Neurother.* 2016;16(6):681–8.
- Cross JH. Differential diagnosis of epileptic seizures in infancy including the neonatal period. *Semin Fetal Neonatal Med.* 2013;18(4):192–5.
- Dooley JM. Tic disorders in childhood. *Semin Pediatr Neurol.* 2006;13(4):231–42.
- Facini C, Spagnoli C, Pisani F. Epileptic and non-epileptic paroxysmal motor phenomena in newborns. *J Matern Fetal Neonatal Med.* 2016:1–8.

- Gallagher RC, Van Hove JL, Scharer G, Hyland K, Plecko B, Waters PJ, Mercimek-Mahmutoglu S, Stockler-Ipsiroglu S, Salomons GS, Rosenberg EH, Struts EA, Jakobs C. Folinic acid-responsive seizures are identical to pyridoxine-dependent epilepsy. *Ann Neurol*. 2009;65(5):550–6. <https://doi.org/10.1002/ana.21568>. PubMed PMID:19142996.
- Ganos C. Tics and Tourette's: update on pathophysiology and tic control. *Curr Opin Neurol*. 2016;29(4):513–8.
- Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia*. 2010;51(6):1069–77.
- McTague A, Howell KB, Cross JH, Kurian MA, Scheffer IE. The genetic landscape of the epileptic encephalopathies of infancy and childhood. *Lancet Neurol*. 2016;15(3):304–16.
- Moosa AN, Wyllie E. Focal epileptogenic lesions. *Handb Clin Neurol*. 2013;111:493–510.
- Panayiotopoulos CP. Typical absence seizures and related epileptic syndromes: assessment of current state and directions for future research. *Epilepsia*. 2008;49(12):2131–9.
- Panayiotopoulos CP, Michael M, Sanders S, Valeta T, Koutoumanidis M. Benign childhood focal epilepsies: assessment of established and newly recognized syndromes. *Brain*. 2008;131(Pt 9):2264–86.
- Park JT, Shahid AM, Jammoul A. Common pediatric epilepsy syndromes. *Pediatr Ann*. 2015;44(2):e30–5.
- Pisani F, Facini C, Pavlidis E, Spagnoli C, Boylan G. Epilepsy after neonatal seizures: literature review. *Eur J Paediatr Neurol*. 2015;19(1):6–14.
- Prasad AN, Hoffmann GF. Early onset epilepsy and inherited metabolic disorders: diagnosis and management. *Can J Neurol Sci*. 2010;37(3):350–8.
- Reilly C, Menlove L, Fenton V, Das KB. Psychogenic nonepileptic seizures in children: a review. *Epilepsia*. 2013;54(10):1715–24.
- Sankhyan N. Non-epileptic paroxysmal events mimicking seizures. *Indian J Pediatr*. 2014;81(9):898–902.
- Shahwan A, Farrell M, Delanty N. Progressive myoclonic epilepsies: a review of genetic and therapeutic aspects. *Lancet Neurol*. 2005;4(4):239–48.
- Sharma S, Prasad AN. Genetic testing of epileptic encephalopathies of infancy: an approach. *Can J Neurol Sci*. 2013;40(1):10–6.
- Sharma S, Prasad AN. Inborn Errors of Metabolism and Epilepsy: Current Understanding, Diagnosis, and Treatment Approaches. *Int J Mol Sci*. 2017;18(7). pii: E1384. <https://doi.org/10.3390/ijms18071384>. Review. PubMed PMID: 28671587; PubMed Central PMCID: PMC5535877.
- St Louis EK, Cascino GD. Diagnosis of epilepsy and related episodic disorders. *Continuum (Minneapolis, MN)*. 2016;22(1 Epilepsy):15–37.
- Szabo L, Siegler Z, Zubek L, Liptai Z, Korhegyi I, Bansagi B, et al. A detailed semiologic analysis of childhood psychogenic nonepileptic seizures. *Epilepsia*. 2012;53(3):565–70.
- Yeh J. Syncope in children and adolescents. *Pediatr Ann*. 2015;44(12):e287–91.



Update in Pediatric Oncology: Section A-New Developments in the Treatment of Pediatric Acute Lymphoblastic Leukemia

Shannon L. Maude and Stephen P. Hunger

Immunophenotype

ALL is a malignancy of lymphoid progenitors. Early progenitors with transforming lesions subsequently acquire additional mutational events. The net result of these genetic events is pathologic alteration of cell growth, differentiation, proliferation, and survival. ALL is classified into subtypes arising from the B and T cell lineages; however, this classification oversimplifies this heterogeneous group of leukemias. B-ALL and T-ALL are distinct not only in the cell of origin and immunophenotype but also in the presentation and, historically, the prognosis.

Malignant B lymphoblasts are typically arrested at the precursor B or earlier stage of differentiation; therefore, they express many of the same cell surface markers as these early stages of development, including immature (i.e. terminal deoxynucleotidyl transferase (TdT), CD10), lymphoid (i.e. CD45), and B cell markers (i.e. CD19, CD22, CD79a) (LeBien 2000). Historically, it was thought that the leukemo-

genic event occurred at the developmental stage the malignant lymphoblasts resembled by immunophenotype; however, it is now understood that transformation occurs in an earlier cell and that somatic mutations in ALL often block differentiation past a specific maturational stage (Campos-Sanchez et al. 2011). It is not uncommon for B-ALLs to express myeloid markers, such as CD13 and CD33. In addition, there is considerable plasticity within the B cell lineage, allowing for the possibility that more mature stages can de-differentiate or that less mature stages can acquire B cell markers (Campos-Sanchez et al. 2011).

B-ALL is by far the more common form, comprising 85% of ALLs, although the frequency of T-ALL begins to increase in adolescents (Linabery and Ross 2008). B-ALL is a disease of the bone marrow, where B cell development occurs. Bone marrow replacement with leukemia leads to impaired hematopoiesis and cytopenias; therefore, B-ALL frequently presents with sequelae of anemia, thrombocytopenia, and neutropenia, including pallor, fatigue, bruising, or infection. Other common presenting symptoms and signs include bone pain, hepatosplenomegaly, and lymphadenopathy.

Much of T cell differentiation occurs in the thymus; therefore, it is common for T-ALL to present with a mediastinal mass that may cause respiratory distress in addition to other common presenting signs and symptoms noted above for

S.L. Maude (✉) • S.P. Hunger
Division of Oncology and Center
for Childhood Cancer Research, The Children's
Hospital of Philadelphia, Philadelphia, PA, USA

Department of Pediatrics, Perelman School
of Medicine at the University of Pennsylvania,
Philadelphia, PA, USA
e-mail: maude@email.chop.edu;
hungers@email.chop.edu

B-ALL. Hyperleukocytosis and CNS involvement are more common in T-ALL compared to B-ALL (Hunger and Mullighan 2015a). Furthermore, T-ALL has a higher incidence in boys and older children and adolescents, in contrast to B-ALL with a peak incidence in the toddler age (Hunger and Mullighan 2015a; Patrick and Vora 2015).

Like B-ALL, T lymphoblasts display an immunophenotype similar to early progenitor counterparts in the T cell lineage. Markers of immaturity, such as TdT, are expressed as well as T cell-specific markers, such as CD2, CD7, and cytoplasmic CD3. A recently identified subtype of T-ALL, termed early T cell precursor (ETP) ALL, is distinguished by a unique immunophenotype (Coustan-Smith et al. 2009). While ETP ALL displays markers of the T cell lineage, it lacks some typical markers such as CD1a and CD8, and expresses stem cell or myeloid markers such as CD13 and CD33. The genetic profile of ETP ALL also differs from the majority of T-ALLs in that it resembles myeloid or stem cell leukemias (Zhang et al. 2012).

Historically, prognosis differed between B-ALL and T-ALL with T-ALL carrying a worse prognosis (Hunger and Mullighan 2015a; Teachey and Hunger 2013). However, with current treatment regimens, survival rates for T-ALL, although inferior, now approach those of B-ALL (Hunger et al. 2012; Patrick and Vora 2015). ETP ALL, which comprises 10–15% of childhood T-ALL, was originally reported to carry a dismal prognosis, with a 19% 10-year overall survival (Coustan-Smith et al. 2009). However, larger studies with modern risk-adapted therapy demonstrate similar outcomes to T-ALL, with survival rates of approximately 80% (Wood et al. 2014). An important difference that remains is the intensity of treatment: children with T-ALL require more intense therapy than the majority of children with B-ALL to achieve these outcomes.

Prognostic Factors

Clinical Features

Several clinical features are prognostic of outcome in pediatric ALL. Age and white blood cell

(WBC) count at diagnosis define initial risk allocation and therapy in B-ALL. An international consensus conference established the National Cancer Institute (NCI)/Rome criteria which separate B-ALL into standard-risk (SR) and high-risk (HR) (Smith et al. 1996). Age between 1 and 10 years and presenting WBC $< 50,000 \mu\text{L}^{-1}$ are both required for classification as SR, while either age ≥ 10 years or presenting WBC $\geq 50,000 \mu\text{L}^{-1}$ are sufficient to classify as HR B-ALL. Therapy intensification has narrowed the gap between SR and HR B-ALL; however, outcomes for HR B-ALL remain inferior despite more intensive therapy. Children with SR B-ALL treated on Children's Oncology Group (COG) ALL clinical trials between 2000 and 2005 had a 5-year survival of 95.0% compared to 82.9% for those with HR B-ALL (Hunger et al. 2012). While the NCI/Rome risk criteria set a cut point, the relationship between prognosis and both age and presenting WBC count is linear, with increasing age and increasing WBC count conferring a worse prognosis. Age and presenting WBC count have limited prognostic value in T-ALL and are not used to alter therapy (Patrick and Vora 2015). Infants < 1 year have significantly inferior outcomes, and for this group, age is inversely related to outcome, with infants < 3 months having the worst survival rates (Dreyer et al. 2015; Pieters et al. 2007). Survival rates have improved significantly over the past few decades for all subgroups of ALL, except infants (Hunger et al. 2012).

Extent of disease, including organ involvement, skin involvement, and lymphadenopathy, is neither prognostic nor therapy altering, for the most part. However, two extramedullary sites of disease, the CNS and the testes, are important to note as the presence of leukemia in these sites requires consideration of directed therapy. Both the CNS and testes are considered sanctuary sites where leukemia cells can evade standard therapy and recur. Children with CNS involvement, defined as WBC count $\geq 5 \mu\text{L}^{-1}$ with blasts present in the cerebrospinal fluid or neurologic signs, receive intensified CNS-directed therapy, including augmented intrathecal chemotherapy with or without cranial radiation therapy (discussed in more detail in "CNS-directed Therapy" section).

Boys with persistent testicular disease receive testicular irradiation. On COG protocols, both of these extramedullary sites up-risk patients to high-risk therapy. Despite intensified therapy, patients with CNS involvement consistently have worse outcomes (Vora et al. 2016).

Other demographic features, such as race, ethnicity, and sex, also appear to be prognostic but have not been used to alter therapy, and NCI/Rome risk group remains the most significant clinical prognostic factor for B-ALL in combined models (Hunger et al. 2012). Despite improvements in outcome, males, blacks, and Hispanics continue to have inferior survival (Hunger et al. 2012; Kadan-Lottick et al. 2003). Underlying biology and genetic determinants likely play a large role in these differences. Males and blacks are disproportionately represented in T-ALL, which continues to carry a worse prognosis, and there is an increased rate of high-risk genetic features in the Hispanic population (Harvey et al. 2010b).

Early Response to Therapy

Across cooperative groups, treatment protocols, and response assays, early response to therapy has proven to be the single most important predictor of prognosis. For many years, bone marrow morphologic assessments during the first month of therapy were used to stratify patients into risk groups based on rapidity of response (Gaynon et al. 1997). Early bone marrow assessments have largely been replaced with more sensitive assays of minimal residual disease (MRD) at the end of the first month of therapy (Borowitz et al. 2008; Coustan-Smith et al. 2000).

One very early assessment of response that is still used widely is the peripheral blood morphologic response to a prednisone pre-phase. The Berlin-Frankfurt-Munster (BFM) study group assesses the response to 7 days of prednisone in combination with one dose of intrathecal methotrexate. A peripheral blast count $<1000 \mu\text{L}^{-1}$ on day 8 is classified as a good response, while a peripheral blast count $\geq 1000 \mu\text{L}^{-1}$ on day 8 is classified as a prednisone poor response (PPR).

The BFM group has shown that PPR confers a significantly worse prognosis in both B-ALL and T-ALL (Schrappe et al. 2000; Lauten et al. 2012). Prednisone response, therefore, has been incorporated into risk allocation in BFM trials, with PPR being a high-risk feature, though this is evolving currently.

MRD assessment of response to therapy is the most important prognostic variable in pediatric ALL, consistently demonstrating independent prognostic value across studies. The assay used to measure MRD varies amongst different cooperative groups, but the power of this technology to predict outcome is unchanged. The COG MRD assay employs multiparameter flow cytometry to characterize the leukemic immunophenotype and can detect aberrant blasts at a level of 0.01%. MRD $\geq 0.01\%$ at the end of the first block of therapy (day 29 of induction) confers a significantly worse outcome for patients with B-ALL (Borowitz et al. 2008). More recent data indicates that these patients can be characterized further by MRD measurement after the first 3 months of therapy (at the end of consolidation): patients with persistent MRD $\geq 0.01\%$ fare much worse, with a 5-year disease-free survival (DFS) of 39% compared to 79% for those with MRD $<0.01\%$ at end-consolidation (Borowitz et al. 2015). The International BFM study group utilizes a PCR-based MRD assay, which tracks immunoglobulin or T cell receptor (TCR) gene rearrangements in the leukemic blasts (Biondi et al. 2000). In a collaborative prospective study of the Associazione Italiana di Ematologie Pediatrica (AIEOP) and BFM study groups, patients treated on AEIOP-BFM ALL 2000 were risk-stratified based on MRD at day 33 and day 78. Those B-ALL patients with MRD $\geq 10^{-3}$ at day 78 had the worst outcome, with a 5-year event-free (EFS) survival of 50.1% (Conter et al. 2010). MRD is also an important prognostic tool in T-ALL, although the time point that is prognostic appears to be different from B-ALL. The kinetics of blast clearance is slower in T-ALL. On AEIOP-BFM ALL 2000, MRD $\geq 10^{-3}$ at the later time point (day 78) was predictive of outcome, regardless of MRD at day 33 (Schrappe et al. 2011). Lastly, infant ALL can be stratified into the highest and

lowest risk groups by MRD. Once again, MRD at end-consolidation was highly predictive of outcome: all patients with MRD $\geq 10^{-4}$ at this time point relapsed (Van der Velden et al. 2009). Conversely, infants who achieved MRD $< 10^{-4}$ at the end of induction fared well with a relapse rate of 13%.

Intensification of therapy based on response measured by MRD has improved survival, yet there remains a subset of ALL patients with persistent MRD at later time points who continue to have poor outcomes (Conter et al. 2010; Borowitz et al. 2015). These patients are likely chemorefractory and may require alternative treatment strategies.

Genetic Features

Genetic alterations present in the leukemic blasts contribute to prognosis and likely influence other prognostic factors, such as presenting WBC count and response to therapy. Cytogenetic classification of ALL offered the first look at the impact of genetic abnormalities on outcome. Particularly in B-ALL, many cytogenetic features were found to have such a major influence on outcome that their presence alters therapy. This is not the case for T-ALL. Recent advances in technology provide a much deeper view of the diverse biology of ALL and may change the way we treat ALL in the future (Hunger and Mullighan 2015b).

Aneuploidy

Karyotype analysis is routinely performed at diagnosis and can easily detect changes in chromosome number. The majority of ALL cases contain whole chromosome gains or losses, and in many cases, the ploidy of the blast population impacts prognosis. Definitions of ploidy relate to the normal diploid complement of 46 chromosomes. Hyperdiploid cells contain >46 chromosomes, while hypodiploid cells contain <46 chromosomes.

Several cooperative groups have found high hyperdiploidy (>50 chromosomes) to be a favorable prognostic feature (Sutcliffe et al. 2005; Paulsson et al. 2013; Moorman et al. 2010). High

hyperdiploid ALL is common, accounting for 25–30% of pediatric B-ALL cases, and is typically associated with other low-risk features, such as low presenting WBC count and age <10 years (Paulsson and Johansson 2009). The same chromosomes (4, 6, 10, 14, 17, 18, 21, and X) are frequently gained, suggesting this event is not random (Paulsson et al. 2015). The gain of chromosomes 4, 10, and 17, termed triple trisomy, was demonstrated to confer a favorable prognosis and historically used for risk allocation in COG treatment studies (Sutcliffe et al. 2005; Schultz et al. 2007). The COG now uses double trisomy of chromosomes 4 and 10 to define low-risk patients. Other groups have documented favorable outcomes with the same or different trisomies (Paulsson et al. 2013; Moorman et al. 2010), but not all use trisomies or hyperdiploidy in risk allocation. Little is known about the etiology of hyperdiploid ALL, but modern genomic technologies are advancing our understanding. Whole genome and whole exome sequencing identified the RAS pathway as frequently involved in hyperdiploid ALL (Paulsson et al. 2015). Future work hopes to delineate risk within this favorable subset and identify targeted therapies.

In contrast to hyperdiploidy, hypodiploid subsets carry a poor prognosis and are uncommon (Harrison et al. 2004; Heerema et al. 1999; Nachman et al. 2007; Raimondi et al. 2003; Pui et al. 1990, 1987). Most hypodiploid ALL has 45 chromosomes, which does not portend an inferior prognosis (Harrison et al. 2004; Raimondi et al. 2003). However, hypodiploidy with <44 chromosomes comprises only 1–2% of B-ALL and confers a dismal outcome (Nachman et al. 2007). This group has been broken down further into low hypodiploid (~ 30 –39 chromosomes) and near haploid (24–29 chromosomes) (Harrison et al. 2004). Due to low incidence, it is unclear in most studies if absolute chromosome number influences prognosis (Raimondi et al. 2003). A study of 139 children with hypodiploid ALL treated on clinical trials of ten study groups found that patients with 44 chromosomes fared better than those with <44 chromosomes, but there was no difference in outcome when the group was broken

down further (Nachman et al. 2007). Recent genomic studies, however, demonstrate distinct genomic profiles amongst these subgroups. Genomic profiling revealed lesions in receptor tyrosine kinase and RAS pathways in ALL cases with 24–31 chromosomes, while >90% of low hypodiploid (32–39 chromosomes) harbored *TP53* alterations and a striking 50% of these had germline *TP53* mutations (Holmfeldt et al. 2013).

Structural Alterations

Sentinel chromosome translocations have long been recognized in ALL. In recent years, numerous rare gene fusions have been identified through next generation sequencing techniques. Many of these inter- and intrachromosomal alterations have prognostic implications and some have treatment implications as well.

The *ETV6-RUNX1* (*TEL-AML1*) gene fusion resulting from the t(12;21), is the single most common translocation in pediatric ALL, accounting for 20–25% of B-ALL in children (Harrison et al. 2010). Screening for this translocation by fluorescence in situ hybridization (FISH) is routinely performed at diagnosis by many groups. A study of newborn blood samples from children who later developed ALL demonstrated the presence of the *ETV6-RUNX1* fusion at birth, indicating that this is an initiating or early event and not sufficient for leukemogenesis (Wiemels et al. 1999). Survival rates for children with B-ALL carrying the *ETV6-RUNX1* gene fusion are outstanding (Moorman et al. 2010; Harrison et al. 2010; Schultz et al. 2007). Moreover, this translocation is associated with favorable prognosis regardless of risk group (Forestier et al. 2008).

The Philadelphia chromosome (Ph) or t(9;22)(q34;q11) is present in approximately 3% of childhood ALL and results in *BCR-ABL1* gene fusion (Bernt and Hunger 2014). The BCR-ABL1 fusion protein functions as a leukemogenic driver through aberrant ABL1 kinase activity. Historically, Ph⁺ ALL had a dismal prognosis, which was only modestly improved with hematopoietic stem cell transplantation (HSCT) (Aricò et al. 2000, 2010). Survival rates have improved significantly with the introduction of the tyrosine kinase inhibitor (TKI) imatinib into

chemotherapy regimens (Schultz et al. 2009; Biondi et al. 2012). The COG reported a 5-year DFS of 70% for children treated with imatinib in combination with an intensified chemotherapy backbone (Schultz et al. 2014).

Translocations involving the mixed lineage leukemia (*MLL*) gene on chromosome 11q23 are present in about 75% of infant ALLs and are also seen in 2–5% of childhood ALL (Dreyer et al. 2015; Schultz et al. 2007). *MLL* has numerous fusion partners, but three make up the majority of cases: *AF4* in t(4;11), *AF9* in t(9;11), and *MLLT1* in t(11;19) (Krivtsov and Armstrong 2007). In infants, *MLL* rearrangement unequivocally confers a worse prognosis (Pieters et al. 2007; Dreyer et al. 2015). In children >1 year of age, the impact is less clear, but *MLL* rearrangement has been associated with inferior EFS in several studies (Pui et al. 2003; Moorman et al. 2010; Schultz et al. 2007).

Several translocations involving *TCF3* (*E2A*) on chromosome 19 have been reported in ALL including the t(1;19) resulting in *TCF3-PBX1* fusion and t(17;19) resulting in *TCF3-HLF* fusion (Hunger et al. 1991, 1992). While initially reported to be high-risk, t(1;19), identified in 5% of pediatric B-ALL, is no longer considered an independent risk factor with modern response-based therapy (Moorman et al. 2010; Hunger 1996). In contrast, t(17;19) is quite rare, accounting for <1% of B-ALL, but is associated with dismal outcomes (Moorman et al. 2010; Minson et al. 2013).

Intrachromosomal amplification of chromosome 21 (iAMP21) is defined by three or more extra copies of *RUNX1* on a single chromosome 21 (Harewood et al. 2003; Soulier et al. 2003). Approximately 2% of childhood ALL harbors iAMP21 (Heerema et al. 2013; Moorman et al. 2013). Several studies showed inferior outcomes in patients with iAMP21, which may be overcome with intensified therapy (Heerema et al. 2013; Moorman et al. 2013; Harrison et al. 2014). Recent COG trials found that SR B-ALL patients with iAMP21 fare particularly poorly with standard-risk therapy; therefore, these patients are currently treated on HR treatment protocols (Heerema et al. 2013).

Genomic Profile

Next generation genomic technologies have dramatically expanded our knowledge of the genomic landscape of ALL beyond aneuploidy and sentinel chromosomal rearrangements. In recent years, several groups identified a very high-risk cohort of B-ALL whose gene expression profile resembles that of Ph⁺ ALL. This subgroup, termed Ph-like or *BCR-ABL1*-like, does not harbor the *BCR-ABL1* translocation but appears to activate similar downstream signaling pathways to Ph⁺ ALL (Den Boer et al. 2009; Harvey et al. 2010b; Mullighan et al. 2009b). Deletion of the lymphoid transcription factor gene *IKZF1*, commonly seen in Ph⁺ ALL, frequently occurs in Ph-like ALL. Due to these similarities, an investigation into other kinase pathways ensued, and several lesions affecting kinase activity and cytokine signaling are implicated in this high-risk cohort.

Approximately 50% of cases harbor rearrangements in *CRLF2* (cytokine receptor-like factor 2), leading to overexpression of this component of the heterodimeric cytokine receptor for thymic stromal lymphopoietin (TSLP) (Mullighan et al. 2009a; Russell et al. 2009). About half of cases with *CRLF2* rearrangements also have point mutations in genes encoding JAK kinases (Russell et al. 2009; Harvey et al. 2010a; Mullighan et al. 2009c; Yoda et al. 2010), a family of tyrosine kinases important for cytokine receptor signaling, cell growth, survival, and differentiation in many cell types, particularly those of the hematopoietic and immune systems. Moreover, *CRLF2*-overexpressing ALL cell lines and primary human leukemias demonstrate aberrant JAK2 signaling through its downstream target, STAT5, *in vitro* (Tasian et al. 2012). Numerous fusions involving kinases continue to be identified in Ph-like ALL. Fusions or oncogenic alterations of *ABL1*, *ABL2*, *JAK2*, *PDGFRB*, *CSF1R*, *EPOR*, and *IL7R* have been identified by next-generation sequencing technologies (Roberts et al. 2012, 2014). Approximately 20% of Ph-like ALL cases have no known lesion in the above-named pathways but are suspected to harbor as yet unidentified genetic lesions affecting signaling pathways important for proliferation and transformation (Roberts et al. 2014).

Ph-like ALL is common, comprising 10–15% of childhood B-ALL, and carries a poor prognosis, with 4–5 year relapse-free survival rates of 21–63%, depending on the cohort examined (Loh et al. 2013; Den Boer et al. 2009; Harvey et al. 2010b). The incidence of Ph-like ALL increases with age with upwards of 25% affected in the 21–39 year age range (Roberts et al. 2014). Male sex and Hispanic ethnicity are enriched in the COG Ph-like ALL cohort (Harvey et al. 2010b). Patients with Ph-like ALL more frequently present with hyperleukocytosis and tend to be chemorefractory, with a higher rate of induction failure (failure to achieve morphologic complete remission (CR) at the end of the first month of therapy) and positive MRD at the end of induction (Harvey et al. 2010b; Loh et al. 2013).

Genetics of T-ALL

Several common genetic lesions occur in T-ALL; however, none are prognostic in isolation, and therefore, none are currently used to stratify by risk or alter therapy. The NOTCH signaling pathway represents the most common family of genetic lesions in childhood T-ALL, affecting more than 50% of T-ALL (Weng et al. 2004). Additional genetic alterations in T-ALL involve *LMO2*, *TALI*, *TLX1*, and *HOX11* (Van Vlierberghe and Ferrando 2012).

The ETP subtype of T-ALL is distinguished not only by immunophenotype but also by gene expression profiles resembling myeloid or stem cell leukemias (Coustan-Smith et al. 2009; Zhang et al. 2012). ETP ALL cases commonly harbor lesions leading to dysregulation of the RAS pathway as well as lesions affecting IL7R and the JAK/STAT pathway (Maude et al. 2015; Zhang et al. 2012). For all subtypes of T-ALL, however, response to therapy by MRD remains the most important prognostic factor.

Current Treatment for Childhood ALL

With the introduction of chemotherapy, childhood ALL changed from a universally fatal disease a half century ago to one in which almost 90% of children are cured in the current era.

Pediatric ALL provides an example of the enormous impact cooperative group clinical trials can have on therapy and outcomes (Pui et al. 2015). In fact, childhood ALL was the first disease to be treated with chemotherapy, paving the way for the future of cancer therapy (Farber et al. 1948). Through both major additions and iterative changes, the treatment for pediatric ALL has evolved to include multi-agent chemotherapy and multi-modality approaches. Two approaches have greatly impacted outcomes: the intensification of therapy based on risk and the introduction of therapy to target the CNS.

Risk-Adapted Therapy

The therapy for childhood ALL includes several combinations of chemotherapy lasting approximately two to three and a half years. While variations exist amongst protocols employed by the different cooperative groups, the basic principles are shared. Therapy is divided into discrete phases, with 6–9 months of intensive chemotherapy followed by 18–30 months of maintenance therapy (Hunger and Mullighan 2015a).

The first phase of therapy, called induction, ranges from 4 to 6 weeks in duration and typically consists of a corticosteroid (prednisone or dexamethasone), vincristine, asparaginase, and may contain an anthracycline. Some cooperative groups, such as the COG, employ different induction regimens for B-ALL based on NCI/Rome risk group, with SR patients receiving only 3 drugs (corticosteroid, vincristine, and asparaginase) and HR patients also receiving an anthracycline. Other groups use four drugs in all patients. After induction therapy, the vast majority of patients enter CR, which is absence of clinical signs of leukemia in the setting of normal hematopoiesis (Miller et al. 1983). Post-induction therapy is commonly altered based on early MRD response (Borowitz et al. 2008; Coustan-Smith et al. 2000).

Subsequent intensive phases of therapy consist of additional cytotoxic and lympholytic chemotherapeutic agents, including cyclophosphamide, cytarabine, methotrexate, mercaptopurine, and thioguanine in addition to the four induction drugs. The combination of drugs used and dose

intensity is adjusted based on risk group. For B-ALL, risk group is determined by a combination of baseline clinical features, genetic features, and early response to therapy.

For both B-ALL and T-ALL, the concept of risk-adapted therapy, whereby therapy is intensified for patients at high risk of relapse, has improved overall outcomes significantly (Teachey and Hunger 2013). Patients with HR B-ALL and all patients with T-ALL require more intense therapy than patients with SR B-ALL. As patients with suboptimal MRD response have been allocated to intensified therapy in modern protocols, the outcome gaps have narrowed. Patients with end-induction MRD treated on a recent COG HR protocol, AALL0232, had much improved disease-free survival if they became MRD-negative with additional therapy (Borowitz et al. 2015).

Lastly, maintenance therapy is important in ALL to maintain remission and reduce the risk of relapse. This phase of therapy consists of repeated cycles of reduced intensity, mostly oral, chemotherapy. Daily oral mercaptopurine and weekly low-dose methotrexate comprise the backbone of maintenance chemotherapy, with some groups also delivering periodic combined pulses of a corticosteroid and vincristine given typically monthly. The length of therapy varies between cooperative groups (Stary et al. 2014; Conter et al. 2014), and in COG protocols, varies between girls and boys, with boys receiving an additional year of therapy. However, the importance of prolonged therapy for boys and the ideal length of maintenance therapy are not known.

CNS-Directed Therapy

With the first introduction of multi-agent chemotherapy, most children achieved CR but subsequently relapsed, and recurrence of disease in the CNS was common. The recognition of the CNS as a leukemia sanctuary site led to the introduction of CNS-directed therapy (George et al. 1968). Many chemotherapeutic agents do not penetrate the CNS when given systemically, or only penetrate when given in high doses; therefore, the response of leukemic blasts in the CNS to systemic chemotherapy may be negligible, slow,

or incomplete. To overcome this relapse risk, cranial or craniospinal radiation was added to therapy. The introduction of radiation therapy dramatically increased long-term survival rates but also produced significant long-term toxicity, including deleterious effects on growth and cognitive development (Aur et al. 1971; Krull et al. 2013). In addition to irradiation, the CNS was targeted by administering chemotherapy via the intrathecal route (injecting chemotherapy into the thecal sac through lumbar puncture). Over time, the use of cranial radiation has decreased significantly with the vast majority of children (80–95%) with ALL no longer undergoing irradiation (Vora et al. 2016). Radiation therapy is more commonly employed in T-ALL (which has a higher incidence of CNS disease) and is still used frequently in B-ALL that presents with CNS disease; however, some groups have nearly or completely eliminated cranial radiation with similar outcomes (Vora et al. 2016; Wilejto et al. 2015; Pui et al. 2009; Veerman et al. 2009). The elimination of irradiation is often achieved both by the use of CNS-penetrating systemic chemotherapy and by increasing the number and/or intensity of intrathecal chemotherapy, which is not without neurocognitive effects (Krull et al. 2013; Duffner et al. 2014). Nevertheless, the introduction of CNS-directed therapy into the management of ALL led to the single largest improvement in overall survival for children with ALL (Aur et al. 1971).

Hematopoietic Stem Cell Transplantation (HSCT)

Approximately 80–85% of children will be cured with chemotherapy alone; however, for high-risk patients who relapse, HSCT is an important component of therapy. Many factors influence prognosis after relapse, including immunophenotype, time to relapse, and site of relapse (bone marrow, extramedullary, or combined) (Raetz and Bhatla 2012). Relapse during primary therapy suggests resistance to chemotherapy, which is often demonstrated through acquired mutations (Ma et al. 2015). HSCT decreases subsequent relapse risk and is therefore recommended for those relapses

considered high-risk, such as early medullary relapses and all T-ALL relapses (Eapen et al. 2006; Uderzo et al. 1995). The role of HSCT in other relapse subsets (late relapse, isolated extramedullary relapse) and in frontline therapy is less clear; however, some cooperative groups utilize HSCT in first remission for patients at high risk of relapse (Peters et al. 2015). A potential benefit of allogeneic HSCT is induction of a graft-versus-leukemia (GVL) effect. A recent COG HSCT clinical trial found a significantly lower risk of subsequent relapse in patients who developed acute graft-versus-host disease (GVHD) after allogeneic HSCT, implying GVL played an important role in leukemia control (Pulsipher et al. 2014). For chemotherapy-resistant leukemias, HSCT may improve outcomes through immune-mediated leukemia cell killing.

Novel Therapy Approaches

Despite advances in therapy for childhood ALL, there remains a subset of patients for whom current treatment approaches are inadequate. For these children who go on to relapse, there has been very little improvement in outcomes (Nguyen et al. 2008; Raetz and Bhatla 2012). Two approaches to overcome this obstacle are employed: (1) identification of patients at high risk for relapse with consequent augmentation of therapy (Teachey and Hunger 2013); (2) introduction of novel therapies into relapse regimens.

New Cytotoxic Agents

Most, if not all, of the chemotherapeutic agents that currently comprise standard-of-care regimens for pediatric ALL were approved by the U.S. Food and Drug Administration (FDA) 40–60 years ago. Only recently, in the last 10 years, have new agents been added to the armamentarium for pediatric ALL.

Bortezomib

Bortezomib is a proteasome inhibitor that specifically inhibits the 26S proteasome, responsible for

degrading proteins in such key cellular pathways as cell cycle regulation, transcription, and apoptosis (Teicher et al. 1999). It was approved by the FDA for refractory mantle cell lymphoma in 2006 and multiple myeloma in 2008.

In initial phase 1 clinical trials of bortezomib in pediatric relapsed/refractory ALL, little single-agent activity was observed (Horton et al. 2007). Due to its mechanism of action, it was suspected that bortezomib may sensitize cancer cells to chemotherapeutic agents (Horton et al. 2006). In a phase 1/2 study of bortezomib in combination with standard chemotherapeutic agents, activity was demonstrated in relapsed/refractory pediatric ALL, with an overall response rate of 73% (Messinger et al. 2012). Toxicities include peripheral neuropathy (Richardson et al. 2009) and severe lung injury, reported in adults, but not children, treated with bortezomib (Miyakoshi et al. 2006; Chew et al. 2007; Yoshizawa et al. 2014; Akosman 2015).

Bortezomib is now incorporated into relapse reinduction regimens by many pediatric oncologists and is considered for chemorefractory leukemias. In addition, the current COG phase 3 trial for newly diagnosed T-ALL is studying bortezomib in frontline therapy.

Clofarabine

The purine nucleoside analog clofarabine was the first cytotoxic chemotherapy approved by the FDA for the indication of pediatric ALL in over 20 years. It received accelerated approval in 2004 for relapsed/refractory pediatric ALL based on a phase 2 study of single agent clofarabine showing a 30% overall response rate in patients refractory to at least two prior regimens (Jeha et al. 2006).

Several prior and subsequent studies have demonstrated the efficacy of clofarabine in ALL (reviewed by Hijiya et al. (2012)). Clofarabine has been studied in combination with cyclophosphamide and etoposide as well as other chemotherapy regimens, with response rates of 44–58% in relapsed/refractory pediatric ALL (Hijiya et al. 2009, 2011; Locatelli et al. 2009; Nelken et al. 2016). The phase 2 portion of the study combining clofarabine with etoposide

and cyclophosphamide demonstrated an initial high rate of severe hepatotoxicity in 4/8 patients, prompting amendment of the study to exclude patients with prior HSCT, viral hepatitis, cirrhosis, and conjugated hyperbilirubinemia (Hijiya et al. 2011). Moreover, the incidence of febrile neutropenia and severe infection was high with this combination (Hijiya et al. 2009).

Due to its promising efficacy in relapsed pediatric ALL, clofarabine was incorporated into the current COG phase 3 trial for newly diagnosed HR B-ALL. However, enrollment onto the clofarabine-containing arm was suspended and subsequently halted due to prolonged cytopenias and infections. A recent trial of the German Co-operative Study Group for treatment of ALL (CoALL) combined clofarabine with asparaginase for children with high-risk ALL defined by high MRD at the end of induction, demonstrating a 61% conversion rate to MRD negativity compared to 46% in historical controls (Escherich et al. 2013).

Nelarabine

Nelarabine, a water-soluble prodrug of the purine nucleoside antimetabolite araG (9-B-arabinofuranosylguanine), received FDA accelerated approval for the treatment of relapsed/refractory T-cell acute lymphoblastic leukemia and lymphoblastic lymphoma in 2005. This approval was based in part on a phase 2 trial conducted by the COG showing single-agent activity of nelarabine with overall response rates of 55% in first relapse and 27% in second or greater relapse (Berg et al. 2005).

A prior phase 1 study of nelarabine in children and adults demonstrated a striking response rate in T-ALL, with 54% achieving a complete or partial response (Kurtzberg et al. 2005). Subsequent clinical trials combined nelarabine with standard chemotherapy. In a pilot study of nelarabine in combination with standard intensive chemotherapy for high-risk T-ALL patients with a slow early response to therapy, the COG found no increased toxicity with the combination and demonstrated similar 5-year EFS rates compared to patients with a rapid early response (Dunsmore et al. 2012).

Significant neurotoxicity has been associated with nelarabine. In the initial phase 1 and 2 studies of nelarabine, the incidence of neurologic events, including peripheral neuropathy, somnolence, seizure, ascending paralysis, ataxia, and coma, is high, occurring in 72% of patients on the phase 1 study (Berg et al. 2005; Kurtzberg et al. 2005). However, in subsequent combination trials, less neurotoxicity was observed, possibly related to the newly diagnosed patient population compared to the heavily pretreated population in the early studies (Dunsmore et al. 2012; Winter et al. 2015).

Nelarabine was introduced into frontline therapy for T-ALL in the COG randomized phase 3 trial, AALL0434. A recent report on the initial safety phase of that study showed no increase in neurotoxicity on the nelarabine arm compared to the control arm (Winter et al. 2015). Efficacy data from this trial is not yet available.

Precision Medicine Therapies

As the understanding of the biology underlying pediatric ALL has expanded, so has the repertoire of therapeutic options (Hunger and Mullighan 2015b). Next-generation sequencing technologies have identified several genetic lesions, thought to either drive leukemogenesis or be important for blast survival, in subsets of ALL at high risk for relapse. Ph⁺ ALL is one such subset harboring a driver genetic lesion, the *BCR-ABL1* translocation leading to constitutive ABL1 kinase activity. The use of the TKI imatinib in Ph⁺ ALL established a paradigm for drugs targeting a specific anomaly found in leukemic blasts.

Recent genomic studies have identified multiple lesions affecting kinases and signaling pathways in a subset of B-ALL termed Ph-like ALL. While some of these lesions are recurring, many are individually rare. Yet several common pathways are affected, notably the ABL kinase family and the JAK kinase family, both of which can be targeted by TKIs (Roberts et al. 2014). A few case reports show the benefit of the TKIs imatinib and dasatinib in select cases with fusions resulting in constitutive kinase activation (Deenik

et al. 2009; Clarke et al. 2011; Weston et al. 2013; Roberts et al. 2014). The COG will soon be incorporating targeted therapies into frontline clinical trials via two paths. Patients whose leukemic blasts carry lesions potentially responsive to ABL kinase inhibition (e.g. fusions involving *ABL1*, *ABL2*, *CSF1R*, and *PDGFRB*) will be eligible to receive dasatinib in combination with cytotoxic chemotherapy on the current phase 3 trial for HR B-ALL, AALL1131 (Hunger and Mullighan 2015b). For patients with B-ALL harboring lesions potentially responsive to JAK kinase inhibition (e.g. lesions in *JAK1*, *JAK2*, *EPOR*, and *IL7R*), a phase 2 trial of ruxolitinib combined with chemotherapy is in development.

Beyond genetic alterations influencing gene expression, some leukemias have dysregulation of transcription through epigenetic mechanisms. The epigenome tightly regulates transcription by controlling DNA availability to transcriptional activators and repressors through methylation and histone formation. Infant ALLs with *MLL* translocations provide one example of hypermethylation in leukemia (Schafer et al. 2010; Stumpel et al. 2011). Due to the suspected contribution of epigenetic dysregulation to chemotherapy resistance, epigenetic agents are attractive targets (Bhatla et al. 2012). Both histone deacetylase inhibitors and demethylating agents are under investigation in pediatric ALL (Burke et al. 2014).

Immunotherapy

The field of immunotherapy for cancer made remarkable strides in several refractory malignancies and received widespread attention in recent years. This alternative approach is particularly attractive for relapsed leukemia or leukemia that is refractory to chemotherapy. Decreased incidence of relapse is largely responsible for the improved survival rates for childhood ALL, with very little improvement in survival rates for children who relapse for more than twenty years (Nguyen et al. 2008; Raetz and Bhatla 2012). These disappointing statistics highlight the need for alternative therapies with novel mechanisms of action. Approaches based on the immune

system may overcome resistance mechanisms intrinsic to cancer cells. The three approaches described herein target unique antigens expressed on the surface of cancer cells.

Antibody Conjugates

In the first immunotherapy approach, a monoclonal antibody against a specific antigen on malignant cells is created. The monoclonal antibody can then be conjugated to a toxin or drug, which is released into the cell upon internalization of the antibody, as is the case for the two antibody conjugates described below.

Moxetumomab pasudotox (formerly known as HA22) is an anti-CD22 monoclonal antibody conjugated to the *Pseudomonas* exotoxin A. CD22 is an early differentiation antigen expressed on the B cell lineage and on 90% of B-ALL blasts. In a phase 1 study of moxetumomab in pediatric B-ALL and non-Hodgkin lymphoma, objective responses were observed in 29% of 17 evaluable patients (Wayne et al. 2011). Neutralizing antibodies were detected in 14% of patients, potentially posing the challenge of resistance. The treatment-related toxicity of capillary leak syndrome was dose-limiting in two patients.

Inotuzumab ozogamicin is a humanized monoclonal antibody against CD22 that has been conjugated to calecheamicin. It has shown considerable promise in relapsed/refractory B-ALL. A phase 2 study of inotuzumab ozogamicin in children and adults with relapsed/refractory B-ALL demonstrated an overall response rate of 58% (Kantarjian et al. 2012, 2013). These results showed remarkable single-agent activity in this population. Early results of the phase 3 randomized trial of inotuzumab ozogamicin in relapsed/refractory adult B-ALL are even higher, with CR rates of 80.7% in the inotuzumab arm compared to 33.3% in the standard-of-care arm (DeAngelo et al. 2015). Toxicities included cytopenias (most commonly thrombocytopenia) and veno-occlusive disease.

Bispecific Antibodies

This approach links two monoclonal antibodies to form a new class of antibodies termed Bispecific T-cell engagers (BiTE). The first-in-

class BiTE blinatumomab joins an anti-CD19 antibody scFv domain with an anti-CD3 scFv domain, thereby linking CD19-expressing target cells with CD3-expressing T cells (Wolf et al. 2005). Antibody binding engages the T cell cytotoxic machinery, leading to target cell lysis. CD19 is an attractive target for immunotherapies due to its near universal expression on B cell malignancies, including B-ALL.

Blinatumomab has an extremely short half-life (approximately 2 h). Lack of objective response with 2- to 4-h intravenous infusion in initial studies prompted a change in administration to continuous intravenous infusion in 4-week cycles (Nagorsen et al. 2012). The first clinical trial of blinatumomab to demonstrate efficacy was a phase 1 trial in adults with refractory lymphomas showing a 35% objective response rate (Bargou et al. 2008). Blinatumomab was subsequently studied in B-ALL in a phase 2 trial of adults with persistent MRD, with 16/20 (80%) evaluable patients becoming MRD-negative within four cycles of treatment (Topp et al. 2011). With a median follow-up of 33 months, relapse-free survival (RFS) was 61% (Topp et al. 2012). Nine patients subsequently received HSCT, and six remained in remission. Six of the 11 patients who did not go on to receive allogeneic HSCT remained in remission with a median follow-up of 31 months. A German phase 2 trial of 36 adults with refractory/relapsed ALL showed 69% achieved CR with a median RFS of 8.8 months and overall survival (OS) of 13 months (Zugmaier et al. 2015). Most of the long-term survivors received HSCT, but two did not, receiving additional courses of blinatumomab. A larger multi-center phase 2 trial in adults with relapsed/refractory ALL demonstrated a lower CR rate of 43% in patients with higher disease burden at the start of treatment (Topp et al. 2015). Results of this study led to accelerated FDA approval of blinatumomab for relapsed/refractory B-ALL. Finally, initial data from a phase 1/2 dose-escalation trial of blinatumomab in children with relapsed/refractory B-ALL showed a CR rate of 39% (Hoffman and Gore 2014).

Notable toxicities associated with blinatumomab include cytokine release syndrome (CRS)

and neurotoxicity. Significant elevations in cytokine levels related to T cell engagement and proliferation result in inflammatory symptoms. CRS manifests as a prodrome of flu-like symptoms, including fever, myalgias, headache, anorexia, and nausea/vomiting (Maude et al. 2014a). In some patients, these symptoms can progress to a severe systemic inflammatory response, including vascular leak, hypotension, pulmonary edema, and coagulopathy (Teachey et al. 2013). Reversible neurologic events, including tremor, encephalopathy, aphasia, and seizure, were commonly seen in patients treated with blinatumomab (52%), most (39%) were grade 1–2 (Topp et al. 2015).

Engineered T Cells

In the third immunotherapy approach, the patient's own T cells are reprogrammed to recognize and kill cells expressing a particular antigen. T cells collected from the patient are engineered to express a chimeric antigen receptor (CAR) consisting of an extracellular scFv domain (derived from a monoclonal antibody) linked to intracellular T cell signaling and costimulatory domains. The scFv domain targets an antigen of interest, one expressed on the surface of malignant cells, such that antigen binding redirects the T cell to the tumor cell, leading to engagement, a cytotoxic response, and T cell proliferation. Because any cell expressing the antigen targeted by the CAR is killed, an ideal antigen would be one that was ubiquitously expressed on malignant cells and unique to malignant cells. While the ideal antigen may not exist, CD19 comes close, as its expression is limited to the B cell lineage and, as noted above, it is expressed on most B cell malignancies, including B-ALL. CARs directed against CD19 have led the way, demonstrating the potential for engineered T cell therapies.

Enthusiasm for the potential of this technology in B-ALL was spurred by early results of several ongoing clinical trials of CD19-targeted CAR-modified T cells, which showed striking clinical responses in patients who were no longer responsive to chemotherapy and considered to be incurable (Brentjens et al. 2013; Grupp et al.

2013). However, these first reports included small numbers of patients. Larger studies have validated these findings, demonstrating CR rates of 70–90%. Importantly, these results have been replicated amongst different groups using distinct vectors and CAR designs (Lee et al. 2014; Maude et al. 2014b; Davila et al. 2014). Our group initially reported a 90% CR rate in 30 patients with relapsed/refractory ALL treated with CTL019 on pediatric and adult phase I trials at the Children's Hospital of Philadelphia (CHOP) and the University of Pennsylvania (Penn), respectively (Maude et al. 2014b). CTL019 cells express a CAR composed of anti-CD19 scFv, CD3 ζ , and 4-1BB domains. In a Memorial Sloan Kettering Cancer Center (MSKCC) study of 19–28z CAR T cells, Davila et al. (2014) reported a similar CR rate of 88% in a cohort of 16 adults with relapsed B-ALL. Lastly, Lee et al. (2014) reported a 70% CR rate in an intent-to-treat analysis of 20 children and young adults with ALL treated on the NCI trial. CR rates as high as 90% are unprecedented in this highly refractory population, making these initial reports encouraging.

Engineered T cells have the potential to act as “a living drug” providing continued protection from relapse. The CAR-expressing T cells described above are permanently modified; however, these engineered T cells need to persist (the minimum time needed is not known). Persistence of CAR-modified T cells varies across studies and may distinguish CAR designs, despite similar CR rates. The manufacturing process and viral vector used for CAR transduction are thought to be important contributors to persistence, but the costimulatory domain may also be an important factor. The CD28 costimulatory domain (used in both the NCI and MSKCC CD19 CARs) is associated with shorter persistence, with loss of CAR T cells and recovery of normal B cells by 1–3 months in both studies (Davila et al. 2014; Lee et al. 2014). We have observed longer persistence (2 years or more) with the 4-1BB costimulatory domain. The probability of CTL019 persistence in our ALL cohort at 6 months was 68% (95% CI: 50–92%) (Maude et al. 2014b). B Cell aplasia

provides a surrogate marker of CD19 CAR function as normal CD19-expressing B cells are also cleared. The longer duration of B cell aplasia (3 years or more) seen with the 4-1BB domain suggests continued effector function of CTL019 cells.

Continued optimism stems from the report of durable remissions with CD19-directed CAR-modified T cells. In the initial report describing the CHOP/Penn cohort of 30 children and adults with ALL, sustained remissions of 2–24 months were observed in 19 patients (15 with no further therapy). At a median follow-up of 6 months, EFS was 67% (95% CI: 51–88%) and OS was 78% (95% CI: 65–95%) (Maude et al. 2014b). In an expanded cohort of 53 pediatric patients with ALL reported at the 2015 American Society of Hematology Annual Meeting, we observed a CR rate of 94% and a 6-month RFS of 72% (95% CI: 59–87%) with a median follow-up of 10.6 months (range 1–39 months) (Grupp et al. 2015). Twenty-nine patients were in continuous remission, with only five of these patients receiving subsequent SCT. Short persistence or, more commonly, loss of the CD19 epitope ($n = 13$) led to relapse in a total of 20 patients. The MSKCC and NCI studies reported sustained remissions in the approximately 50% of patients who proceeded to allogeneic SCT (Davila et al. 2014; Lee et al. 2014). Further studies with expanded cohorts and more mature follow-up across CAR designs will be needed to better elucidate differences and determine the full potential of engineered T cell therapy.

Toxicities of engineered T cells are similar to those observed with the T cell engaging bispecific antibody blinatumomab. CRS, the most notable and serious toxicity, is associated with supraphysiologic T cell proliferation and significant cytokine elevations, as its name suggests. Nearly all ALL patients treated with highly active CAR-modified T cell therapies experience some degree of CRS. We and others have reported that severe CRS correlates with high disease burden and can be effectively reversed with cytokine blockade by the IL6R inhibitor tocilizumab (Davila et al. 2014; Grupp et al. 2013; Lee et al. 2014; Maude et al.

2014b). Neurotoxicity ranging from confusion and delirium to aphasia, global encephalopathy, and seizure has been reported in several CD19 CAR clinical trials (Davila et al. 2014; Lee et al. 2014; Maude et al. 2014b). In our experience, neurotoxicity resolves without intervention or apparent long-term sequelae. An on-target off-tumor toxicity is B cell aplasia related to depletion of all cells of the B lineage, which express CD19, and leading to hypogammaglobulinemia requiring immunoglobulin replacement. Lastly, although GVHD is a potential concern with activated T cells in patients with a prior history of allogeneic SCT, it has not been reported to date in these studies (Davila et al. 2014; Lee et al. 2014; Maude et al. 2014b).

Moving Novel Therapies into Frontline Treatment

As we learn more about the biology of ALL as well as the characteristics of these new approaches, ALL therapy has the potential to change significantly. Much of the progress made to improve outcomes for children with ALL evolved from decreasing the incidence of relapse. That approach is likely to continue to improve outcomes in the future. With ever-increasing advances in technologies and analyses to not only identify patients at high risk for relapse but also discover key features underlying their leukemia, it may be possible in the near future to match patients with specific therapy schemas best suited to their disease. The chemotherapy backbones that brought pediatric ALL outcomes to their current high level will undoubtedly remain an important part of therapy, but the addition of new agents targeted against driver genetic lesions or specific leukemogenic mechanisms may improve outcomes further for a subset of patients. Moreover, the incorporation of approaches with novel mechanisms, such as immunotherapies, may decrease relapse rates for ALLs that are refractory to chemotherapy. Pediatric oncology cooperative groups are developing approaches to incorporate several of the above novel approaches into frontline therapy.

Conclusions

The history of therapy for childhood ALL is a prime example of progress in medicine over the last half century. Remarkable gains in survival rates result from the introduction of multi-agent chemotherapy schemas and clinical trials studying iterative changes and new approaches. Improved understanding of leukemia biology goes hand in hand with advances in treatment. We are at a time in cancer research when ALL therapy has the potential to both decrease rates of relapse and improve the chance of cure when relapse does occur. Moreover, reducing toxicity and late effects of therapy has been and will continue to be a major focus of the field. There is reason to hope that we can improve both long-term survival and quality of life for children afflicted with this once universally devastating disease.

Conflicts of Interest Dr. Maude has received consulting fees from Novartis Pharmaceuticals. Dr. Hunger has received consulting fees and/or honoraria from Jazz Pharmaceuticals, Sigma Tau Pharmaceuticals, and Spectrum Pharmaceuticals. Dr. Hunger owns common stock in Amgen, Merck, and Pfizer.

References

- Akosman CC. Development of acute pulmonary hypertension after bortezomib treatment in a patient with multiple myeloma: a case report and the review of the literature. *Am J Ther*. 2015;22(3):e88–92. <https://doi.org/10.1097/O1.mjt.0000433941.91996.5f>.
- Aricò M, Schrappe M, Hunger SP, Carroll WL, Conter V, Galimberti S, Manabe A, Saha V, Baruchel A, Vettenranta K, Horibe K, Benoit Y, Pieters R, Escherich G, Silverman LB, Pui C-H, Valsecchi MG. Clinical outcome of children with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia treated between 1995 and 2005. *J Clin Oncol*. 2010;28(31):4755–61.
- Aricò M, Valsecchi MG, Camitta B, Schrappe M, Chessells J, Baruchel A, Gaynon P, Silverman L, Janka-Schaub G, Kamps W, Pui C-H, Conter V, Riehm H, Heerema N, Sallan S, Pullen J, Shuster J, Carroll A, Raimondi S, Richards S, Masera G. Outcome of treatment in children with Philadelphia chromosome-positive acute lymphoblastic leukemia. *N Engl J Med*. 2000;342(14):998–1006. <https://doi.org/10.1056/NEJM200004063421402>.
- Aur RJA, Simone J, Hustu HO, Walters T, Borella L, Pratt C, Pinkel D. Central nervous system therapy and combination chemotherapy of childhood lymphocytic leukemia. *Blood*. 1971;37(3):272–81.
- Bargou R, Leo E, Zugmaier G, Klinger M, Goebeler M, Knop S, Noppeney R, Viardot A, Hess G, Schuler M, Einsele H, Brandl C, Wolf A, Kirchinger P, Klappers P, Schmidt M, Riethmuller G, Reinhardt C, Baeuerle PA, Kufer P. Tumor regression in cancer patients by very low doses of a T cell-engaging antibody. *Science*. 2008;321(5891):974–7. <https://doi.org/10.1126/science.1158545>.
- Berg SL, Blaney SM, Devidas M, Lampkin TA, Murgo A, Bernstein M, Billett A, Kurtzberg J, Reaman G, Gaynon P, Whitlock J, Krailo M, Harris MB. Phase II study of nelarabine (compound 506U78) in children and young adults with refractory T-cell malignancies: a report from the Children's Oncology Group. *J Clin Oncol*. 2005;23(15):3376–82. <https://doi.org/10.1200/jco.2005.03.426>.
- Bernt KM, Hunger SP. Current concepts in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia. *Front Oncol*. 2014;4:54. <https://doi.org/10.3389/fonc.2014.00054>.
- Bhatla T, Wang J, Morrison DJ, Raetz EA, Burke MJ, Brown P, Carroll WL. Epigenetic reprogramming reverses the relapse-specific gene expression signature and restores chemosensitivity in childhood B-lymphoblastic leukemia. *Blood*. 2012;119(22):5201–10. <https://doi.org/10.1182/blood-2012-01-401687>.
- Biondi A, Schrappe M, De Lorenzo P, Castor A, Lucchini G, Gandemer V, Pieters R, Stary J, Escherich G, Campbell M, Li C-K, Vora A, Aricò M, Röttgers S, Saha V, Valsecchi MG. Imatinib after induction for treatment of children and adolescents with Philadelphia-chromosome-positive acute lymphoblastic leukaemia (EsPhALL): a randomised, open-label, intergroup study. *Lancet Oncol*. 2012;13(9):936–45. [https://doi.org/10.1016/S1470-2045\(12\)70377-7](https://doi.org/10.1016/S1470-2045(12)70377-7).
- Biondi A, Valsecchi MG, Seriu T, D'Aniello E, Willemse MJ, Fasching K, Pannunzio A, Gadner H, Schrappe M, Kamps WA, Bartram CR, van Dongen JJ, Panzer-Grumayer ER. Molecular detection of minimal residual disease is a strong predictive factor of relapse in childhood B-lineage acute lymphoblastic leukemia with medium risk features. A case control study of the International BFM study group. *Leukemia*. 2000;14(11):1939–43.
- Borowitz MJ, Devidas M, Hunger SP, Bowman WP, Carroll AJ, Carroll WL, Linda S, Martin PL, Pullen DJ, Viswanatha D, Willman CL, Winick N, Camitta BM. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study. *Blood*. 2008;111(12):5477–85. <https://doi.org/10.1182/blood-2008-01-132837>.
- Borowitz MJ, Wood BL, Devidas M, Loh ML, Raetz EA, Salzer WL, Nachman JB, Carroll AJ, Heerema NA, Gastier-Foster JM, Willman CL, Dai Y, Winick NJ, Hunger SP, Carroll WL, Larsen E. Prognostic signifi-

- cance of minimal residual disease in high risk B-ALL: a report from Children's Oncology Group study AALL0232. *Blood*. 2015;126(8):964–71. <https://doi.org/10.1182/blood-2015-03-633685>.
- Brentjens RJ, Davila ML, Riviere I, Park J, Wang X, Cowell LG, Bartido S, Stefanski J, Taylor C, Olszewska M, Borquez-Ojeda O, Qu J, Wasielewska T, He Q, Bernal Y, Rijo IV, Hedvat C, Kobos R, Curran K, Steinherz P, Jurcic J, Rosenblat T, Maslak P, Frattini M, Sadelain M. CD19-targeted T cells rapidly induce molecular remissions in adults with chemotherapy-refractory acute lymphoblastic leukemia. *Sci Transl Med*. 2013;5(177):177ra138. <https://doi.org/10.1126/scitranslmed.3005930>.
- Burke MJ, Lamba JK, Pounds S, Cao X, Ghodke-Puranaik Y, Lindgren BR, Weigel BJ, Verneris MR, Miller JS. A therapeutic trial of decitabine and vorinostat in combination with chemotherapy for relapsed/refractory acute lymphoblastic leukemia (ALL). *Am J Hematol*. 2014;89(9):889–95. <https://doi.org/10.1002/ajh.23778>.
- Campos-Sanchez E, Toboso-Navasa A, Romero-Camarero I, Barajas-Diego M, Sánchez-García I, Cobaleda C. Acute lymphoblastic leukemia and developmental biology. *Cell Cycle*. 2011;10(20):3473–86. <https://doi.org/10.4161/cc.10.20.17779>.
- Chew E, Filshie R, Wei A. Development of fatal bortezomib induced acute lung injury despite concurrent therapy with high-dose dexamethasone. *Leuk Lymphoma*. 2007;48(1):212–3. <https://doi.org/10.1080/10428190600988010>.
- Clarke S, O'Reilly J, Romeo G, Cooney J. NUP214-ABL1 positive T-cell acute lymphoblastic leukemia patient shows an initial favorable response to imatinib therapy post relapse. *Leuk Res*. 2011;35(7):e131–3. <https://doi.org/10.1016/j.leukres.2011.03.025>.
- Conter V, Bartram CR, Valsecchi MG, Schrauder A, Panzer-Grümayer R, Mörücke A, Aricò M, Zimmermann M, Mann G, De Rossi G, Stanulla M, Locatelli F, Basso G, Niggli F, Barisone E, Henze G, Ludwig W-D, Haas OA, Cazzaniga G, Koehler R, Silvestri D, Bradtke J, Parasole R, Beier R, van Dongen JJM, Biondi A, Schrappe M. Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: results in 3184 patients of the AIEOP-BFM ALL 2000 study. *Blood*. 2010;115(16):3206–14. <https://doi.org/10.1182/blood-2009-10-248146>.
- Conter V, Valsecchi MG, Parasole R, Putti MC, Locatelli F, Barisone E, Lo Nigro L, Santoro N, Aricò M, Ziino O, Pession A, Testi AM, Micalizzi C, Casale F, Zecca M, Casazza G, Tamaro P, La Barba G, Notarangelo LD, Silvestri D, Colombini A, Rizzari C, Biondi A, Masera G, Basso G. Childhood high-risk acute lymphoblastic leukemia in first remission: results after chemotherapy or transplant from the AIEOP ALL 2000 study. *Blood*. 2014;123(10):1470–8.
- Coustan-Smith E, Mullighan CG, Onciu M, Behm FG, Raimondi SC, Pei D, Cheng C, Su X, Rubnitz JE, Basso G, Biondi A, Pui CH, Downing JR, Campana D. Early T-cell precursor leukaemia: a subtype of very high-risk acute lymphoblastic leukaemia. *Lancet Oncol*. 2009;10(2):147–56. [https://doi.org/10.1016/S1470-2045\(08\)70314-0](https://doi.org/10.1016/S1470-2045(08)70314-0).
- Coustan-Smith E, Sancho J, Hancock ML, Boyett JM, Behm FG, Raimondi SC, Sandlund JT, Rivera GK, Rubnitz JE, Ribeiro RC, Pui C-H, Campana D. Clinical importance of minimal residual disease in childhood acute lymphoblastic leukemia. *Blood*. 2000;96(8):2691–6.
- Davila ML, Riviere I, Wang X, Bartido S, Park J, Curran K, Chung SS, Stefanski J, Borquez-Ojeda O, Olszewska M, Qu J, Wasielewska T, He Q, Fink M, Shinglot H, Youssif M, Satter M, Wang Y, Hosey J, Quintanilla H, Halton E, Bernal Y, Bouhassira DCG, Arcila ME, Gonen M, Roboz GJ, Maslak P, Douer D, Frattini MG, Giralt S, Sadelain M, Brentjens R. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. *Sci Transl Med*. 2014;6(224):224ra225. <https://doi.org/10.1126/scitranslmed.3008226>.
- DeAngelo DJ, Stelljes M, Martinelli G, Kantarjian H, Liedtke M, Stock W, Goekbuget N, Wang K, Pacagnella L, Sleight B, Vandendries E, Advani AS. Efficacy and safety of inotuzumab ozogamicin (INO) vs standard of care (SOC) in salvage 1 or 2 patients with acute lymphoblastic leukemia (ALL): An ongoing global phase 3 study. *Haematologica: European hematology association annual meeting abstracts LB2073*. 2015.
- Deenik W, Beverloo HB, van der Poel-van de Luytgaard SC, Wattel MM, van Esser JW, Valk PJ, Cornelissen JJ. Rapid complete cytogenetic remission after upfront dasatinib monotherapy in a patient with a NUP214-ABL1-positive T-cell acute lymphoblastic leukemia. *Leukemia*. 2009;23(3):627–9. <https://doi.org/10.1038/leu.2008.318>.
- Den Boer ML, van Slegtenhorst M, De Menezes RX, Cheok MH, Buijs-Gladdins JG, Peters ST, Van Zutven LJC, Beverloo HB, Van der Spek PJ, Escherich G, Horstmann MA, Janka-Schaub GE, Kamps WA, Evans WE, Pieters R. A subtype of childhood acute lymphoblastic leukaemia with poor treatment outcome: a genome-wide classification study. *Lancet Oncol*. 2009;10(2):125–34. [https://doi.org/10.1016/S1470-2045\(08\)70339-5](https://doi.org/10.1016/S1470-2045(08)70339-5).
- Dreyer ZE, Hilden JM, Jones TL, Devidas M, Winick NJ, Willman CL, Harvey RC, Chen IM, Behm FG, Pullen J, Wood BL, Carroll AJ, Heerema NA, Felix CA, Robinson B, Reaman GH, Salzer WL, Hunger SP, Carroll WL, Camitta BM. Intensified chemotherapy without SCT in infant ALL: results from COG P9407 (Cohort 3). *Pediatr Blood Cancer*. 2015;62(3):419–26. <https://doi.org/10.1002/pbc.25322>.
- Duffner PK, Armstrong FD, Chen L, Helton KJ, Brecher ML, Bell B, Chauvenet AR. Neurocognitive and neuroradiologic central nervous system late effects in children treated on Pediatric Oncology Group (POG) P9605 (standard risk) and P9201 (lesser risk) acute lymphoblastic leukemia protocols (ACCL0131):

- a methotrexate consequence? A report from the Children's Oncology Group. *J Pediatr Hematol Oncol.* 2014;36(1):8–15. <https://doi.org/10.1097/mph.0000000000000000>.
- Dunsmore KP, Devidas M, Linda SB, Borowitz MJ, Winick N, Hunger SP, Carroll WL, Camitta BM. Pilot study of nelarabine in combination with intensive chemotherapy in high-risk t-cell acute lymphoblastic leukemia: a report from the Children's Oncology Group. *J Clin Oncol.* 2012;30(22):2753–9. <https://doi.org/10.1200/jco.2011.40.8724>.
- Eapen M, Raetz E, Zhang MJ, Muehlenbein C, Devidas M, Abshire T, Billett A, Homans A, Camitta B, Carroll WL, Davies SM, Children's Oncology G, Center for International B, Marrow Transplant R. Outcomes after HLA-matched sibling transplantation or chemotherapy in children with B-precursor acute lymphoblastic leukemia in a second remission: a collaborative study of the Children's Oncology Group and the Center for International Blood and Marrow Transplant Research. *Blood.* 2006;107(12):4961–7. <https://doi.org/10.1182/blood-2005-12-4942>.
- Escherich G, Zur-Stadt U, Zimmermann M, Horstmann MA, ALL C. Clofarabine in combination with pegylated asparaginase in the frontline treatment of childhood acute lymphoblastic leukaemia: a feasibility report from the CoALL 08-09 trial. *Br J Haematol.* 2013;163(2):240–7. <https://doi.org/10.1111/bjh.12520>.
- Farber S, Diamond LK, Mercer RD, Sylvester RF, Wolff JA. Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl-glutamic acid (aminopterin). *N Engl J Med.* 1948;238(23):787–93. <https://doi.org/10.1056/NEJM194806032382301>.
- Forestier E, Heyman M, Andersen MK, Autio K, Blennow E, Borgström G, Golovleva I, Heim S, Heinonen K, Hovland R, Johannsson JH, Kerndrup G, Nordgren A, Rosenquist R, Swolin B, Johannsson B, The Nordic Society of Paediatric Haematology OtSCLSG, the NLCSG. Outcome of ETV6/RUNX1-positive childhood acute lymphoblastic leukaemia in the NOPHO-ALL-1992 protocol: frequent late relapses but good overall survival. *Br J Haematol.* 2008;140(6):665–72. <https://doi.org/10.1111/j.1365-2141.2008.06980.x>.
- Gaynon PS, Desai AA, Bostrom BC, Hutchinson RJ, Lange BJ, Nachman JB, Reaman GH, Sather HN, Steinherz PG, Trigg ME, Tubergen DG, Uckun FM. Early response to therapy and outcome in childhood acute lymphoblastic leukemia: a review. *Cancer.* 1997;80(9):1717–26.
- George P, Hernandez K, Hustu O, Borella L, Holton C, Pinkel D. A study of "total therapy" of acute lymphocytic leukemia in children. *J Pediatr.* 1968;72(3):399–408. [https://doi.org/10.1016/S0022-3476\(68\)80217-3](https://doi.org/10.1016/S0022-3476(68)80217-3).
- Grupp SA, Kalos M, Barrett D, Aplenc R, Porter DL, Rheingold SR, Teachey DT, Chew A, Hauck B, Wright JF, Milone MC, Levine BL, June CH. Chimeric antigen receptor–modified T cells for acute lymphoid leukemia. *N Engl J Med.* 2013;368(16):1509–18. <https://doi.org/10.1056/NEJMoa1215134>.
- Grupp SA, Maude SL, Shaw PA, Aplenc R, Barrett DM, Callahan C, Lacey SF, Levine BL, Melenhorst JJ, Motley L, Rheingold SR, Teachey DT, Wood PA, Porter D, June CH. Durable remissions in children with relapsed/refractory ALL treated with T cells engineered with a CD19-targeted chimeric antigen receptor (CTL019). *Blood.* 2015;126(23):681.
- Harewood L, Robinson H, Harris R, Al-Obaidi MJ, Jalali GR, Martineau M, Moorman AV, Sumption N, Richards S, Mitchell C, Harrison CJ. Amplification of AML1 on a duplicated chromosome 21 in acute lymphoblastic leukemia: a study of 20 cases. *Leukemia.* 2003;17(3):547–53.
- Harrison CJ, Haas O, Harbott J, Biondi A, Stanulla M, Trka J, Izraeli S, Biology, Diagnosis Committee of International Berlin-Frankfurt-Munster Study Group. Detection of prognostically relevant genetic abnormalities in childhood B-cell precursor acute lymphoblastic leukaemia: recommendations from the Biology and Diagnosis Committee of the International Berlin-Frankfurt-Munster study group. *Br J Haematol.* 2010;151(2):132–42. <https://doi.org/10.1111/j.1365-2141.2010.08314.x>.
- Harrison CJ, Moorman AV, Broadfield ZJ, Cheung KL, Harris RL, Reza Jalali G, Robinson HM, Barber KE, Richards SM, Mitchell CD, Eden TOB, Hann IM, Hill FGH, Kinsey SE, Gibson BES, Lilleyman J, Vora A, Goldstone AH, Franklin IM, Durrant J, Martineau M, Childhood, Adult Leukaemia Working P. Three distinct subgroups of hypodiploidy in acute lymphoblastic leukaemia. *Br J Haematol.* 2004;125(5):552–9. <https://doi.org/10.1111/j.1365-2141.2004.04948.x>.
- Harrison CJ, Moorman AV, Schwab C, Carroll AJ, Raetz EA, Devidas M, Strehl S, Nebral K, Harbott J, Teigler-Schlegel A, Zimmerman M, Dastuge N, Baruchel A, Soulier J, Auclerc MF, Attarbaschi A, Mann G, Stark B, Cazzaniga G, Chilton L, Vandenbergh P, Forestier E, Haltrich I, Raimondi SC, Parihar M, Bourquin JP, Tchinda J, Haferlach C, Vora A, Hunger SP, Heerema NA, Haas OA. An international study of intrachromosomal amplification of chromosome 21 (iAMP21): cytogenetic characterization and outcome. *Leukemia.* 2014;28(5):1015–21. <https://doi.org/10.1038/leu.2013.317>.
- Harvey RC, Mullighan CG, Chen IM, Wharton W, Mikhail FM, Carroll AJ, Kang H, Liu W, Dobbin KK, Smith MA, Carroll WL, Devidas M, Bowman WP, Camitta BM, Reaman GH, Hunger SP, Downing JR, Willman CL. Rearrangement of CRLF2 is associated with mutation of JAK kinases, alteration of IKZF1, Hispanic/Latino ethnicity, and a poor outcome in pediatric B-progenitor acute lymphoblastic leukemia. *Blood.* 2010a;115(26):5312–21. doi:blood-2009-09-245944 [pii] 1182/blood-2009-09-245944
- Harvey RC, Mullighan CG, Wang X, Dobbin KK, Davidson GS, Bedrick EJ, Chen IM, Atlas SR, Kang H, Ar K, Wilson CS, Wharton W, Murphy M, Devidas M, Carroll AJ, Borowitz MJ, Bowman WP,

- Downing JR, Relling M, Yang J, Bhojwani D, Carroll WL, Camitta B, Reaman GH, Smith M, Hunger SP, Willman CL. Identification of novel cluster groups in pediatric high-risk B-precursor acute lymphoblastic leukemia with gene expression profiling: correlation with genome-wide DNA copy number alterations, clinical characteristics, and outcome. *Blood*. 2010b;116(23):4874–84. doi:blood-2009-08-239681 [pii] 1182/blood-2009-08-239681
- Heerema NA, Carroll AJ, Devidas M, Loh ML, Borowitz MJ, Gastier-Foster JM, Larsen EC, Mattano LA, Maloney KW, Willman CL, Wood BL, Winick NJ, Carroll WL, Hunger SP, Raetz EA. Intrachromosomal amplification of chromosome 21 is associated with inferior outcomes in children with acute lymphoblastic leukemia treated in contemporary standard-risk Children's Oncology Group studies: a report from the Children's Oncology Group. *J Clin Oncol*. 2013;31(27):3397–402. <https://doi.org/10.1200/jco.2013.49.1308>.
- Heerema NA, Nachman JB, Sather HN, SENSEL MG, Lee MK, Hutchinson R, Lange BJ, Steinherz PG, Bostrom B, Gaynon PS, Uckun F. Hypodiploidy with less than 45 chromosomes confers adverse risk in childhood acute lymphoblastic leukemia: a report from the children's cancer group. *Blood*. 1999;94(12):4036–45.
- Hijiya N, Barry E, Arceci RJ. Clofarabine in pediatric acute leukemia: current findings and issues. *Pediatr Blood Cancer*. 2012;59(3):417–22. <https://doi.org/10.1002/pbc.24112>.
- Hijiya N, Gaynon P, Barry E, Silverman L, Thomson B, Chu R, Cooper T, Kadota R, Rytting M, Steinherz P, Shen V, Jeha S, Abichandani R, Carroll WL. A multi-center phase I study of clofarabine, etoposide and cyclophosphamide in combination in pediatric patients with refractory or relapsed acute leukemia. *Leukemia*. 2009;23(12):2259–64.
- Hijiya N, Thomson B, Isakoff MS, Silverman LB, Steinherz PG, Borowitz MJ, Kadota R, Cooper T, Shen V, Dahl G, Thottassery JV, Jeha S, Maloney K, Paul J-A, Barry E, Carroll WL, Gaynon PS. Phase 2 trial of clofarabine in combination with etoposide and cyclophosphamide in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. *Blood*. 2011;118(23):6043–9. <https://doi.org/10.1182/blood-2011-08-374710>.
- Hoffman L, Gore L. Blinatumomab, a bispecific anti-CD19/CD3 BiTE[®] antibody for the treatment of acute lymphoblastic leukemia: perspectives and current pediatric applications. *Front Oncol*. 2014;4:63.
- Holmfeldt L, Wei L, Diaz-Flores E, Walsh M, Zhang J, Ding L, Payne-Turner D, Churchman M, Andersson A, Chen SC, McCastlain K, Becksfors J, Ma J, Wu G, Patel SN, Heatley SL, Phillips LA, Song G, Easton J, Parker M, Chen X, Rusch M, Boggs K, Vadodaria B, Hedlund E, Drenberg C, Baker S, Pei D, Cheng C, Huether R, Lu C, Fulton RS, Fulton LL, Tabib Y, Dooling DJ, Ochoa K, Minden M, Lewis ID, To LB, Marlton P, Roberts AW, Raca G, Stock W, Neale G, Drexler HG, Dickins RA, Ellison DW, Shurtleff SA, Pui CH, Ribeiro RC, Devidas M, Carroll AJ, Heerema NA, Wood B, Borowitz MJ, Gastier-Foster JM, Raimondi SC, Mardis ER, Wilson RK, Downing JR, Hunger SP, Loh ML, Mullighan CG. The genomic landscape of hypodiploid acute lymphoblastic leukemia. *Nat Genet*. 2013;45(3):242–52. <https://doi.org/10.1038/ng.2532>.
- Horton TM, Gannavarapu A, Blaney SM, D'Argenio DZ, Plon SE, Berg SL. Bortezomib interactions with chemotherapy agents in acute leukemia in vitro. *Cancer Chemother Pharmacol*. 2006;58(1):13–23. <https://doi.org/10.1007/s00280-005-0135-z>.
- Horton TM, Pati D, Plon SE, Thompson PA, Bomgaars LR, Adamson PC, Ingle AM, Wright J, Brockman AH, Paton M, Blaney SM. A phase I study of the proteasome inhibitor bortezomib in pediatric patients with refractory leukemia: a Children's Oncology Group study. *Clin Cancer Res*. 2007;13(5):1516–22. <https://doi.org/10.1158/1078-0432.ccr-06-2173>.
- Hunger SP. Chromosomal translocations involving the E2A gene in acute lymphoblastic leukemia: clinical features and molecular pathogenesis. *Blood*. 1996;87(4):1211–24.
- Hunger SP, Galili N, Carroll AJ, Crist WM, Link MP, Cleary ML. The t(1;19)(q23;p13) results in consistent fusion of E2A and PBX1 coding sequences in acute lymphoblastic leukemias. *Blood*. 1991;77(4):687–93.
- Hunger SP, Lu X, Devidas M, Camitta BM, Gaynon PS, Winick NJ, Reaman GH, Carroll WL. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the Children's Oncology Group. *J Clin Oncol*. 2012;30(14):1663–9. <https://doi.org/10.1200/jco.2011.37.8018>.
- Hunger SP, Mullighan CG. Acute lymphoblastic leukemia in children. *N Engl J Med*. 2015a;373(16):1541–52. <https://doi.org/10.1056/NEJMra1400972>.
- Hunger SP, Mullighan CG. Redefining ALL classification: toward detecting high-risk ALL and implementing precision medicine. *Blood*. 2015b;125(26):3977–87.
- Hunger SP, Ohyashiki K, Toyama K, Cleary ML. Hlf, a novel hepatic bZIP protein, shows altered DNA-binding properties following fusion to E2A in t(17;19) acute lymphoblastic leukemia. *Genes Dev*. 1992;6(9):1608–20. <https://doi.org/10.1101/gad.6.9.1608>.
- Jeha S, Gaynon PS, Razzouk BI, Franklin J, Kadota R, Shen V, Luchtman-Jones L, Rytting M, Bomgaars LR, Rheingold S, Ritchey K, Albano E, Arceci RJ, Goldman S, Griffin T, Altman A, Gordon B, Steinherz L, Weitman S, Steinherz P. Phase II study of clofarabine in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. *J Clin Oncol*. 2006;24(12):1917–23. <https://doi.org/10.1200/jco.2005.03.8554>.
- Kadan-Lottick NS, Ness KK, Bhatia S, Gurney JG. Survival variability by race and ethnicity in childhood acute lymphoblastic leukemia. *JAMA*. 2003;290(15):2008–14. <https://doi.org/10.1001/jama.290.15.2008>.

- Kantarjian H, Thomas D, Jorgensen J, Jabbour E, Kebriaei P, Rytting M, York S, Ravandi F, Kwari M, Faderl S, Rios MB, Cortes J, Fayad L, Tarnai R, Wang SA, Champlin R, Advani A, O'Brien S. Inotuzumab ozogamicin, an anti-CD22–calicheamicin conjugate, for refractory and relapsed acute lymphocytic leukaemia: a phase 2 study. *Lancet Oncol.* 2012;13(4):403–11. [https://doi.org/10.1016/S1470-2045\(11\)70386-2](https://doi.org/10.1016/S1470-2045(11)70386-2).
- Kantarjian H, Thomas D, Jorgensen J, Kebriaei P, Jabbour E, Rytting M, York S, Ravandi F, Garris R, Kwari M, Faderl S, Cortes J, Champlin R, O'Brien S. Results of inotuzumab ozogamicin, a CD22 monoclonal antibody, in refractory and relapsed acute lymphocytic leukemia. *Cancer.* 2013;119(15):2728–36. <https://doi.org/10.1002/ncr.28136>.
- Krivtsov AV, Armstrong SA. MLL translocations, histone modifications and leukaemia stem-cell development. *Nat Rev Cancer.* 2007;7(11):823–33.
- Krull KR, Brinkman TM, Li C, Armstrong GT, Ness KK, Srivastava DK, Gurney JG, Kimberg C, Krasin MJ, Pui C-H, Robison LL, Hudson MM. Neurocognitive outcomes decades after treatment for childhood acute lymphoblastic leukemia: a report from the St Jude Lifetime Cohort Study. *J Clin Oncol.* 2013;31(35):4407–15. <https://doi.org/10.1200/jco.2012.48.2315>.
- Kurtzberg J, Ernst TJ, Keating MJ, Gandhi V, Hodge JP, Kisor DF, Lager JJ, Stephens C, Levin J, Krenitsky T, Elion G, Mitchell BS. Phase I study of 506U78 administered on a consecutive 5-day schedule in children and adults with refractory hematologic malignancies. *J Clin Oncol.* 2005;23(15):3396–403. <https://doi.org/10.1200/jco.2005.03.199>.
- Lauten M, Möricke A, Beier R, Zimmermann M, Stanulla M, Meissner B, Odenwald E, Attarbaschi A, Niemeyer C, Niggli F, Riehm H, Schrappe M. Prediction of outcome by early bone marrow response in childhood acute lymphoblastic leukemia treated in the ALL-BFM 95 trial: differential effects in precursor B-cell and T-cell leukemia. *Haematologica.* 2012;97(7):1048–56. <https://doi.org/10.3324/haematol.2011.047613>.
- LeBien TW. Fates of human B-cell precursors. *Blood.* 2000;96(1):9–23.
- Lee DW, Kochenderfer JN, Stetler-Stevenson M, Cui YK, Delbrook C, Feldman SA, Fry TJ, Orentas R, Sabatino M, Shah NN, Steinberg SM, Stronck D, Tschernia N, Yuan C, Zhang H, Zhang L, Rosenberg SA, Wayne AS, Mackall CL. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. *Lancet.* 2014. [https://doi.org/10.1016/S0140-6736\(14\)61403-3](https://doi.org/10.1016/S0140-6736(14)61403-3).
- Linabery AM, Ross JA. Trends in childhood cancer incidence in the U.S. (1992–2004). *Cancer.* 2008;112(2):416–32. <https://doi.org/10.1002/ncr.23169>.
- Locatelli F, Testi AM, Bernardo ME, Rizzari C, Bertaina A, Merli P, Pession A, Giraldi E, Parasole R, Barberi W, Zecca M. Clofarabine, cyclophosphamide and etoposide as single-course re-induction therapy for children with refractory/multiple relapsed acute lymphoblastic leukaemia. *Br J Haematol.* 2009;147(3):371–8. <https://doi.org/10.1111/j.1365-2141.2009.07882.x>.
- Loh ML, Zhang J, Harvey RC, Roberts K, Payne-Turner D, Kang H, Wu G, Chen X, Becksfort J, Edmonson M, Buetow KH, Carroll WL, Chen IM, Wood B, Borowitz MJ, Devidas M, Gerhard DS, Bowman P, Larsen E, Winick N, Raetz E, Smith M, Downing JR, Willman CL, Mullighan CG, Hunger SP. Tyrosine kinase sequencing of pediatric acute lymphoblastic leukemia: a report from the Children's Oncology Group TARGET Project. *Blood.* 2013;121(3):485–8.
- Ma X, Edmonson M, Yergeau D, Muzny DM, Hampton OA, Rusch M, Song G, Easton J, Harvey RC, Wheeler DA, Ma J, Doddapaneni H, Vadodaria B, Wu G, Nagahawatte P, Carroll WL, Chen IM, Gastier-Foster JM, Relling MV, Smith MA, Devidas M, Auvil JMG, Downing JR, Loh ML, Willman CL, Gerhard DS, Mullighan CG, Hunger SP, Zhang J. Rise and fall of subclones from diagnosis to relapse in pediatric B-acute lymphoblastic leukaemia. *Nat Commun.* 2015;6. <https://doi.org/10.1038/ncomms7604>.
- Maude SL, Barrett D, Teachey DT, Grupp SA. Managing cytokine release syndrome associated with novel T cell-engaging therapies. *Cancer J.* 2014a;20(2):119–22. <https://doi.org/10.1097/PPO.0000000000000035>.
- Maude SL, Dolai S, Delgado-Martin C, Vincent T, Robbins A, Selvanathan A, Ryan T, Hall J, Wood AC, Tasian SK, Hunger SP, Loh ML, Mullighan CG, Wood BL, Hermiston ML, Grupp SA, Lock RB, Teachey DT. Efficacy of JAK/STAT pathway inhibition in murine xenograft models of early T-cell precursor (ETP) acute lymphoblastic leukemia. *Blood.* 2015;125(11):1759–67. <https://doi.org/10.1182/blood-2014-06-580480>.
- Maude SL, Frey N, Shaw PA, Aplenc R, Barrett DM, Bunin NJ, Chew A, Gonzalez VE, Zheng Z, Lacey SF, Mahnke YD, Melenhorst JJ, Rheingold SR, Shen A, Teachey DT, Levine BL, June CH, Porter DL, Grupp SA. Chimeric antigen receptor T cells for sustained remissions in leukemia. *N Engl J Med.* 2014b;371(16):1507–17. <https://doi.org/10.1056/NEJMoa1407222>.
- Messinger YH, Gaynon PS, Sposto R, van der Giessen J, Eckroth E, Malvar J, Bostrom BC. Bortezomib with chemotherapy is highly active in advanced B-precursor acute lymphoblastic leukemia: therapeutic advances in childhood leukemia & lymphoma (TACL) study. *Blood.* 2012;120(2):285–90. <https://doi.org/10.1182/blood-2012-04-418640>.
- Miller DR, Leikin S, Albo V, Sather H, Karon M, Hammond D. Prognostic factors and therapy in acute lymphoblastic leukemia of childhood: CCG-141: a report from children's cancer study group. *Cancer.* 1983;51(6):1041–9. [https://doi.org/10.1002/1097-0142\(19830315\)51:6<1041::AID-CNCR2820510612>3.0.CO;2-G](https://doi.org/10.1002/1097-0142(19830315)51:6<1041::AID-CNCR2820510612>3.0.CO;2-G).
- Moorman AV, Ensor HM, Richards SM, Chilton L, Schwab C, Kinsey SE, Vora A, Mitchell CD, Harrison CJ. Prognostic effect of chromosomal abnormali-

- ties in childhood B-cell precursor acute lymphoblastic leukaemia: results from the UK Medical Research Council ALL97/99 randomised trial. *Lancet Oncol.* 2010;11(5):429–38. [https://doi.org/10.1016/S1470-2045\(10\)70066-8](https://doi.org/10.1016/S1470-2045(10)70066-8).
- Minson KA, Prasad P, Vear S, Borinstein S, Ho R, Domm J, Frangoul H. T(17;19) in children with acute lymphocytic leukemia: a report of 3 cases and a review of the literature. *Case Rep Hematol.* 2013;2013:563291.
- Miyakoshi S, Kami M, Yuji K, Matsumura T, Takatoku M, Sasaki M, Narimatsu H, Fujii T, Kawabata M, Taniguchi S, Ozawa K, Oshimi K. Severe pulmonary complications in Japanese patients after bortezomib treatment for refractory multiple myeloma. *Blood.* 2006;107(9):3492–4. <https://doi.org/10.1182/blood-2005-11-4541>.
- Moorman AV, Robinson H, Schwab C, Richards SM, Hancock J, Mitchell CD, Goulden N, Vora A, Harrison CJ. Risk-directed treatment intensification significantly reduces the risk of relapse among children and adolescents with acute lymphoblastic leukemia and intrachromosomal amplification of chromosome 21: a comparison of the MRC ALL97/99 and UKALL2003 trials. *J Clin Oncol.* 2013;31(27):3389–96. <https://doi.org/10.1200/jco.2013.48.9377>.
- Mullighan CG, Collins-Underwood JR, Phillips LA, Loudin MG, Liu W, Zhang J, Ma J, Coustan-Smith E, Harvey RC, Willman CL, Mikhail FM, Meyer J, Carroll AJ, Williams RT, Cheng J, Heerema NA, Basso G, Pession A, Pui CH, Raimondi SC, Hunger SP, Downing JR, Carroll WL, Rabin KR. Rearrangement of CRLF2 in B-progenitor- and Down syndrome-associated acute lymphoblastic leukemia. *Nat Genet.* 2009a;41(11):1243–6. doi:ng.469 [pii] 1038/ng.469
- Mullighan CG, Su X, Zhang J, Radtke I, Phillips LA, Miller CB, Ma J, Liu W, Cheng C, Schulman BA, Harvey RC, Chen IM, Clifford RJ, Carroll WL, Reaman G, Bowman WP, Devidas M, Gerhard DS, Yang W, Relling MV, Shurtleff SA, Campana D, Borowitz MJ, Pui CH, Smith M, Hunger SP, Willman CL, Downing JR. Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. *N Engl J Med.* 2009b;360(5):470–80. 1056/NEJMoa0808253
- Mullighan CG, Zhang J, Harvey RC, Collins-Underwood JR, Schulman BA, Phillips LA, Tasian SK, Loh ML, Su X, Liu W, Devidas M, Atlas SR, Chen IM, Clifford RJ, Gerhard DS, Carroll WL, Reaman GH, Smith M, Downing JR, Hunger SP, Willman CL. JAK mutations in high-risk childhood acute lymphoblastic leukemia. *Proc Natl Acad Sci U S A.* 2009c;106(23):9414–8. <https://doi.org/10.1073/pnas.0811761106>.
- Nachman JB, Heerema NA, Sather H, Camitta B, Forestier E, Harrison CJ, Dastugue N, Schrappe M, Pui CH, Basso G, Silverman LB, Janka-Schaub GE. Outcome of treatment in children with hypodiploid acute lymphoblastic leukemia. *Blood.* 2007;110(4):1112–5. <https://doi.org/10.1182/blood-2006-07-038299>.
- Nagorsen D, Kufer P, Baeuerle PA, Bargou R. Blinatumomab: a historical perspective. *Pharmacol Ther.* 2012;136(3):334–42. <https://doi.org/10.1016/j.pharmthera.2012.07.013>.
- Nelken B, Cave H, Leverger G, Galambrun C, Plat G, Schmitt C, Thomas C, V  rit   C, Brethon B, Gandemer V, Bertrand Y, Baruchel A, Rohrlrich P. A phase I study of clofarabine with multiagent chemotherapy in childhood high risk relapse of acute lymphoblastic leukemia (VANDEVOL study of the French SFCE Acute Leukemia Committee). *Pediatr Blood Cancer.* 2016;63(2):270–5. <https://doi.org/10.1002/pbc.25751>.
- Nguyen K, Devidas M, Cheng SC, La M, Raetz EA, Carroll WL, Winick NJ, Hunger SP, Gaynon PS, Loh ML. Factors influencing survival after relapse from acute lymphoblastic leukemia: a Children's Oncology Group study. *Leukemia.* 2008;22(12):2142–50.
- Patrick K, Vora A. Update on biology and treatment of T-cell acute lymphoblastic leukaemia. *Curr Opin Pediatr.* 2015;27(1):44–9. <https://doi.org/10.1097/mop.0000000000000171>.
- Paulsson K, Forestier E, Andersen MK, Autio K, Barbany G, Borgstr  m G, Cavelier L, Golovleva I, Heim S, Heinonen K, Hovland R, Johannsson JH, Kjeldsen E, Nordgren A, Palmqvist L, Johannsson B. High modal number and triple trisomies are highly correlated favorable factors in childhood B-cell precursor high hyperdiploid acute lymphoblastic leukemia treated according to the NOPHO ALL 1992/2000 protocols. *Haematologica.* 2013;98(9):1424–32. <https://doi.org/10.3324/haematol.2013.085852>.
- Paulsson K, Johannsson B. High hyperdiploid childhood acute lymphoblastic leukemia. *Genes Chromosomes Cancer.* 2009;48(8):637–60. <https://doi.org/10.1002/gcc.20671>.
- Paulsson K, Lilljebjorn H, Biloglav A, Olsson L, Rissler M, Castor A, Barbany G, Fogelstrand L, Nordgren A, Sjogren H, Fioretos T, Johannsson B. The genomic landscape of high hyperdiploid childhood acute lymphoblastic leukemia. *Nat Genet.* 2015;47(6):672–6. <https://doi.org/10.1038/ng.3301>.
- Peters C, Schrappe M, von Stackelberg A, Schrauder A, Bader P, Ebell W, Lang P, Sykora K-W, Schrum J, Kremens B, Ehlert K, Albert MH, Meisel R, Matthes-Martin S, Gungor T, Holter W, Strahm B, Gruhn B, Schulz A, Woessmann W, Poetschger U, Zimmermann M, Klingebiel T. Stem-cell transplantation in children with acute lymphoblastic leukemia: a prospective international multicenter trial comparing sibling donors with matched unrelated donors—the ALL-SCT-BFM-2003 trial. *J Clin Oncol.* 2015;33(11):1265–74.
- Pieters R, Schrappe M, De Lorenzo P, Hann I, De Rossi G, Felice M, Hovi L, LeBlanc T, Szczepanski T, Ferster A, Janka G, Rubnitz J, Silverman L, Stary J, Campbell M, Li CK, Mann G, Suppiah R, Biondi A, Vora A, Valsecchi MG. A treatment protocol for infants younger than 1 year with acute lymphoblastic leukaemia (Interfant-99): an observational study and a multicentre randomised trial. *Lancet.* 2007;370(9583):240–50. [https://doi.org/10.1016/S0140-6736\(07\)61126-X](https://doi.org/10.1016/S0140-6736(07)61126-X).

- Pui C-H, Campana D, Pei D, Bowman WP, Sandlund JT, Kaste SC, Ribeiro RC, Rubnitz JE, Raimondi SC, Onciu M, Coustan-Smith E, Kun LE, Jeha S, Cheng C, Howard SC, Simmons V, Bayles A, Metzger ML, Boyett JM, Leung W, Handgretinger R, Downing JR, Evans WE, Relling MV. Treating childhood acute lymphoblastic leukemia without cranial irradiation. *N Engl J Med.* 2009;360(26):2730–41. <https://doi.org/10.1056/NEJMoa0900386>.
- Pui C-H, Yang JJ, Hunger SP, Pieters R, Schrappe M, Biondi A, Vora A, Baruchel A, Silverman LB, Schmiegelow K, Escherich G, Horibe K, Benoit YCM, Izraeli S, Yeoh AEJ, Liang D-C, Downing JR, Evans WE, Relling MV, Mullighan CG. Childhood acute lymphoblastic leukemia: progress through collaboration. *J Clin Oncol.* 2015;33(27):2938–48. <https://doi.org/10.1200/jco.2014.59.1636>.
- Pui CH, Carroll AJ, Raimondi SC, Land VJ, Crist WM, Shuster JJ, Williams DL, Pullen DJ, Borowitz MJ, Behm FG, et al. Clinical presentation, karyotypic characterization, and treatment outcome of childhood acute lymphoblastic leukemia with a near-haploid or hypodiploid less than 45 line. *Blood.* 1990;75(5):1170–7.
- Pui CH, Chessells JM, Camitta B, Baruchel A, Biondi A, Boyett JM, Carroll A, Eden OB, Evans WE, Gardner H, Harbott J, Harms DO, Harrison CJ, Harrison PL, Heerema N, Janka-Schaub G, Kamps W, Masera G, Pullen J, Raimondi SC, Richards S, Riehm H, Sallan S, Sather H, Shuster J, Silverman LB, Valsecchi MG, Vilmer E, Zhou Y, Gaynon PS, Schrappe M. Clinical heterogeneity in childhood acute lymphoblastic leukemia with 11q23 rearrangements. *Leukemia.* 2003;17(4):700–6.
- Pui CH, Williams DL, Raimondi SC, Rivera GK, Look AT, Dodge RK, George SL, Behm FG, Crist WM, Murphy SB. Hypodiploidy is associated with a poor prognosis in childhood acute lymphoblastic leukemia. *Blood.* 1987;70(1):247–53.
- Pulsipher MA, Langholz B, Wall DA, Schultz KR, Bunin N, Carroll WL, Raetz E, Gardner S, Gastier-Foster JM, Howrie D, Goyal RK, Douglas JG, Borowitz M, Barnes Y, Teachey DT, Taylor C, Grupp SA. The addition of sirolimus to tacrolimus/methotrexate GVHD prophylaxis in children with ALL: a phase 3 Children's Oncology Group/Pediatric Blood and Marrow Transplant Consortium trial. *Blood.* 2014;123(13):2017–25.
- Raetz EA, Bhatla T. Where do we stand in the treatment of relapsed acute lymphoblastic leukemia? *ASH Educ Program Book.* 2012;2012(1):129–36. <https://doi.org/10.1182/asheducation-2012.1.129>.
- Raimondi SC, Zhou Y, Mathew S, Shurtleff SA, Sandlund JT, Rivera GK, Behm FG, Pui C-H. Reassessment of the prognostic significance of hypodiploidy in pediatric patients with acute lymphoblastic leukemia. *Cancer.* 2003;98(12):2715–22. <https://doi.org/10.1002/cncr.11841>.
- Richardson PG, Sonneveld P, Schuster MW, Stadtmauer EA, Facon T, Harousseau JL, Ben-Yehuda D, Lonial S, Goldschmidt H, Reece D, Blade J, Boccadoro M, Cavenagh JD, Boral AL, Esseltine DL, Wen PY, Amato AA, Anderson KC, San Miguel J. Reversibility of symptomatic peripheral neuropathy with bortezomib in the phase III APEX trial in relapsed multiple myeloma: impact of a dose-modification guideline. *Br J Haematol.* 2009;144(6):895–903. <https://doi.org/10.1111/j.1365-2141.2008.07573.x>.
- Ries L, Smith M, Gurney J, et al. Cancer incidence and survival among children and adolescents: United States SEER Program 1975–1995. SEER Program. Bethesda, MD: National Cancer Institute; 1999.
- Roberts KG, Li Y, Payne-Turner D, Harvey RC, Yang Y-L, Pei D, McCastlain K, Ding L, Lu C, Song G, Ma J, Becksfort J, Rusch M, Chen S-C, Easton J, Cheng J, Boggs K, Santiago-Morales N, Iacobucci I, Fulton RS, Wen J, Valentine M, Cheng C, Paugh SW, Devidas M, Chen I-M, Reshmi S, Smith A, Hedlund E, Gupta P, Nagahawatte P, Wu G, Chen X, Yergeau D, Vadodaria B, Mulder H, Winick NJ, Larsen EC, Carroll WL, Heerema NA, Carroll AJ, Grayson G, Tasian SK, Moore AS, Keller F, Frei-Jones M, Whitlock JA, Raetz EA, White DL, Hughes TP, Guidry Auvil JM, Smith MA, Marcucci G, Bloomfield CD, Mrózek K, Kohlschmidt J, Stock W, Kornblau SM, Konopleva M, Paietta E, Pui C-H, Jeha S, Relling MV, Evans WE, Gerhard DS, Gastier-Foster JM, Mardis E, Wilson RK, Loh ML, Downing JR, Hunger SP, Willman CL, Zhang J, Mullighan CG. Targetable kinase-activating lesions in ph-like acute lymphoblastic leukemia. *N Engl J Med.* 2014;371(11):1005–15. <https://doi.org/10.1056/NEJMoa1403088>.
- Roberts KG, Morin RD, Zhang J, Hirst M, Zhao Y, Su X, Chen SC, Payne-Turner D, Churchman ML, Harvey RC, Chen X, Kasap C, Yan C, Becksfort J, Finney RP, Teachey DT, Maude SL, Tse K, Moore R, Jones S, Mungall K, Birol I, Edmonson MN, Hu Y, Buetow KE, Chen IM, Carroll WL, Wei L, Ma J, Kleppe M, Levine RL, Garcia-Manero G, Larsen E, Shah NP, Devidas M, Reaman G, Smith M, Paugh SW, Evans WE, Grupp SA, Jeha S, Pui CH, Gerhard DS, Downing JR, Willman CL, Loh M, Hunger SP, Marra MA, Mullighan CG. Genetic alterations activating kinase and cytokine receptor signaling in high-risk acute lymphoblastic leukemia. *Cancer Cell.* 2012;22(2):153–66. [1016/j.ccr.2012.06.005](https://doi.org/10.1016/j.ccr.2012.06.005)
- Russell LJ, Capasso M, Vater I, Akasaka T, Bernard OA, Calasanz MJ, Chandrasekaran T, Chapiro E, Gesk S, Griffiths M, Guttery DS, Haferlach C, Harder L, Heidenreich O, Irving J, Kearney L, Nguyen-Khac F, Machado L, Minto L, Majid A, Moorman AV, Morrison H, Rand V, Strefford JC, Schwab C, Tonnies H, Dyer MJ, Siebert R, Harrison CJ. Deregulated expression of cytokine receptor gene, CRLF2, is involved in lymphoid transformation in B-cell precursor acute lymphoblastic leukemia. *Blood.* 2009;114(13):2688–98. doi:blood-2009-03-208397 [pii] 1182/blood-2009-03-208397
- Schafer E, Irizarry R, Negi S, McIntyre E, Small D, Figueroa ME, Melnick A, Brown P. Promoter hypermethylation in MLL-r infant acute lymphoblastic

- leukemia: biology and therapeutic targeting. *Blood*. 2010;115(23):4798–809. <https://doi.org/10.1182/blood-2009-09-243634>.
- Schrappe M, Reiter A, Zimmermann M, Harbott J, Ludwig WD, Henze G, Gadner H, Odenwald E, Riehm H. Long-term results of four consecutive trials in childhood ALL performed by the ALL-BFM study group from 1981 to 1995. Berlin-Frankfurt-Munster. *Leukemia*. 2000;14(12):2205–22.
- Schrappe M, Valsecchi MG, Bartram CR, Schrauder A, Panzer-Grümayer R, Möricke A, Parasole R, Zimmermann M, Dworzak M, Buldini B, Reiter A, Basso G, Klingebiel T, Messina C, Ratei R, Cazzaniga G, Koehler R, Locatelli F, Schäfer BW, Aricò M, Welte K, van Dongen JJM, Gadner H, Biondi A, Conter V. Late MRD response determines relapse risk overall and in subsets of childhood T-cell ALL: results of the AIEOP-BFM-ALL 2000 study. *Blood*. 2011;118(8):2077–84. <https://doi.org/10.1182/blood-2011-03-338707>.
- Schultz KR, Bowman WP, Aledo A, Slayton WB, Sather H, Devidas M, Wang C, Davies SM, Gaynon PS, Trigg M, Rutledge R, Burden L, Jorstad D, Carroll A, Heerema NA, Winick N, Borowitz MJ, Hunger SP, Carroll WL, Camitta B. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a children's oncology group study. *J Clin Oncol Off J Am Soc Clin Oncol*. 2009;27(31):5175–81.
- Schultz KR, Carroll A, Heerema NA, Bowman WP, Aledo A, Slayton WB, Sather H, Devidas M, Zheng HW, Davies SM, Gaynon PS, Trigg M, Rutledge R, Jorstad D, Winick N, Borowitz MJ, Hunger SP, Carroll WL, Camitta B, Children's Oncology G. Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: Children's Oncology Group study AALL0031. *Leukemia*. 2014;28(7):1467–71. <https://doi.org/10.1038/leu.2014.30>.
- Schultz KR, Pullen DJ, Sather HN, Shuster JJ, Devidas M, Borowitz MJ, Carroll AJ, Heerema NA, Rubnitz JE, Loh ML, Raetz EA, Winick NJ, Hunger SP, Carroll WL, Gaynon PS, Camitta BM. Risk- and response-based classification of childhood B-precursor acute lymphoblastic leukemia: a combined analysis of prognostic markers from the Pediatric Oncology Group (POG) and Children's Cancer Group (CCG). *Blood*. 2007;109(3):926–35. <https://doi.org/10.1182/blood-2006-01-024729>.
- Smith M, Arthur D, Camitta B, Carroll AJ, Crist W, Gaynon P, Gelber R, Heerema N, Korn EL, Link M, Murphy S, Pui CH, Pullen J, Reamon G, Sallan SE, Sather H, Shuster J, Simon R, Trigg M, Tullberg D, Uckun F, Ungerleider R. Uniform approach to risk classification and treatment assignment for children with acute lymphoblastic leukemia. *J Clin Oncol*. 1996;14(1):18–24.
- Smith MA, Seibel NL, Altekruse SF, Ries LAG, Melbert DL, O'Leary M, Smith FO, Reaman GH. Outcomes for children and adolescents with cancer: challenges for the twenty-first century. *J Clin Oncol*. 2010;28(15):2625–34. <https://doi.org/10.1200/jco.2009.27.0421>.
- Soulier J, Trakhtenbrot L, Najfeld V, Lipton JM, Mathew S, Avet-Loiseau H, De Braekeleer M, Salem S, Baruchel A, Raimondi SC, Raynaud SD. Amplification of band q22 of chromosome 21, including AML1, in older children with acute lymphoblastic leukemia: an emerging molecular cytogenetic subgroup. *Leukemia*. 2003;17(8):1679–82.
- Sary J, Zimmermann M, Campbell M, Castillo L, Dibarc E, Donska S, Gonzalez A, Izraeli S, Janic D, Jazbec J, Konja J, Kaiserova E, Kowalczyk J, Kovacs G, Li C-K, Magyarosy E, Popa A, Stark B, Jabali Y, Trka J, Hrusak O, Riehm H, Masera G, Schrappe M. Intensive chemotherapy for childhood acute lymphoblastic leukemia: results of the randomized intercontinental trial ALL IC-BFM 2002. *J Clin Oncol*. 2014;32(3):174–84. <https://doi.org/10.1200/jco.2013.48.6522>.
- Stumpel DJPM, Schotte D, Lange-Turenhout EAM, Schneider P, Seslija L, de Menezes RX, Marquez VE, Pieters R, den Boer ML, Stam RW (2011) Hypermethylation of specific microRNA genes in MLL-rearranged infant acute lymphoblastic leukemia: major matters at a micro scale. *Leukemia* 25(3):429–439. doi:<http://www.nature.com/leu/journal/v25/n3/supinfo/leu2010282s1.html>.
- Sutcliffe MJ, Shuster JJ, Sather HN, Camitta BM, Pullen J, Schultz KR, Borowitz MJ, Gaynon PS, Carroll AJ, Heerema NA (2005) High concordance from independent studies by the Children's Cancer Group (CCG) and Pediatric Oncology Group (POG) associating favorable prognosis with combined trisomies 4, 10, and 17 in children with NCI Standard-Risk B-precursor Acute Lymphoblastic Leukemia: a Children's Oncology Group (COG) initiative. *Leukemia* 19 (5)734–740. doi:<http://www.nature.com/leu/journal/v19/n5/supinfo/2403673s1.html>
- Tasian SK, Doral MY, Borowitz MJ, Wood BL, Chen IM, Harvey RC, Gastier-Foster JM, Willman CL, Hunger SP, Mullighan CG, Loh ML. Aberrant STAT5 and PI3K/mTOR pathway signaling occurs in human CRLF2-rearranged B-precursor acute lymphoblastic leukemia. *Blood*. 2012;120(4):833–42. <https://doi.org/10.1182/blood-2011-12-389932>.
- Teachey DT, Hunger SP. Predicting relapse risk in childhood acute lymphoblastic leukaemia. *Br J Haematol*. 2013;162(5):606–20. <https://doi.org/10.1111/bjh.12442>.
- Teachey DT, Rheingold SR, Maude SL, Zugmaier G, Barrett DM, Seif AE, Nichols KE, Suppa EK, Kalos M, Berg RA, Fitzgerald JC, Aplenc R, Gore L, Grupp SA. Cytokine release syndrome after blinatumomab treatment related to abnormal macrophage activation and ameliorated with cytokine-directed therapy. *Blood*. 2013;121(26):5154–7. <https://doi.org/10.1182/blood-2013-02-485623>.
- Teicher BA, Ara G, Herbst R, Palombella VJ, Adams J. The proteasome inhibitor PS-341 in cancer therapy. *Clin Cancer Res*. 1999;5(9):2638–45.

- Topp MS, Gökbüget N, Stein AS, Zugmaier G, O'Brien S, Bargou RC, Dombret H, Fielding AK, Heffner L, Larson RA, Neumann S, Foà R, Litzow M, Ribera J-M, Rambaldi A, Schiller G, Brüggemann M, Horst HA, Holland C, Jia C, Maniar T, Huber B, Nagorsen D, Forman SJ, Kantarjian HM. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. *Lancet Oncol.* 2015;16(1):57–66. [https://doi.org/10.1016/S1470-2045\(14\)71170-2](https://doi.org/10.1016/S1470-2045(14)71170-2).
- Topp MS, Gökbüget N, Zugmaier G, Degenhard E, Goebeler M-E, Klinger M, Neumann SA, Horst HA, Raff T, Viardot A, Stelljes M, Schaich M, Köhne-Volland R, Brüggemann M, Ottmann OG, Burmeister T, Baeuerle PA, Nagorsen D, Schmidt M, Einsele H, Riethmüller G, Kneba M, Hoelzer D, Kufer P, Bargou RC. Long-term follow-up of hematologic relapse-free survival in a phase 2 study of blinatumomab in patients with MRD in B-lineage ALL. *Blood.* 2012;120(26):5185–7.
- Topp MS, Kufer P, Gökbüget N, Goebeler M, Klinger M, Neumann S, Horst HA, Raff T, Viardot A, Schmid M, Stelljes M, Schaich M, Degenhard E, Köhne-Volland R, Brüggemann M, Ottmann O, Pfeifer H, Burmeister T, Nagorsen D, Schmidt M, Lutterbüse R, Reinhardt C, Baeuerle PA, Kneba M, Einsele H, Riethmüller G, Hoelzer D, Zugmaier G, Bargou RC. Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival. *J Clin Oncol.* 2011;29(18):2493–8. <https://doi.org/10.1200/JCO.2010.32.7270>.
- Uderzo C, Valsecchi MG, Bacigalupo A, Meloni G, Messina C, Polchi P, Di Girolamo G, Dini G, Miniero R, Locatelli F, et al. Treatment of childhood acute lymphoblastic leukemia in second remission with allogeneic bone marrow transplantation and chemotherapy: ten-year experience of the Italian Bone Marrow Transplantation Group and the Italian Pediatric Hematology Oncology Association. *J Clin Oncol Off J Am Soc Clin Oncol.* 1995;13(2):352–8.
- Van der Velden VHJ, Corral L, Valsecchi MG, Jansen MWJC, De Lorenzo P, Cazzaniga G, Panzer-Grumayer ER, Schrappe M, Schrauder A, Meyer C, Marschalek R, Nigro LL, Metzler M, Basso G, Mann G, Den Boer ML, Biondi A, Pieters R, Van Dongen JJM. Prognostic significance of minimal residual disease in infants with acute lymphoblastic leukemia treated within the Interfant-99 protocol. *Leukemia.* 2009;23(6):1073–9.
- Van Vlierberghe P, Ferrando A. The molecular basis of T cell acute lymphoblastic leukemia. *J Clin Invest.* 2012;122(10):3398–406. <https://doi.org/10.1172/JCI61269>.
- Veerman AJ, Kamps WA, van den Berg H, van den Berg E, Bökkerink JPM, Bruin MCA, van den Heuvel-Eibrink MM, Korbijn CM, Korhof ET, van der Pal K, Stijnen T, van Weel Sipman MH, van Weerden JF, van Wering ER, van der Does-van den Berg A. Dexamethasone-based therapy for childhood acute lymphoblastic leukaemia: results of the prospective Dutch Childhood Oncology Group (DCOG) protocol ALL-9 (1997–2004). *Lancet Oncol.* 2009;10(10):957–66. [https://doi.org/10.1016/S1470-2045\(09\)70228-1](https://doi.org/10.1016/S1470-2045(09)70228-1).
- Vora A, Andreano A, Pui C-H, Hunger SP, Schrappe M, Moericke A, Biondi A, Escherich G, Silverman LB, Goulden N, Taskinen M, Pieters R, Horibe K, Devidas M, Locatelli F, Valsecchi MG. Influence of cranial radiotherapy on outcome in children with acute lymphoblastic leukemia treated with contemporary therapy. *J Clin Oncol.* 2016;34:919–26. <https://doi.org/10.1200/jco.2015.64.2850>.
- Wayne AS, Bhojwani D, Silverman LB, Richards K, Stetler-Stevenson M, Shah NN, Jeha S, Pui C-H, Buzoianu M, FitzGerald DJ, Kreitman RJ, Ibrahim R, Pastan I. A novel anti-CD22 immunotoxin, moxetumomab pasudotox: phase I study in pediatric acute lymphoblastic leukemia (ALL). *Blood.* 2011;118(21):248.
- Weng AP, Ferrando AA, Lee W, Morris JP, Silverman LB, Sanchez-Irizarry C, Blacklow SC, Look AT, Aster JC. Activating mutations of NOTCH1 in human T cell acute lymphoblastic leukemia. *Science.* 2004;306(5694):269–71.
- Weston BW, Hayden MA, Roberts KG, Bowyer S, Hsu J, Fedorow G, Rao KW, Mullighan CG. Tyrosine kinase inhibitor therapy induces remission in a patient with refractory EBF1-PDGFRB-positive acute lymphoblastic leukemia. *J Clin Oncol.* 2013;31(25):e413–6. <https://doi.org/10.1200/JCO.2012.47.6770>.
- Wiemels JL, Cazzaniga G, Daniotti M, Eden OB, Addison GM, Maserà G, Saha V, Biondi A, Greaves MF. Prenatal origin of acute lymphoblastic leukaemia in children. *Lancet.* 1999;354(9189):1499–503.
- Wileto M, Giuseppe GD, Hitzler J, Gupta S, Abula O. Treatment of young children with CNS-positive acute lymphoblastic leukemia without cranial radiotherapy. *Pediatr Blood Cancer.* 2015;62(11):1881–5. <https://doi.org/10.1002/psc.25620>.
- Winter SS, Dunsmore KP, Devidas M, Eisenberg N, Asselin BL, Wood BL, Leonard RN MS, Murphy J, Gastier-Foster JM, Carroll AJ, Heerema NA, Loh ML, Raetz EA, Winick NJ, Carroll WL, Hunger SP. Safe integration of nelarabine into intensive chemotherapy in newly diagnosed T-cell acute lymphoblastic leukemia: Children's Oncology Group Study AALL0434. *Pediatr Blood Cancer.* 2015;62(7):1176–83. <https://doi.org/10.1002/psc.25470>.
- Wolf E, Hofmeister R, Kufer P, Schlereth B, Baeuerle PA. BiTEs: bispecific antibody constructs with unique anti-tumor activity. *Drug Discov Today.* 2005;10(18):1237–44. [https://doi.org/10.1016/S1359-6446\(05\)03554-3](https://doi.org/10.1016/S1359-6446(05)03554-3).
- Wood BL, Winter SS, Dunsmore KP, Devidas M, Chen S, Asselin B, Esiashvili N, Loh ML, Winick NJ, Carroll WL, Raetz EA, Hunger SP. T-Lymphoblastic leukemia (T-ALL) shows excellent outcome, lack of significance of the early thymic precursor (ETP) immunophenotype, and validation of the prognostic value

- of end-induction minimal residual disease (MRD) in Children's Oncology Group (COG) study AALL0434. *ASH Annual Meeting Abstracts*. 2014;124(21):1.
- Yoda A, Yoda Y, Chiaretti S, Bar-Natan M, Mani K, Rodig SJ, West N, Xiao Y, Brown JR, Mitsiades C, Sattler M, Kutok JL, DeAngelo DJ, Wadleigh M, Piciocchi A, Dal Cin P, Bradner JE, Griffin JD, Anderson KC, Stone RM, Ritz J, Foa R, Aster JC, Frank DA, Weinstock DM. Functional screening identifies CRLF2 in precursor B-cell acute lymphoblastic leukemia. *Proc Natl Acad Sci U S A*. 2010;107(1):252–7. [1073/pnas.0911726107](https://doi.org/10.1073/pnas.0911726107)
- Yoshizawa K, Mukai HY, Miyazawa M, Miyao M, Ogawa Y, Ohyashiki K, Katoh T, Kusumoto M, Gemma A, Sakai F, Sugiyama Y, Hatake K, Fukuda Y, Kudoh S. Bortezomib therapy-related lung disease in Japanese patients with multiple myeloma: Incidence, mortality and clinical characterization. *Cancer Sci*. 2014;105(2):195–201. <https://doi.org/10.1111/cas.12335>.
- Zhang J, Ding L, Holmfeldt L, Wu G, Heatley SL, Payne-Turner D, Easton J, Chen X, Wang J, Rusch M, Lu C, Chen SC, Wei L, Collins-Underwood JR, Ma J, Roberts KG, Pounds SB, Ulyanov A, Becksfort J, Gupta P, Huether R, Kriwacki RW, Parker M, McGoldrick DJ, Zhao D, Alford D, Espy S, Bobba KC, Song G, Pei D, Cheng C, Roberts S, Barbato MI, Campana D, Coustan-Smith E, Shurtleff SA, Raimondi SC, Kleppe M, Cools J, Shimano KA, Hermiston ML, Doulatov S, Eppert K, Laurenti E, Notta F, Dick JE, Basso G, Hunger SP, Loh ML, Devidas M, Wood B, Winter S, Dunsmore KP, Fulton RS, Fulton LL, Hong X, Harris CC, Dooling DJ, Ochoa K, Johnson KJ, Obenauer JC, Evans WE, Pui CH, Naeve CW, Ley TJ, Mardis ER, Wilson RK, Downing JR, Mullighan CG. The genetic basis of early T-cell precursor acute lymphoblastic leukaemia. *Nature*. 2012;481(7380):157–63. <https://doi.org/10.1038/nature10725>.
- Zugmaier G, Gökbuğet N, Klinger M, Viardot A, Stelljes M, Neumann S, Horst H-A, Marks R, Faul C, Diedrich H, Reichle A, Brüggemann M, Holland C, Schmidt M, Einsele H, Bargou RC, Topp MS. Long-term survival and T-cell kinetics in relapsed/refractory ALL patients who achieved MRD response after blinatumomab treatment. *Blood*. 2015;126(24):2578–84.



Update in Pediatric Oncology: Section B—Solid Tumors of Childhood

19

Allison F. O'Neill

The care of pediatric patients with solid tumors is complex given the tissues and organs affected by disease, the multidisciplinary nature to clinical decision-making, treatment toxicities, and the complex medical and psychosocial care required during and in the aftermath of treatment. Therapeutic regimens are selected on the basis of patient risk-stratification, which for many tumors is tailored to account for disease histology, extent of spread, and in some cases molecular profile. Treatment considerations focus on the primary tumor (i.e. local control) as well as metastatic or microscopic circulating disease (i.e. systemic therapy). Local control can consist of surgery, radiotherapy, or a combination of the two. “Neoadjuvant” treatment is the term given to systemic agents administered prior to surgery with the term “adjuvant” assigned to treatment given post-operatively. Over the last decade, goals of therapy have evolved to maintain excellent outcomes for patients with low-risk disease, while reducing overall therapy, minimizing toxicity, and improving outcomes for patients with high-risk disease through treatment intensification. In the era of personalized medicine and genomic tumor profiling, our understanding of the molecular drivers of disease as well as targeted approaches to therapy

continues to improve. The goals of this chapter are to focus on the epidemiology, pathophysiology, presenting symptoms, work-up, and standard treatment for the most common extracranial solid tumors (focusing predominantly on the North American, Children’s Oncology Group approach) while highlighting recent advances in therapy and overall outcomes.

Imaging, Biopsy, and Surgical Considerations

Suspicion of a new solid tumor diagnosis on physical exam prompts great anxiety on the part of the family and patient and a perceived urgent need for work-up on the part of the treating physician. However, the work-up for a new diagnosis has migrated, whenever possible, to the outpatient setting assuming patient stability, familial comfort with outpatient care, and a reliable primary caregiver. Initial tumor imaging with X-ray or ultrasound and attention to laboratory work are crucial to guide further work-up. Pursuit of computed tomography (CT) scans, magnetic resonance imaging (MRI), or positron emission tomography (PET) can be deferred until the patient is further evaluated by a multidisciplinary team to assure that the appropriate considerations (imaging modality and field, ionizing radiation dose, use of contrast, and need for sedation) are met. Biopsy specifics (percutaneous versus open, core versus fine needle,

A.F. O'Neill, M.D.
Dana-Farber Cancer Institute, Massachusetts, USA
e-mail: allison_oneill@dfci.harvard.edu

interventional versus surgical, placement of the needle track, and procurement of sufficient tissue for both diagnosis and genomic studies) are likewise important to consider prior to any procedure. An experienced oncologic surgeon should be consulted for all upfront or delayed resections such that margins, field, and surgical approach are well planned.

Delivery of Bad News

More often than not, initial conversations regarding a potential new diagnosis are performed in the outpatient setting prior to referral to a subspecialty center. An initial introduction to disease can follow the approach outlined in the literature regarding delivery of bad news: (1) acknowledgement of an abnormal finding on exam, laboratory work, or imaging; (2) inability to assign the abnormality a name or diagnosis until further studies are obtained; (3) anticipation that a diagnosis will be made and treatments will be available; and (4) emphasis on the fact that the family and child played no role, nor had any fault in the diagnosis (Mack and Grier 2004). While intuitive, this upfront approach will lay invaluable groundwork for conversations to follow regarding disease specifics, treatment plan, and prognosis.

Neuroblastoma

Epidemiology, Pathophysiology, and Genetic Predisposition

Neuroblastoma is the most common extracranial solid tumor affecting approximately 650 pediatric patients annually in North America (Howlander et al. 2012). About a third of cases occur in infancy and 90% of children diagnosed are younger than 5 years of age (London et al. 2005). The disease can occur in adolescence but is rare and tends to follow a more indolent course. Neuroblastoma arises from cells of neural crest origin and can present as a solitary adrenal mass, at a site along the sympathetic chains, or at the organ of zuckerkindl, a chromaffin body

located at the bifurcation of the aorta. Tumors can metastasize to neighboring lymph nodes, encasing vital structures within the thoracic or abdominal cavities, and spread hematogenously to the bone and bone marrow. Neuroblastoma is rarely familial (1–2% of patients) but when heritable is secondary to a mutation in the anaplastic lymphoma kinase (ALK) gene, the PHOX2B gene (associated with central hypoventilation syndrome and/or Hirschsprung's disease), or a deletion at the 1p36 or 11q14–23 locus (Mosse et al. 2008, 2004; Satge et al. 2003).

Presenting Symptoms

Presenting symptoms vary substantially dependent on location and extent of disease. The most common presenting symptom is that of an abdominal mass, however smaller, incidentally discovered adrenal neuroblastomas are often not palpable. Symptoms can be caused by mass effect from the primary tumor and/or metastases. Vital sign changes can include intermittent, low-grade fevers without clear origin, tachypnea or diminished O₂ saturations caused by thoracic disease or a large abdominal primary causing restrictive lung patterns, tachycardia secondary to anemia, or hypertension due to tumor catecholamine release or impingement on the renal vasculature. Physical exam findings can include abdominal distension with a palpable mass, proptosis or periorbital ecchymoses secondary to retrobulbar metastases, a Horner's syndrome caused by an apical mass arising from the stellate ganglion, or weakness or paralysis secondary to invasion of the tumor into the spinal canal (Mahoney et al. 2006). Rarely, bluish discolored skin nodules can be seen but only in a subset of infants with disease designated as "stage 4S" (see below). Children with periorbital ecchymosis are occasionally, inadvertently evaluated for non-accidental trauma prior to a diagnosis of neuroblastoma (Bohdiewicz et al. 1995).

Rarely, patients can present with a paraneoplastic syndrome, presumed immunologic, with symptoms that include cerebellar ataxia or opsoclonus/myoclonus (irregular eye

movements, cognitive deficits, and psychomotor retardation). These symptoms don't necessarily resolve following treatment and are curiously associated with neuroblastomas of smaller size and favorable pathology (Matthay et al. 2005; Rudnick et al. 2001). Laboratory abnormalities can include pancytopenia or anemia secondary to bone marrow involvement or chronic disease. Rarely, patients with rapidly growing tumors have an elevated uric acid indicative of tumor lysis (Milano et al. 2003). As neuroblastoma tumors secrete catecholamines, a single-void urine for elevated catecholamine metabolites (vanillylmandelic acid, VMA, and homovanillic acid, HVA) can be utilized both as a diagnostic tool and later for assessment of disease response to therapy. Additional history may reveal irritability in excess of baseline, verbalized bony pain, or watery diarrhea secondary to tumoral secretion of vasoactive peptide (Bourdeaut et al. 2009). Physicians should have a low threshold of suspicion for further work-up should a child present with any of the symptoms on this broad spectrum.

Histology and Molecular Profile

After preliminary imaging studies are obtained (per below), percutaneous, core-needle biopsy of an accessible lesion is pursued to obtain a diagnosis. In the age of molecular and genomic tumor analyses, the need for viable, pre-treatment specimens is of increasing relevance. While studies have been performed to estimate the median number of needle cores required for a diagnosis of soft tissue tumors, the number of cores required to complete a work-up across solid tumors is poorly defined (Acord and Shaikh 2015). Neuroblastomas can develop central necrosis making it difficult to reliably obtain viable tissue. For all of these reasons, some centers have transitioned to obtaining tissue via an open approach. Under the microscope, neuroblastoma tumors are characterized by the presence of small round blue cells, varying in degree of differentiation, upon a background of nerve fibers, or neuropil.

The International Neuroblastoma Pathology Classification (INPC), or Shimada system, allows

a uniform, prognostic evaluation of tumor tissue sampled at diagnosis taking into account the extent of Schwannian stroma, degree of neuroblastic maturation, mitoses, and patient age (Shimada et al. 1999, 2001; Teshiba et al. 2014). A different approach to classification, the International Neuroblastoma Risk Group (INRG), focuses more on cellular characteristics allowing age and other clinical and molecular characteristics to factor into assigned treatment algorithms later on (Cohn et al. 2009). The molecular abnormality of greatest prognostic value is MYCN copy number, amplification of which denotes high-risk disease (Cohn et al. 2009; Schleiermacher et al. 2012). DNA index, presence of somatic activating mutations in the ALK gene, expression of neurotrophin receptor kinase B (TrkB), and genomic alterations resulting in telomere elongation are among additional factors associated with high-risk disease (Bresler et al. 2014; Maris and Matthay 1999; Peifer et al. 2015).

Staging

Staging for neuroblastoma, as for all solid tumors, is designed to evaluate sites of known tumor spread.

As neuroblastoma can invade local structures, spread via the lymphatics, and to distant sites via the blood stream, a comprehensive staging work-up is required. Imaging with pan-CT or chest CT scan and/or abdominopelvic MRI is required for evaluation of the chest, abdomen, and pelvis. For a subset of infants with small adrenal masses discovered prenatally, serial ultrasounds may be sufficient to follow tumors for regression. Intratumoral calcifications, detected on X-ray or CT, are a hallmark of disease but can also be seen in other diagnoses (Fig. 19.1). Paraspinal tumors may require more emergent evaluation with spine MRI to image for spinal cord impingement. Metaiodobenzylguanidine (MIBG) imaging is pursued for all patients and consists of injection of a radiopharmaceutical (iodine-123) that localizes to noradrenergic tissues and illuminates sites of disease. A Curie score is assigned to sites of disease at diagnosis and following therapy to allow a



Fig. 19.1 Sagittal CT images demonstrating a large left-sided retroperitoneal neuroblastoma with internal necrosis and calcifications. The tumor arises from the left adrenal gland and encases the intra-abdominal vasculature

quantitative measure of avidity and prediction of prognosis (Yanik et al. 2013). Patients must take potassium iodine before and after the injection/scan to protect thyroid function. Occasionally PET/CT scans are pursued for tumors that fail to illuminate with I-123 (10% of tumors) or that require anatomic co-localization as MIBG scans fail to provide this level of specificity (Sharp et al. 2009). Sampling of the bone marrow from bilateral iliac crests is also a required evaluation.

Staging has historically followed the International Neuroblastoma Staging System (INSS), which categorizes disease on the basis of surgical resectability (Brodeur et al. 1993, 1988). An over-simplified summary of this staging system is as follows: localized tumor with gross excision or with microscopic residual (stage I); localized tumor with incomplete gross resection and ipsilateral nodes negative or localized tumor with or without complete resection and ipsilateral nodes positive (stage II); unresectable tumor crossing the midline (defined by the vertebral column), localized tumor with contralateral lymph node involvement, or a midline tumor with bilateral extension and infiltration of the lymph nodes

(stage III); or disseminated disease to distant lymph nodes, bone, bone marrow, liver, skin, or other organs except as defined by 4S (stage IV). Stage 4S disease occurs in infants younger than 12 months who present with a localized primary tumor and dissemination limited to the skin, liver, or bone marrow. More recently, the International Neuroblastoma Risk Group Staging System (INRGSS) was developed; this system focuses more specifically on image defined risk factors (IDRFs) that may preclude a successful surgery and uses 18 months as a cut-off for 4S disease (Fig. 19.2) (Pinto et al. 2015). Newer treatment protocols through the Children's Oncology Group (COG) have relied upon the INRGSS approach.

Treatment and Outcomes

Historically, patients with neuroblastoma have been risk-stratified taking into account patient age, INPC categorization, ploidy, INSS staging, and MYCN status. More recent studies have relied upon the INRG staging system. While patient risk assignments will continue to evolve, generally, disease falls into one of three categories: low, intermediate, or high risk. Patients of younger age, favorable histology, limited disease, and absence of MYCN tend to fall into a low risk category while older age, unfavorable histology and MYCN amplification denote high risk. Patients with low-risk disease can be (1) observed, (2) undergo surgery with subsequent observation, or (3) receive chemotherapy. Observation without biopsy has been safely used to treat perinatal small adrenal tumors; on the COG ANBL00P2 study 81% of patients demonstrated spontaneous regression with a 3-year overall survival (OS) of 100% (Nuchtern et al. 2012). The phenomenon of tumor regression has also been described for patients with 4S disease, therefore these patients are often closely observed without treatment. Infant screening programs (assessing for urine spot HVA/VMA) have been pursued in the hopes of detecting high risk disease; however, most tumors detected fall into this low risk category and will spontaneously regress, thereby rendering screening of little benefit (Woods et al.

Fig. 19.2 The International Neuroblastoma Risk Group Staging System (INRGSS) with definition of image defined risk factors (IDRFs)

| Stage | Description |
|-------|--|
| L1 | Localized tumor confined to one body compartment and not involving vital structures as defined by IDRFs* |
| L2 | Locoregional tumor with one or more IDRFs |
| M | Distant metastases (excluding MS) |
| MS | Metastatic disease in a child <18 months with metastases confined to skin, liver, and/or marrow |

*IDRFs (image defined risk factors): ipsilateral tumor extension within two body compartments, infiltration of adjacent organs/structures, encasement of major vessels or brachial plexus, compression of the trachea or central bronchi, infiltration of the porto-hepatic or hepato-duodenal ligament, infiltration of the costo-vertebral junction between T9 and T12, tumors crossing the sciatic notch or invading the renal pedicle, extension of tumor to the base of the skull, intraspinal tumor extension (>1/3 of spinal canal invaded, leptomeningeal space obliterated, or spinal cord MRI signal abnormal)

2002; Schilling et al. 2002). A subset of low-risk patients will undergo surgical resection of their disease and then be observed post-operatively also achieving excellent outcomes (Strother et al. 2012). Neuroblastoma remains one of the few tumors for which a positive surgical margin may remain and does not impact outcome. A small subset of low-risk patients, those who are symptomatic, have unfavorable histology, or have unresectable progressive disease after surgery, will receive chemotherapy. Infants with 4S disease can present with a fulminant course (rapid disease growth and organ dysfunction) also requiring chemotherapy. Agents utilized are typically extrapolated from regimens used to treat intermediate-risk disease and include carboplatin, cyclophosphamide, doxorubicin, and etoposide. Even with the need for chemotherapy, these patients achieve excellent outcomes (Strother et al. 2012).

For patients with intermediate-risk disease chemotherapy is often given prior to resection. A select group of infants with intermediate disease have been observed following upfront resection, but more often than not, these children receive neoadjuvant treatment (De Bernardi et al. 2009). COG protocol A3961 investigated outcomes following a reduction in chemotherapy, for

patients with favorable histology, demonstrating a retained 3-year OS of 95% (Baker et al. 2010). More recently, COG ANBL0531 investigated a response-based approach to treatment, further tailoring the amount to chemotherapy patients received. While publication remains pending, preliminary results have been promising. Patients with high-risk disease have an unfortunately poor prognosis. Treatment is intensive requiring induction chemotherapy (cyclophosphamide, topotecan, cisplatin, etoposide, cyclophosphamide, doxorubicin, and vincristine), surgery, radiation, tandem autologous stem cell transplants, and immune therapy with an anti-GD2 antibody and concomitant isotretinoin, the latter of which encourages maturation of residual neuroblastoma cells to ganglioneuroma. Addition of immune therapy was the most recent therapeutic change to result in an improvement in 5-year EFS from 46% to 66% (Yu et al. 2010). Therapeutic MIBG, utilizing a slightly different radioisotope than that for the diagnostic scans (I-131), has been studied in pilot protocols for patients with upfront high-risk disease or poor disease response to therapy; long-term efficacy has not yet been determined.

Radiation is occasionally used in emergent situations such as severe respiratory compromise or

spinal cord impingement. As neuroblastoma is an exquisitely chemotherapy-sensitive tumor, time to onset of action of chemotherapy compared with radiotherapy is similar therefore chemotherapy is preferentially pursued when possible. Rapid referral to a tertiary care center for work-up and treatment initiation is therefore prudent. Targeted therapies, i.e. ALK inhibitors for patients with exonic mutations, can be considered but have not been extensively studied given that the fraction of patients harboring this mutation is small (Bresler et al. 2014). A complete response to therapy by INRG criteria includes: no evidence of tumor on imaging studies, resolved MIBG uptake and resolution of urine HVA and VMA elevations.

Kidney Tumors

Epidemiology, Pathophysiology, and Genetic Predisposition

Wilms tumor is the most common pediatric renal tumor with approximately 650 cases diagnosed annually in the United States, typically affecting children less than 5 years of age, and accounting for approximately 7% of all childhood cancers (Howlader et al. 2012). Renal cell carcinoma (RCC), the second most common renal tumor, is extremely rare and typically affects pediatric patients aged 15–19 years. Apart from these two tumor types, the differential for renal tumors is broad and includes: rhabdoid tumors, clear cell sarcoma, Ewing sarcoma of the kidney, desmoplastic small round blue cell tumor, renal synovial sarcoma, anaplastic sarcoma, and congenital mesoblastic nephroma (to name a few). This portion of the chapter will focus on the two most common diagnoses: i.e. Wilms tumor and RCC. While renal tumors typically arise from one kidney, Wilms tumor can affect one or both kidneys (the latter more common in the context of a cancer predisposition syndrome) (Porteus et al. 2000; Huff 1998). Nephrogenic rests of the kidney are a benign neoplasm, caused by clustered, retained embryonic kidney precursor cells; nephroblastomatosis refers to the presence of diffuse or multifocal rests. These rests denote

an increased risk for tumor formation and can have imaging characteristics difficult to differentiate from malignancy (Perlman et al. 2006). Nephrogenic rests are found in 1% of pediatric autopsies, approximately a third of unilateral Wilms tumor cases, nearly all bilateral cases, and in patients with heritable causes of Wilms tumor (Beckwith 1993).

Renal tumors arise within the kidney, can rupture through the renal capsule or extend through the renal vasculature, spread to regional or contralateral lymph nodes, or hematogenously to the lungs. Approximately 10% of Wilms tumors arise in the context of a congenital anomaly (hemihypertrophy or gigantism, urinary tract abnormalities, phenotypic abnormalities including aniridia) or germline mutations in the WT1 (i.e. WAGR syndrome, Denys-Drash and Fraiser syndrome) or WT2 genes (Beckwith-Wiedemann) (Narod et al. 1997; Scott et al. 2006). Wilms tumor has also been described in association with germline TP53 mutations, i.e. in individuals with Li Fraumeni Syndrome. Familial Wilms tumors occur rarely and have been reported in association with FWT1 or 2 mutations, or inactivating CTR9 mutations (Ruteshouser and Huff 2004; Hanks et al. 2014). Additional mutations resulting in impaired expression of tumor-suppressing miRNAs have been reported including those of the DICER1 gene (Palculict et al. 2016).

Presenting Symptoms

Children with a primary renal tumor often present with an acute increase in abdominal size with or without parental reports of a palpable mass. Nearly half of all children describe vague symptoms of abdominal pain and may endorse nausea and vomiting. Gross hematuria occurs in about 18% of Wilms tumor patients, occasionally concurrent with incidental trauma making the history more difficult to interpret (Green 1985). Anorexia, fatigue and weight loss can also occur. While many renal tumors can metastasize to the lung, respiratory symptoms at presentation are rare. Vital sign changes typically include hypertension caused by renal vascular involvement

and activation of the renin-angiotensin system. Low grade fevers without clear origin can also be reported. Laboratory abnormalities can include hypercalcemia (more frequently seen with rhabdoid tumors or congenital mesoblastic nephroma) and microscopic hematuria on urinalysis (approximately 25% of patients). Approximately 1–8% of patients presenting with Wilms tumor have acquired von Willebrands disease but are typically asymptomatic (Callaghan et al. 2013). Children should be carefully evaluated for signs of associated cancer syndromes, i.e. aniridia, developmental delay, urinary tract abnormalities, or overgrowth. Children with known cancer predisposition syndromes or hemihyperplasia are typically screened for Wilms tumor with an abdominal ultrasound every 3 months until 6–8 years of age.

Histology and Molecular Profile

While biopsy of most pediatric solid tumors is required for diagnosis, molecular profiling, and risk stratification, hesitation is warranted before biopsy of a renal lesion. Needling of the renal capsule in a patient with Wilms tumor is felt to cause tumor rupture with spillage and upstaging of disease. For this reason, clinicians must rely upon imaging characteristics working closely with an oncologic radiologist and an oncologic surgeon or urologist to determine ease of upfront tumor resection (as resection of the primary tumor remains a consideration even in the context of metastases to allow for pre-treatment evaluation of histology). Biopsy of the mass may be required if the primary tumor is not amenable to upfront resection or if radiographic characteristics are inconsistent with Wilms tumor.

Wilms tumors are felt to arise from the clonal expansion of a nephrogenic rest. Mutations in many somatic genes can contribute to this malignant transformation including WT1, CTNNB1, WTX or TP53 (Ruteshouser et al. 2008). Under the microscope, Wilms tumors are also small, round, blue cell tumors that are separated into one of two histopathologic categories: favorable or anaplastic. Favorable histology demonstrates

the presence of three distinct tissues reminiscent of normal kidney development: blastemal, epithelial (tubular), and stromal. Not all tumors are triphasic and monophasic patterns may predominate. Anaplastic histology accounts for about 10% of all Wilms tumor cases and is an important predictor of survival given an associated poor response to chemotherapy. Anaplastic Wilms tends to occur more frequently in older patients or those with bilateral disease (Popov et al. 2011; Hamilton et al. 2011). Focal anaplasia does not carry the same poor prognosis as diffuse anaplasia. Germline TP53 mutations have been strongly associated with anaplastic Wilms tumors (Bardeesy et al. 1994). Gains in chromosome 1q are the single most powerful predictor of poor outcome across all Wilms tumor histologies (Gratias et al. 2016). Loss of heterozygosity of both 16q and 1p are also felt to confer a poor overall survival (Grundy et al. 2005). Confirmation of retention of INI1, immunohistochemical loss of which is associated with rhabdoid tumors, is important for ruling out a diagnosis of rhabdoid tumor as it carries a worse outcome.

Staging

Preliminary tumor imaging with abdominal X-ray or abdominal ultrasound with dopplers can be informative. Ultimately, chest, abdomen, and pelvis CT with contrast serves to more definitively characterize sites of disease as well as vascular spread. A characteristic “claw sign,” formed by the rim of residual renal tissue cupping the primary tumor, is often seen (Fig. 19.3). Abdominal CT can fall short with regards to interpretation of lymph node involvement or characterization of nephrogenic rests. Abdominal MRI can often better help to differentiate rests from malignant tumor (Servaes et al. 2015). Staging of renal tumors follows a surgical approach which, in oversimplified terms, is as follows: intact, completely resected, non-ruptured primary without lymph node involvement (stage I); non-ruptured but with regional extension and penetration of the capsule, or involvement of the renal sinus or vessels if resected en-bloc (stage II); lymph

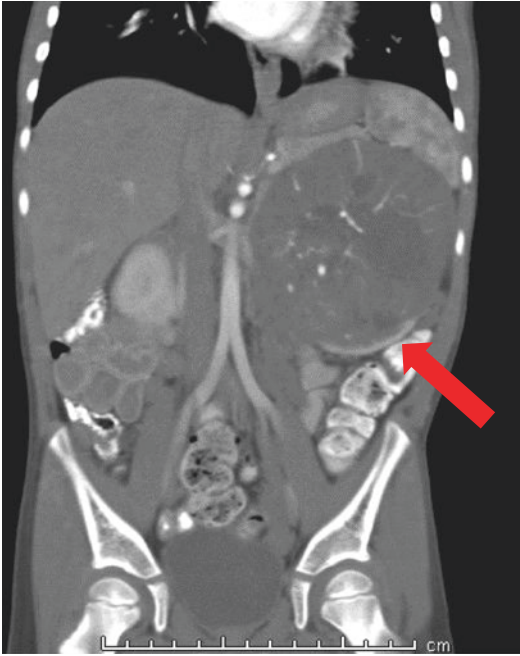


Fig. 19.3 Sagittal CT images demonstrating a left-sided renal tumor obliterating much of the original kidney. An inferior rim of residual kidney can be visualized and is radiographically referred to as a “claw sign.” (arrow)

node involvement in the abdomen or pelvis, local infiltration into vital structures, or tumor rupture either spontaneous or secondary to biopsy (stage III); hematogenous metastatic disease or lymph node spread outside the abdomen (stage IV); or bilateral disease (stage V) (Perlman 2005).

Treatment and Outcomes

The global cure rate for Wilms tumors remains excellent with receipt of combination chemotherapy, surgery, and occasionally inclusion of radiotherapy. Favorable prognosis is linked to histopathologic features (favorable vs. anaplastic histology), stage, molecular characteristics, and patient age. While chemotherapy plays an important role in the treatment of Wilms tumor, surgical removal of disease is crucial for cure. Patients less than 24 months of age diagnosed with a stage I Wilms tumor of favorable histology weighing less than 550 g can be observed without additional therapy. These patients can achieve an OS

of 98% (Shamberger et al. 2010). Patients with stage I disease falling outside of these parameters typically receive two chemotherapeutic agents (vincristine and actinomycin, termed EE4A) \pm radiotherapy depending on whether anaplastic features are present. Outcomes for those with favorable histology reach 98% with the presence of anaplasia conferring a slightly worse prognosis, ranging from 79% to 89% (Shamberger et al. 2010). Patients with stage II disease likewise receive EE4A following tumor resection however, the presence of focal anaplasia earns addition of doxorubicin (DD4A) and radiotherapy while diffuse anaplasia receives an even more aggressive regimen (Dome et al. 2006). The focus of the most recent COG trial studied addition of doxorubicin to patients with stage I or II disease and favorable histology but loss of 16q and 1p; incorporation of doxorubicin for these patients has now become standard.

Patients with stage III disease and favorable histology and/or focal anaplasia receive DD4A and flank radiotherapy while those with diffuse anaplasia are again treated with a more intense regimen. Typically radiotherapy is limited to the involved flank unless diffuse rupture is suspected in which case whole abdominal radiotherapy is pursued. Outcomes for patients with stage III favorable histology are upwards of 94% while those with diffuse anaplasia fall as low as 50% (Dome et al. 2006). Patients with stage IV favorable histology disease have, until recently, received DD4A, with flank and lung radiotherapy (Dome et al. 2006; Grundy et al. 2012). The most recent COG trial (AREN0533) studied addition of cyclophosphamide and etoposide to DD4A (termed Regimen M) for patients with favorable histology and a slow lung nodule response. Early results to this trial demonstrated an excellent 3-year OS of 92%. There is no standard approach for patients with stage V Wilms tumor; at present treatment is focused on the use of pre-operative chemotherapy, renal-sparing surgery when possible, and renal transplantation if required once an extended remission is documented (Breslow et al. 2005). Patients are often treated without undergoing an upfront biopsy; if no response is achieved within 12 weeks of treatment initiation,

biopsy is warranted for histologic evaluation (Hamilton et al. 2011).

Other Renal Tumors

Renal cell carcinoma (RCC), while the second most common renal tumor in pediatric patients, remains rare affecting only four in one million adolescent children annually. A small subset of RCCs is familial, associated with an inherited chromosomal translocation involving chromosome 3 (Wang and Perkins 1984). Others cases have been described in associated with von Hippel-Lindau disease and tuberous sclerosis (Bruder et al. 2004; Pea et al. 1998). A rare subset of RCC, renal medullary carcinoma, has been seen in association with sickle cell hemoglobinopathy trait (Swartz et al. 2002). RCCs have also been reported as a consequence of therapy in patients previously treated for other malignancies. Translocation-positive RCCs, involving the TFE3 gene, are a distinct entity seen more commonly in children (Geller et al. 2015). Children with RCC often present with an abdominal mass, pain, or hematuria. Prognosis is very strongly linked to stage and lymph node involvement, as surgical resection with radical nephrectomy is necessary for cure. Survival rates of ~90% have been quoted for stage I–II disease but unfortunately <15% of children with metastatic disease are cured (Indolfi et al. 2003). Interestingly, children with local lymph node involvement but absence of distant metastases fair better than adults (~75% OS) (Geller and Dome 2004). There are no standard therapies for patients with unresectable disease. Immune therapies such as interferon-alpha and interleukin-2 may have some efficacy and case reports have demonstrated response to tyrosine kinase inhibitors in pediatric translocation-positive disease however global outcomes remain poor. ALK mutations should be explored in translocation-positive patients given the option for targeted therapy.

Rhabdoid tumors and clear cell sarcomas represent the two most commonly diagnosed renal tumors following RCC. Rhabdoid tumors often occur in very young children (<12 months of age)

and typically demonstrate an advanced stage at presentation. They can metastasize to the lung and brain. Molecularly, they demonstrate loss of function of the SMARCB1 gene leading to the abnormal function of the SWI/SNF chromatin remodeling complex which is important for gene transcription (Eaton et al. 2011). Germline mutations in SMARCB1 have also been detected in one-third of cases but are typically *de novo*; these patients are noted to have a worse prognosis (Biegel et al. 1999). Tumor immunohistochemistry demonstrates INI1 loss. Stage I and II disease has been reported to have an OS of 42%. Advanced stage disease remains incurable. EZH2 inhibitors are currently under study given that inactivation of SMARCB1 leads to oncogenic dependency on EZH2. Clear cell sarcoma arises from a unilateral kidney and has the propensity to spread to bone, brain, or soft tissue. Doxorubicin-containing chemotherapy, radiotherapy and surgery are a mainstay of treatment. While patients with early stage disease fare well (85–95%), outcomes are poor for those with stage IV disease (45%) (Siebel et al. 2006).

Sarcomas

Bone Tumors

Epidemiology, Pathophysiology, and Genetic Predisposition

Osteosarcoma and Ewing sarcoma are the two most common bone tumors affecting pediatric patients, with approximately 450 cases of osteosarcoma and 120 cases of Ewing sarcoma diagnosed each year (Howlader et al. 2012). While both diseases tend to occur in adolescents a fraction can occur in children <12 years of age. Osteosarcoma tends to originate from the long bones surrounding the knee (distal femur, proximal tibia/fibula) but can likewise arise from the proximal humerus, pelvis, or rarely, the soft tissues. Ewing sarcoma tumors tend to arise from the diaphyses of the flat bones; these tumors can more commonly affect the rib (termed an Askin tumor of the chest), mid-femur, or pelvis. Ewing sarcomas can likewise arise from the soft

tissues with the trunk being the most common site; subcutaneous Ewing sarcomas are rare but have an excellent prognosis (Di Giannatale et al. 2015). Both tumors have a propensity to metastasize to the lungs or to other bones. Osteosarcoma has been described in association with familial TP53 or Rb gene mutations (the latter of which confers a risk for ocular retinoblastoma in early childhood but osteosarcoma later in life particularly following radiotherapy) (Ognjanovic et al. 2012; Wong et al. 1997). Other heritable conditions associated with osteosarcoma include Bloom syndrome, Pagets disease, and Rothmund-Thomson syndrome (German 1997; Grimer et al. 2003; Wang et al. 2003). Ewing sarcoma has not been associated with any genetic predisposition syndromes.

Presenting Symptoms

Patients diagnosed with osteosarcoma or Ewing sarcoma typically note pain at the site of the tumor often paired with a temporally related injury. Pathologic fracture at the tumor site is more common with osteosarcoma and may correlate with a worse prognosis (Sun et al. 2015). Eventual visualization of a mass at the primary site, unless the primary is pelvic, is common. Children with Ewing sarcoma may have recurrent, low-grade fevers, anorexia, or weight loss; systemic symptoms are typically lacking in children with osteosarcoma (Bacci et al. 2000a). Vital sign abnormalities may include elevated blood pressures secondary to pain at the primary tumor or sites of bony metastases. While bone tumors can metastasize to the lung, respiratory symptoms at presentation are rare. Physical exam findings include limitations to range of motion of the involved limb or joint and/or a palpable extremity mass. Laboratory abnormalities are non-specific however elevated LDH levels have been implicated with poor prognosis for patients with both osteo- and Ewing sarcomas (Bacci et al. 2000a; Ferrari et al. 2001).

Histology and Molecular Profile

Percutaneous core-needle biopsy should be pursued following X-ray and MRI of the primary site (see below). Needle tract placement should be cautiously planned in a region anticipated to be

resected during local control surgery. It has been postulated that failure to resect the needle tract portends a higher risk for recurrence (Andreou et al. 2011). Histologically, osteosarcoma tumors are unique; tumor cell formation of osteoid is visualized in the specimen. Osteosarcoma tumors are separated into one of two subtypes: central (or medullary) and surface (or peripheral) tumors. Central tumors include conventional central osteosarcomas (the most common pathologic subtype), as well as intraosseous low-grade osteosarcomas, telangiectatic tumors, and small-cell osteosarcomas. Surface tumors include parosteal low-grade tumors as well as periosteal low- to intermediate- and surface high grade tumors. Osteosarcomas are characterized molecularly by an exceptionally high number of structural variants and chromosomal instability (Chen et al. 2014). Somatic mutations in the TP53 gene are present in most cases.

Ewing sarcoma tumors are histologically small, round, and blue (Fig. 19.4) and characterized by diffuse membranous staining for CD99, a transmembrane protein (Kovar et al. 1990). A translocation involving the EWSR1 gene and a TET family member (i.e. FLI1 or ERG) is reported in 85% of cases (Sankar et al. 2013). Alternative translocations have also been reported (i.e. CIC:DUX4); tumors harboring these chromosomal abnormalities while felt to be in the Ewing sarcoma family at present, may be re-categorized going forth as they tend to carry a worse prognosis (Smith et al. 2015). Somatic mutations in STAG2 and TP53 in classic Ewing tumors have been associated with poor outcomes (Tirode et al. 2014; Crompton et al. 2014).

Staging

The recommended staging approach for both osteosarcoma and Ewing sarcoma is similar given the pattern of spread for both diseases. X-rays of the primary site may demonstrate one of two abnormalities in the periosteum at the bony cortex: (1) a starburst formation (tenting of the periosteum caused by calcification and bone formation) denoting osteosarcoma or (2) onion skinning (lifting of the periosteum) denoting Ewing sarcoma (Fig. 19.5). An MRI of the primary site can best delineate the degree of soft

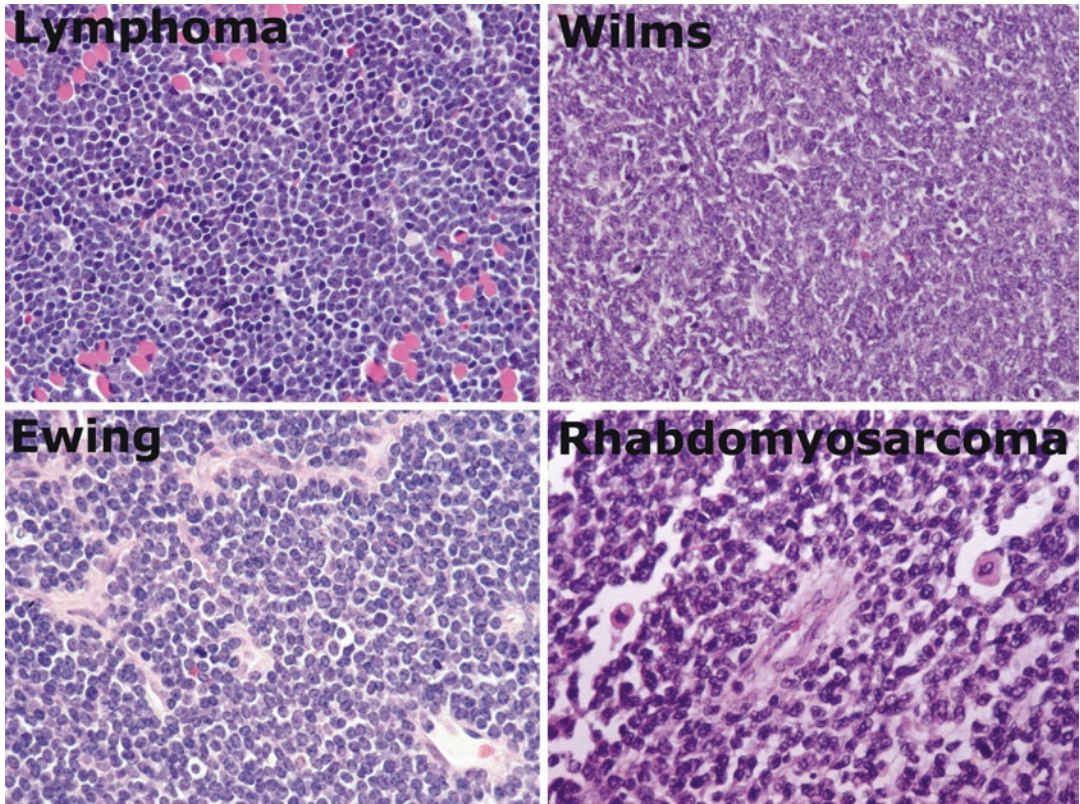


Fig. 19.4 Under the microscope, Ewing sarcoma tumors, like many other childhood malignancies, are small round and blue in appearance. The similarity between tumors on hematoxylin-eosin (H&E) staining underscores the

importance of obtaining additional immunohistochemical and molecular studies to make the diagnosis. This figure is courtesy of Antonio R. Perez-Atayde, M.D., Ph.D.

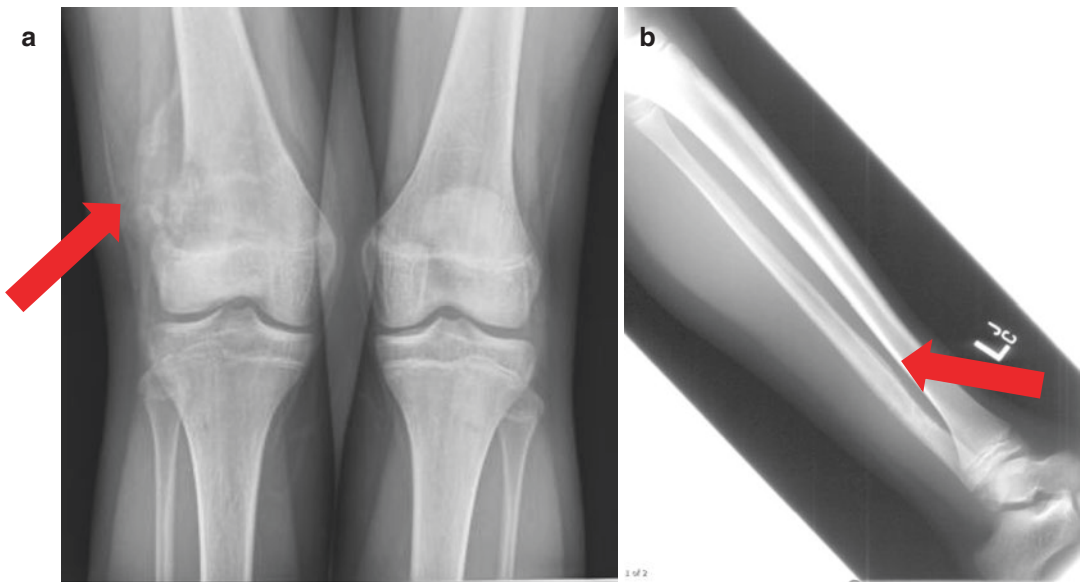


Fig. 19.5 Radiographs demonstrating characteristic periosteal reactions in patients diagnosed with (a) osteosarcoma (sunburst) and (b) Ewing sarcoma (onion skinning)

tissue, joint, and bony involvement and can help with local control planning. For osteosarcoma, the bone above and below the primary tumor should be imaged to rule out skip metastases (Kager et al. 2006). A chest CT is warranted for evaluation of lung metastases. More recently, use of PET scan in Ewing sarcoma has gained favor both as a means of evaluating the primary site of disease as well as assessing for bony involvement (Newman et al. 2013). Osteosarcoma, while PET avid, still more traditionally relies upon the use of bone scan to evaluate for bony spread (Byun et al. 2013). Staging of Ewing sarcoma traditionally involves assessment for marrow involvement with bilateral bone marrow aspirates and biopsies. However, patients with single-site disease are highly unlikely to have isolated marrow spread therefore a shift from this paradigm may occur. (Kopp et al. 2015). Staging of bony tumors departs from the more traditional surgical or imaging based approaches utilized for other tumors. Prognostically, high-grade osteosarcomas and Ewing sarcoma tumors fall into one of two categories: metastatic or non-metastatic.

Treatment and Outcomes

Pre-treatment factors dictating outcome in patients with osteosarcoma include primary tumor site, size, and the presence of metastatic disease as all of these factors impact the ability to perform a complete resection (Donati et al. 2004; Pakos et al. 2009; Harris et al. 1998). As osteosarcoma tumors are not very radiosensitive, complete surgical resection is crucial for cure. Axial skeletal tumors and those of large size carry a poor prognosis; patients with bilateral pulmonary metastases, unresectable skip metastases, and bony metastases fare worse (<20% OS). High grade osteosarcoma of either central or surface etiology requires systemic chemotherapy and surgical resection. Patients with single-site, surgically resectable disease can achieve a 65% OS. Standard of care chemotherapy consists of cisplatin, doxorubicin, and high-dose methotrexate (MAP); 90% necrosis of the primary tumor after induction cycles of chemotherapy has been linked to a lower rate of recurrence (Kim et al. 2007; Anninga et al. 2011).

Patients with lung metastases must undergo thoracotomies for removal of disease that does not resolve with chemotherapy. The EURAMOS-1 (European and American Sarcoma Study Group) trial investigated the addition of ifosfamide and etoposide to the standard MAP backbone for patients with poor tumoral necrosis; addition of these agents did not impact outcome (Marina et al. 2016). Low-grade osteosarcomas can be treated with wide resection alone (Grimer et al. 2005). Nearly 80% of patients with extremity osteosarcoma can be treated with limb-sparing procedures to avoid amputation (Bacci et al. 2000b).

Pre-treatment factors dictating outcome in patients with Ewing sarcoma also include tumor site, size/volume, and the presence of metastases (Cash et al. 2016; Rodriguez-Galindo et al. 2007). Given that Ewing sarcoma tumors are exquisitely sensitive to chemotherapy, treatment response is likewise an important prognostic factor (Paulussen et al. 2001; Wunder et al. 1998). Treatment hinges upon systemic chemotherapy and surgery and/or radiotherapy for local control (the latter for positive margins, an unresectable tumor, or lung metastases) (Donaldson 2004; Liu et al. 2011). Unlike for osteosarcoma, outcomes are equivalent for patients receiving surgery versus radiotherapy for local control of the primary tumor; surgery is prioritized when possible to avoid the late effects associated with radiotherapy (DuBois et al. 2015). Results from the COG AEWS0031 trial delivering interval compressed chemotherapy every 2 weeks, alternating between vincristine, doxorubicin, and cyclophosphamide and ifosfamide, etoposide demonstrated an improvement in event-free survival to 73% at 5 years (Womer et al. 2012). A recent pilot study (COG AEWS1031) incorporating cyclophosphamide and topotecan, agents efficacious in the relapsed setting, to upfront use demonstrated tolerability when incorporated with interval compressed therapy (Mascarenhas et al. 2016). There have been no recent improvements in overall survival for patient with metastatic disease (<30%). An ongoing COG trial (COG AEWS 1221) is investigating the use of an anti-IGFR (insulin-like growth factor receptor) antibody combined with conventional chemotherapy. High dose che-

motherapy with hematopoietic stem cell rescue has been studied for patients with high risk of relapse and has demonstrated little proven benefit (Meyers et al. 2001).

Local control options have advanced dramatically over the last few decades; while amputation for extremity tumors was a previous standard, limb-sparing procedures with use of metal prostheses and/or bony allografts are increasingly pursued. Internal or external hemipelvectomies with reconstruction remain promising for the treatment of pelvic primaries. Rotationplasty, a technique best suited for patients with a distal femur primaries (typically osteosarcoma) requiring an above-the-knee amputation, remains an approach requiring specialized skill but allowing for excellent post-surgical functionality (Han et al. 2016).

Soft Tissue Sarcomas

Epidemiology, Pathophysiology, and Genetic Predisposition

Soft tissue sarcomas fall into one of two categories on the basis of histology: rhabdomyosarcoma (RMS) and non-rhabdomyosarcoma (non-RMS). These tumors are of mesenchymal origin: i.e. striated muscle (rhabdomyosarcoma), smooth muscle, connective, nerve, or vascular tissue and account for approximately 7% of all childhood malignancies (Pappo and Pratt 1997; Gurney et al. 1995). Soft tissue sarcomas can arise in any age group with certain histologies preferentially affecting different age ranges. For example, alveolar RMS is more commonly seen in adolescents while embryonal RMS is more typically seen in younger children with a peak incidence in the 0–4 year age range (Ognjanovic et al. 2009). Non-RMS tumors more typically affect adolescents and adults. RMS tumors most commonly involve the head and neck region, genitourinary tract, and extremities while non-RMS tumors typically arise from the trunk and extremities (Crist et al. 1995; Maurer et al. 1993; Dillon et al. 1992). Both tumors can spread to regional or distant lymph nodes, or hematogenously to lung and bone. RMS tumors have the capability to spread to bone marrow. A diagnosis of sarcoma in any

individual under 40 years of age should prompt concern for a hereditary cause, most notably Li Fraumeni Syndrome (Li and Fraumeni 1969; Diller et al. 1995) Anaplasia in RMS cases has also been linked to germline TP53 mutation carriage (Hettmer et al. 2014). Large birth weight and gestational size have been linked to an increased incidence of embryonal RMS (Ognjanovic et al. 2010). While other, hereditary cancer syndromes have been implicated, they are paired to rare subsets of non-RMS tumors and will not be further explored in this chapter.

Presenting Symptoms

Given the range of tissues from which these tumors can arise, symptoms are largely dependent upon the site of the primary tumor, degree of local invasion to adjacent structures, and metastases. Dependent upon histology, patients may present with a slow, indolently growing lesion (synovial sarcoma) or a rapidly enlarging mass. Pain at the sites of metastases may also be reported. Vital sign changes can include hypertension secondary to pain, tachycardia secondary to anemia (of chronic disease or due to bone marrow involvement), or weight loss. Physical exam findings include palpation of the primary mass, which is often firm and immobile. Patients with the botryoid variant of RMS may have a tumor mimicking a “cluster of grapes” protruding from a body orifice such as the vagina, bladder, or nasopharynx.

Histology and Molecular Profile

Percutaneous core-needle biopsy should be pursued from the primary tumor site or a metastatic site if more readily amenable to needle access. RMS can be divided into three histologic categories: embryonal (which accounts for approximately 60–70% of cases), alveolar, and pleomorphic or anaplastic. Embryonal tumors typically involve the head, neck or GU track but can occur at any site (Parham and Ellison 2006). Alveolar RMS account for approximately 20% of RMS tumors and have a propensity to arise from the extremities, trunk and perineum (Parham and Ellison 2006). Pleomorphic RMS is rarely seen in pediatric patients. Molecularly, approximately a third of embryonal RMS tumors demonstrate a

Ras pathway mutation (Chen et al. 2013). These tumors can also contain anaplasia, more commonly seen in children with TP53 mutations (Hettmer et al. 2014). 70–80% of alveolar RMS cases harbor a translocation between the FOXO1 gene and the PAX3 or PAX7 genes (Barr et al. 2006).

Non-RMS tumors include a wide range of histologies including: alveolar soft part sarcoma, clear cell sarcoma, dermatofibrosarcoma protuberans, desmoid fibromatosis, epithelioid sarcoma, infantile fibrosarcoma, inflammatory myofibroblastic tumors, malignant peripheral nerve sheath tumors, and synovial sarcomas (to name only a few). Each has a unique histologic appearance, some have unique imaging characteristics, and many have a characteristic chromosomal translocation. Tumor grade is based upon cellularity, cellular pleomorphism, mitotic activity, necrosis, and invasion (Parham et al. 1995).

Staging

Imaging of RMS and non-RMS tumors relies upon the use of MRI both for delineation of the soft tissues as well as for radiation planning given that patients who require radiotherapy for an unresectable primary receive doses based upon diagnostic tumor volumes (Wolden et al. 1999). Chest CT should likewise be obtained to evaluate for lung metastases. For patients with a paratesticular primary, thin-cut abdominopelvic CT images should be obtained to evaluate the size and shape of retroperitoneal nodes and a retroperitoneal lymph node dissection should be pursued for patients >10 years of age (Wiener et al. 2001). PET scan is now routinely used to help verify sides of nodal involvement as well as for the detection of bony metastases (Federico et al. 2013; Grant et al. 2010). Patients with a diagnosis of RMS must also undergo bilateral bone marrow aspirates and biopsies. For patients with a parameningeal RMS tumor, brain/spine MRI and lumbar puncture are likewise warranted. Sentinel node biopsy is recommended at diagnosis for all patients with RMS and for a handful of patients with non-RMS (dictated by histology: epithelioid, synovial, clear cell for example) given the prog-

nostic and therapeutic significance of regional lymph node spread (Kayton et al. 2008; Alcorn et al. 2013; Andreou et al. 2013).

RMS follows a complex staging algorithm (stage I through IV) determined by the tumor's primary site, size, and the presence or absence of regional lymph nodes or distant metastases. The tumor's primary site is deemed either favorable or non-favorable. Oversimplified, stage I tumors are of favorable site without distant spread, stage II or III tumors are of unfavorable site (and of variable size and lymph node involvement) and stage IV tumors are metastatic. Tumors are likewise grouped by their degree of resectability: completely resected with clear margins (group I), resected with microscopic margins and/or with involved but resected lymph nodes (group II), gross residual disease (group III), and distant metastases (group IV). The stage and group of each tumor is subsequently coupled with histology (embryonal or alveolar) to determine the patient's risk status (Fig. 19.6). Non-RMS tumors are risk-stratified by tumor grade, the presence or absence of metastases, tumor size, and surgical margins.

Treatment and Outcomes

Prognostic factors for RMS include age at diagnosis, tumor size, and site of primary disease. Patients >9 years or <1 year, with tumors >5 cm, or alveolar histology have a worse prognosis (Crist et al. 1995; Malempati et al. 2011; Ferrari et al. 2010; Meza et al. 2006). Treatment for RMS tumors typically involves receipt of chemotherapy (with the regimen dependent upon risk status) and local control by means of surgery, radiotherapy or a combination of the two. Use of radiotherapy is reserved for alveolar tumors (even if completely resected), residual disease after tumor resection, inoperable tumors, metastases, or the presence of involved lymph nodes. Tumors are resected at diagnosis if possible; this approach is pursued only if the tumor can be removed without disfigurement or functional compromise. Low risk patients (25% of patients) are those with embryonal tumors in favorable sites that have been grossly resected, embryonal tumors of the orbit, or localized

a

| Site Classification | Sites |
|---------------------|--|
| Favorable | Orbit, head and neck (non-meningeal), genitourinary (non-bladder, non-prostate), biliary tract/liver |
| Unfavorable | Parameningeal, bladder/prostate, extremity, trunk and retroperitoneum (non-biliary tract/liver), other |

b

| Risk | Histology | Stage | Sites | Group |
|--------------|-----------------------|---------|-------------|----------------------|
| Low | Embryonal | 1 | Favorable | I, II, III (orbital) |
| | | 2, 3 | Unfavorable | I, II |
| Intermediate | Embryonal | 2, 3 | Unfavorable | III |
| | Alveolar | 1, 2, 3 | | I, II, III |
| High | Embryonal or Alveolar | 4 | | IV |

Fig. 19.6 Rhabdomyosarcoma follows a complex staging algorithm contingent upon site of disease, histology, and surgical resectability. Table (a) delineates favorable

vs. unfavorable sites of disease. Table (b) delineates the risk stratification schema used to select an appropriate chemotherapeutic regimen

embryonal tumors in an unfavorable site that have been grossly resected. Low risk patients can achieve survival rates greater than 90% when treated with vincristine and actinomycin (VA), vincristine, actinomycin, and cyclophosphamide (VAC), or shorter-duration VAC with transition to VA ± radiation if tumors are incompletely excised (Raney et al. 2011; Walterhouse et al. 2014). Intermediate risk group patients (50% of patients) are those with embryonal RMS of unfavorable sites with gross residual disease or non-metastatic alveolar RMS. The most recent COG trial ARST0531 found no improvement in outcome (3-year OS ~85%) for patients treated with VAC alternating with vincristine and irinotecan (VAC/VI) but fewer toxicities, therefore this regimen has been adopted as standard and will serve as the backbone in the next clinical trial (Crist et al. 2001). For high-risk patients, those with metastatic disease of either histology, outcomes remain quite poor at less than 50% (Breneman et al. 2003). Treatment intensification (inclusion of doxorubicin, irinotecan, ifosfamide, and etoposide) has failed to improve outcomes, only delaying relapse, therefore VAC/VI has been adopted in many institutions as a standard

treatment regimen for high-risk patients with the goal to diminish toxicity and maintain quality of life (Weigel et al. 2016).

Treatment of non-RMS patients is dichotomized depending on the presence or absence of metastatic disease and is modeled after the approach laid forth in a recent COG trial (ARST0332) with use of ifosfamide and doxorubicin for all risk categories (Spunt et al. 2014). Low risk patients are those with grossly resected, non-metastatic disease of either (1) low histologic grade and any tumor size or (2) high histologic grade but small tumor size (<5 cm). Patients with low-grade histology can be observed status-post resection even if microscopic positive margins remain. Patients with high-grade histology and microscopic margins receive adjuvant radiotherapy. Intermediate risk patients have either grossly resected, high-grade histology, and tumors >5 cm, or unresectable high-grade tumors for which delayed resection is planned. Those with grossly resected disease receive adjuvant chemo- and radiation therapy while those with a planned resection receive neoadjuvant chemo- and radiation therapy. Finally, high risk patients are those with metastatic disease: (1) of low grade

histology, completely resected (observation), (2) of low or high grade histology and grossly resected (adjuvant chemotherapy and radiotherapy) or (3) that remains unresectable (neoadjuvant treatment). Patients meeting guidelines for observation can achieve 99% OS, those receiving adjuvant radiotherapy 100% OS, those receiving adjuvant chemoradiotherapy 81%, and those requiring neoadjuvant treatment 66% OS (Spunt et al. 2014). Patients with unresectable, metastatic non-RMS tumors have a poor outcome.

Rare Tumors

Germ Cell Tumors

Epidemiology, Pathophysiology, and Genetic Predisposition

Germ cell tumors (GCTs) arise from primordial germ cells that fail to migrate to the gonads during embryonic development (Dehner 1983). As a result, the vast majority grow in close approximation to the midline (mediastinum, retroperitoneum, coccyx). Germ cell tumors fall into two categories on the basis of their location: gonadal and extragonadal. More globally, these tumors can be mature (benign), immature, or malignant. Tumors can be further subdivided into histologic categories: germinomas (dysgerminoma of the ovary or seminoma of the testis) or nongerminomas (teratoma—mature or immature, yolk sac or endodermal sinus tumors, choriocarcinoma, gonadoblastoma, embryonal carcinoma, or mixed tumors). GCTs account for approximately 3% of cancers in children less than 15 years of age with teratomas more frequently occurring in the fetal or neonatal age group (Kaatsch et al. 2015). Extracranial GCTs account for approximately 14% of cancers in adolescents aged 15–19 years. DICER1 mutations have been described in association with a small subset of germinomas (juvenile granulosa cell tumors) (Schultz et al. 2011). Patients with Klinefelter or Turner syndrome are at increased risk for GCTs as are children with cryptorchidism (Dexeus et al. 1988; Tanaka et al. 1994; Johnson et al. 2009). GCTs have a propensity to spread to the liver, bone, brain, and lung.

Presenting Symptoms

As germ cell tumors typically arise from the midline, patients with a mediastinal tumor can present with a persistent cough, difficulties lying flat, or other non-specific respiratory symptoms. Others can present with abdominopelvic distension, pain, and a palpable abdominal or testicular mass. Vital sign changes may include tachypnea, altered O₂ saturations, or hypertension secondary to pain. Yolk sac tumors produce alfa-fetoprotein (AFP) while germinomas and choriocarcinomas produce beta-human chorionic gonadotropin (beta-hCG). Most pediatric malignant germ cell tumors have a component of yolk sac tumor thereby causing an elevation in AFP. Fetal teratomas, while technically benign, can be diagnosed in utero and result in hydrops fatalis or a difficult delivery (Heerema-McKenney et al. 2005). Clinicians must be cognizant that in a child <3 years of age, baseline AFP levels are elevated due to residual circulating AFP synthesized by the yolk sac and fetal liver. This can pose a challenge for interpreting elevated AFP levels at diagnosis or when following decline of levels during treatment (Blohm et al. 1998).

Histology and Molecular Profile

Percutaneous, core-needle biopsy is pursued to sample tumors of the mediastinum or abdomen/pelvis unless the lesion is readily amenable to upfront resection. If the mass is testicular or ovarian, care must be taken when planning the surgical approach. Radial orchiectomy as opposed to a transscrotal biopsy is preferred to avoid scrotal contamination while ovarian tumor mobilization, peritoneal washes, and lymph node sampling are crucial both to avoid spillage and to complete the staging work-up. Biopsy of a mass might miss immature elements but histology coupled with serum tumor markers can help complete the diagnostic picture. Mature teratomas typically occur in the ovary and at extragonadal locations while immature teratomas more frequently occur in young children at extragonadal sites and in the ovaries of peri-pubertal females (Gobel et al. 1998; Heifetz et al. 1998). Malignant GCTs contain frank malignant tissues with a fraction of mature or immature teratoma also present. Testicular GCTs in early childhood can be either

teratomas or malignant pure yolk sac. Testicular tumors in adolescents can be of either pure or mixed histology. Ovarian GCTs include benign teratomas, immature teratomas, dysgerminomas, yolk sac tumors or mixed tumors. Extragonadal tumors in young children are often present at birth or during early childhood and are typically benign (Malogolowkin et al. 1990). However, malignant GCTs most frequently occur in the mediastinum in older children and adolescents. Age greater than 11 years and advanced stage of disease have been demonstrated to be poor prognostic factors (Marina et al. 2006; Bokemeyer et al. 2002).

Staging

The work-up of a patient with known or presumed malignant GCT includes MRI of the abdomen \pm spine dependent upon the site of tumor origin, chest CT, and either radionuclide bone scan or PET scan to assess for bony disease or to further delineate sites of soft tissue involvement. A brain MRI might also be considered to rule out intracranial disease. Disease staging is highly dependent upon histologic subtype. The Children's Oncology Group stages non-germinomatous testicular GCTs as follows: limited to the testis (stage I), transscrotal orchiectomy with tumor spillage or microscopic disease in the scrotum or high in the spermatic cord with failure of tumor markers to normalize post-operatively (stage II), gross residual disease or retroperitoneal lymph node involvement (stage III), and distant metastases (stage IV). Retroperitoneal lymph node dissection is not required in males <15 years of age but is routinely pursued in older adolescents and adults (de Wit and Fizazi 2006). The COG ovarian GCT staging is similar: localized disease that is completely resected with no evidence of capsular rupture and negative peritoneal cytology (stage I), microscopic residual, capsular invasion, or microscopic lymph node involvement (stage II), gross residual disease including cytologic evidence of tumor cells in ascites (stage III), and disseminated disease (stage IV). Extragonadal, extracranial GCTs follow a surgical algorithm similar to that for other solid tumors distinguishing completely resected disease from that with microscopic, gross margins, or metastatic disease.

Treatment and Outcomes

Prognosis for pediatric GCTs typically depends upon histology, patient age, disease stage, and primary disease site (Frazier et al. 2015). Patients with non-sacroccygeal mature teratomas and stage I immature teratomas, as well as mature and immature sacroccygeal teratomas can be observed following surgery with a >95% OS (Gobel et al. 1998; Marina et al. 1999). Resection of a sacroccygeal mass requires removal of the coccyx in an effort to minimize the risk of tumor recurrence (Gobel et al. 1998). Higher stage immature teratomas do not respond well to chemotherapy and typically portend a poor prognosis (Norris et al. 1976). The half-life of AFP is approximately 7 days; when post-operative observation is perused, values are serially followed to assure return-to-normal.

Patients with completely resected gonadal tumors (stage I) can be closely observed following resection with excellent survival rates approaching 100% (Rescorla et al. 2015; Dark et al. 1997). The treatment of higher stage malignant gonadal GCTs and all extragonadal GCTs typically requires surgical resection of disease, when possible, and administration of platinum-based chemotherapy (cisplatin, etoposide and bleomycin termed PEB) to achieve an OS >90% (Rogers et al. 2004; Cushing et al. 2004). Treatment of higher stage testicular disease in adolescents (>15 years) typically follows an adult treatment approach involving RPLND, risk stratification on the basis of histology, tumor markers, measure of serum LDH, and cisplatin-based chemotherapy with weekly bleomycin (termed BEP) (Williams et al. 1987). The combination of carboplatin, etoposide, and bleomycin, as a means by which to limit platinum exposure and lessen ototoxicity, has been studied in the UK; outcomes using this regimen were comparable to cisplatin-based therapies but a head-to-head trial has not yet been performed (Mann et al. 2000). The successful treatment of extragonadal disease is highly dependent upon patient age and disease location. Patients with stage I or II disease can achieve a 90% OS while those with stage III or IV disease can achieve an 80% OS. As noted, patients >12 years of age with mediastinal

disease have a worse outcome with less than 60% OS (Bokemeyer et al. 2002).

Liver Tumors

Epidemiology, Pathophysiology, and Genetic Predisposition

Liver tumors comprise approximately 1% of all pediatric malignancies (Meyers 2007; Czauderna et al. 2001). Hepatoblastoma (HB) accounts for greater than two-thirds of all tumors while hepatocellular carcinoma (HCC) is the second most common. Other primary pediatric liver malignancies include undifferentiated sarcoma, rhabdoid tumors, and angiosarcoma but these diagnoses are exceedingly rare. HB is traditionally diagnosed in children less than 3 years of age while HCC is more typically diagnosed in adolescence. Liver tumors can directly extend through the portal or hepatic vasculature or advance locally to regional lymph nodes. Distant metastases most frequently occur in the lung but rarely can affect the bone or brain. Very-low-birth weight premature infants are at substantially higher risk of developing hepatoblastoma than those of average birth weight (Ikeda et al. 1998). Inheritance of an APC gene mutation (familial adenomatous polyposis) has been linked to a higher risk of developing hepatoblastoma, particularly multifocal disease, as is a diagnosis of Beckwith-Weidemann (Gupta et al. 2013; Maas et al. 2016). Hepatocellular carcinoma has been linked to Hepatitis B or C infection, the former less common since institution of widespread vaccination programs, and other more rare hereditary syndromes predisposing to underlying liver dysfunction (e.g., glycogen storage disease, biliary atresia, alpha-1-antitrypsin deficiency, etc.) (Tajiri et al. 2011; Bhadri et al. 2005; Labrune et al. 1997).

Presenting Symptoms

Pediatric patients with HB or HCC typically present with an enlarged abdomen and a palpable abdominal mass. Vital sign changes may include tachypnea secondary to restrictive lung indices or hypertension secondary to pain. Younger children

may demonstrate irritability in excess of baseline. Similar to malignant GCTs, HB and up to two-thirds of HCCs secrete AFP. Clinicians must again be cognizant that in a child <3 years of age, baseline AFP levels are elevated due to residual circulating AFP synthesized by the yolk sac and fetal liver. This can pose a challenge for interpreting elevated AFP levels at diagnosis or when following decline of levels during treatment (Blohm et al. 1998). A small subset of HB tumors likewise secrete hCG leading to precocious puberty (Eren et al. 2009). Additional laboratory abnormalities include thrombocytosis, given that HB has been associated with higher levels of thrombopoietin (Komura et al. 1998).

Histology and Molecular Profile

Percutaneous core-needle biopsy is again recommended when making the diagnosis of HB and HCC. Biopsy of "normal" liver tissue is useful to obtain concurrent with tumor biopsy to aid with evaluation of liver dysfunction or an underlying predisposition for HCC. Tumors can demonstrate a range of histologies: HB tumors can be epithelial (including pure fetal with or without mitoses, mixed embryonal/fetal, macrotrabecular, and small cell undifferentiated) or mixed epithelial and mesenchymal (with teratoid or non-teratoid features) (Lopez-Terrada et al. 2014). Small cell undifferentiated (SCU) features, with the presence of rhabdoid elements (with immunohistochemical INI-1 loss), are associated with a low AFP and portend a worse prognosis (Meyers et al. 2009; Trobaugh-Lotrario et al. 2009). HB tumors are characterized by abnormalities in the WNT pathway with the majority of tumors demonstrating CTNNB1 activation mutations or deletions (Eichenmuller et al. 2014). Tumors with mixed HB and HCC histologies have also been described in late childhood and early adolescence and are termed transitional cell tumors or HCC not otherwise specified (HCC NOS) (Lopez-Terrada et al. 2014). These tumors are variably chemotherapy responsive and portend a poor prognosis. HCC tumors are of two specific histologies: classic and fibrolamellar. Classic HCC can arise *de novo* or in the context

of underlying liver dysfunction secondary to infection or hereditary metabolic syndromes. These tumors are characterized by chromosomal instability, TP53, and TERT mutations (Sumazin et al. 2016). Fibrolamellar HCC, conversely, arises in the context of a healthy liver and is not associated with an elevated AFP. These tumors have recently been found to uniformly harbor a DNAJB1: PRKACA chimeric fusion transcript (Honeyman et al. 2014).

Staging

Liver ultrasound can be obtained as first-pass imaging for a new liver tumor. A more focused evaluation of the liver parenchyma is subsequently required and best achieved by the use of MRI with Eovist contrast agent, which allows delineation of disease, differentiation between benign and malignant entities, and an evaluation for multifocality (Meyers et al. 2012; Asayama et al. 2016). Chest CT is required for evaluation of pulmonary metastases. Liver tumors are staged by one of two methods: the COG Evans surgical staging approach or the European imaging-based PRETEXT method. COG surgical staging, greatly oversimplified, relies upon the ability to resect a tumor at diagnosis: completely resectable (stage I), resectable with positive microscopic margins (stage II), unresectable—i.e. attempts would leave macroscopic disease behind (stage III), and metastatic (stage IV). PRETEXT staging relies upon the anatomic and radiographic division of the liver into four quadrants. Tumor involvement of one quadrant (PRETEXT I), two adjoining quadrants (PRETEXT II), three adjoining or two non-adjoining quadrants (PRETEXT III) or all four quadrants (PRETEXT IV) is established at diagnosis and demonstrated to be prognostic (Brown et al. 2000; Maibach et al. 2012; Roebuck et al. 2007; Aronson et al. 2005). Suffixes are likewise applied to the PRETEXT algorithm to further describe tumor extent: portal venous involvement (P), vena cava or hepatic venous involvement (V), extrahepatic disease (E), multifocality (F), rupture (R), lymph node involvement (N) or metastases (M). The most recent COG

liver tumor trial (AHEP0731) sought to adopt PRETEXT staging in addition to surgical staging. The staging system for HCC in pediatric patients is not as well defined but generally follows a surgical staging approach.

Treatment, Outcomes, and Surveillance

Prognosis is clearly linked to surgical resectability, histology, PRETEXT/stage, vascular involvement, and serum AFP levels although recent retrospective data suggests that age may likewise play a role (Fuchs et al. 2002; Czauderna et al. 2016). Poor prognosis has been linked to an upfront unresectable tumor, metastatic disease, a low AFP (<100 ng/mL), and small cell undifferentiated features. Cisplatin is a staple chemotherapeutic for the treatment of HB with addition of doxorubicin for higher risk cases. Surgical resection of the primary tumor is crucial for cure. Patients with completely resection (stage I), pure fetal histology with <2 mitoses per 10 high powered fields can be observed post-operatively with excellent outcomes approaching 100% (Malogolowkin et al. 2011). Those with stage I or II upfront resected disease of other histologies (excluding small cell undifferentiated) have, on COG protocols, traditionally received adjuvant chemotherapy consisting of cisplatin, 5-FU, and vincristine (C5V). An arm of the current COG AHEP0731 trial focused on a reduction in the number of cycles administered post-operatively with the goal to maintain excellent survival rates of ~90%; results to this arm of the trial remain pending (Douglass et al. 1993; Ortega et al. 2000). COG AHEP0731 also studied the addition of doxorubicin to C5V (i.e. C5VD) for patients with unresectable stage III disease and low stage SCU disease. While survival for this cohort previously approximated 70–80%, the preliminary 3-year OS for patients on protocol has been reported at 92% (publication pending). The increasing use of liver transplantation in this patient population has likewise contributed to improved survival rates however the long-term outcome of children undergoing liver transplantation remains under study (Malek et al. 2010; Tiao et al. 2005).

Patients with metastatic disease are often prescribed a doxorubicin-containing regimen (C5VD) given that their outcomes remain quite poor. COG AHEP0731 studied the addition of vincristine and irinotecan (VI) to C5VD. Results demonstrated a 62% 3-year OS, improved from the historically reported outcomes of 20–50% for this cohort (Katzenstein et al. 2017). Our European colleagues have focused their study on eliminating doxorubicin from patients perceived to be at lower risk (PRETEXT I-III) while escalating therapy intensity for those with metastatic disease (Perilongo et al. 2009). A recent pilot for patients with metastatic disease receiving dose-dense cisplatin (i.e. weekly), doxorubicin, and carboplatin achieved a 79% 3-year OS (Zsiros et al. 2013). Controversy still remains regarding the appropriate treatment approach for lung metastases and whether metastatectomy is warranted to improve overall survival (O'Neill et al. 2017). For patients undergoing liver transplantation, metastatectomy is typically pursued to render patients free of extrahepatic disease. The upcoming Pediatric Hepatic tumor International Therapeutic Trial (PHITT) will be the first international collaborative trial aimed at determining the optimal treatment approach for patients with localized and metastatic disease (both for HB and HCC), while allowing an opportunity for the study of biology and toxicity.

The treatment of hepatocellular carcinoma remains challenging; while 50% of patients respond to upfront chemotherapy, only a small fraction become resectable. Current treatment regimens employ use of cisplatin and doxorubicin with or without sorafenib given data in adults that sorafenib single-agent therapy is life-prolonging (Schmid et al. 2012; Llovet et al. 2008). Immunotherapy (PD-1 inhibition) has shown promise in adult HCC but further study is warranted (El-Khoueiry et al. 2015). Liver transplantation is utilized conservatively for patients with disease confined to the liver (Patel et al. 2012). While patients with upfront surgically resectable disease can achieve a greater than 80% OS, those with metastatic disease have a dismal prognosis of <15% OS (Katzenstein et al. 2002; Czuderna et al. 2002). The role for transarterial

chemoembolization (TACE), while utilized routinely in adult patients as a bridge to resection or liver transplantation, remains under study for both the pediatric HB and HCC populations.

Other Tumors

Retinoblastoma

Retinoblastoma is a tumor arising from the retina commonly affecting children less than 3 years of age. It is frequently detected by families and outpatient practitioners and can be successfully treated if diagnosed early. Families often report the absence of a red reflex or a “white” appearing pupil (leukocoria) in photographs with outpatient practitioners identifying the same phenomenon on exam. Eye tumors are “grouped” according to size, degree of retinal and vitreous involvement, as well as location and proximity to the foveola and optic disc (Shields et al. 2006). Metastatic disease to the intracranial space or distantly to the bone marrow is possible although rare in developed countries. Exams under anesthesia are crucial for grouping, as is the use of MRI to define disease extent and evaluate for intracranial spread. For higher risk patients (i.e. those with extraocular disease or more aggressive histology), lumbar puncture and bilateral bone marrow aspirates are pursued. Children with retinoblastoma should be tested for a germline Rb mutation as carriage dictates risk for “bilateral” disease involving the contralateral eye, “trilateral” disease involving the pineal gland, disease at a young age, multiple tumors, and secondary cancers (Abramson et al. 1998). Use of intra-arterial and intravitreal chemotherapy has been adopted as a means by which to preserve vision and avoid enucleation and systemic chemotherapy whenever possible (Gobin et al. 2011).

Adrenocortical Carcinoma

Adrenocortical carcinoma is a rare but aggressive cancer arising from the adrenal gland and affecting adolescents and adults. As these tumors can secrete cortisol, aldosterone, testosterone or estrogen, findings on exam may include cushingoid features and hirsutism (cortisol), high blood

pressure (cortisol and aldosterone) acne (testosterone) or irregular menstrual periods in females (testosterone, estrogen). Single site, surgically resectable disease carries an excellent prognosis whereas metastatic disease confers a poor prognosis as the tumor is poorly responsive to chemotherapy or hormonally- directed therapies (Allolio and Fassnacht 2006).

Survivorship/Late Effects

The prognosis for children with solid tumors continues to improve however not without long-term consequence. While new therapeutic protocols aim to diminish toxicity while maintaining overall survival, treatment intensification is still required for those with high-risk disease and a poor prognosis. Treatment effects on growth, development, organ function, and musculoskeletal health remain significant. In the aftermath of therapy, patients undergo serial surveillance imaging and laboratory tests along with studies of organ function: echocardiograms to screen for anthracycline-mediated cardiotoxicity, audiograms to screen for platinum-based ototoxicity, pulmonary function tests and cardiac stress tests in the aftermath of whole-lung or mediastinal radiotherapy, and nuclear medicine glomerular filtration rates to screen for renal toxicity. Fertility may be compromised by treatment as well as bone marrow health. Radiotherapy confers a high rate of secondary malignancy while surgery can be disfiguring or impact mobility. The emotional and psychological toll of treatment, even if successful, cannot be down-played. Patients typically require long-term multidisciplinary care and a comprehensive network of outpatient providers long past the period of oncologic treatment. As we continue to learn more about genetic predisposition syndromes associated with pediatric malignancy, the need for genetic counseling and referral for genetic testing has become paramount. In the era of personalized medicine, an improved understanding of tumor genomics may allow for more targeted therapies thereby reducing systemic toxicity. While improvements in outcome continue to be met, there remains much

work to be done in the treatment of pediatric solid tumor malignancies.

References

- Abramson DH, et al. Familial retinoblastoma: where and when? *Acta Ophthalmol Scand*. 1998;76(3):334–8.
- Acord M, Shaikh R. Predictors of diagnostic success in image-guided pediatric soft-tissue biopsies. *Pediatr Radiol*. 2015;45(10):1529–34.
- Alcorn KM, et al. Sentinel lymph node biopsy in pediatric soft tissue sarcoma patients: utility and concordance with imaging. *J Pediatr Surg*. 2013;48(9):1903–6.
- Allolio B, Fassnacht M. Clinical review: adrenocortical carcinoma: clinical update. *J Clin Endocrinol Metab*. 2006;91(6):2027–37.
- Andreou D, et al. The influence of tumor- and treatment-related factors on the development of local recurrence in osteosarcoma after adequate surgery. An analysis of 1355 patients treated on neoadjuvant Cooperative Osteosarcoma Study Group protocols. *Ann Oncol*. 2011;22(5):1228–35.
- Andreou D, et al. Sentinel node biopsy in soft tissue sarcoma subtypes with a high propensity for regional lymphatic spread—results of a large prospective trial. *Ann Oncol*. 2013;24(5):1400–5.
- Anninga JK, et al. Chemotherapeutic adjuvant treatment for osteosarcoma: where do we stand? *Eur J Cancer*. 2011;47(16):2431–45.
- Aronson DC, et al. Predictive value of the pretreatment extent of disease system in hepatoblastoma: results from the International Society of Pediatric Oncology Liver Tumor Study Group SIOPEL-1 study. *J Clin Oncol*. 2005;23(6):1245–52.
- Asayama Y, et al. Heterogeneity of non-cancerous liver parenchyma on gadoteric acid-enhanced MRI: an imaging biomarker for hepatocellular carcinoma development in chronic liver disease. *Clin Radiol*. 2016;71(5):432–7.
- Bacci G, et al. Prognostic factors in nonmetastatic Ewing's sarcoma of bone treated with adjuvant chemotherapy: analysis of 359 patients at the Istituto Ortopedico Rizzoli. *J Clin Oncol*. 2000a;18(1):4–11.
- Bacci G, et al. Long-term outcome for patients with non-metastatic osteosarcoma of the extremity treated at the istituto ortopedico rizzoli according to the istituto ortopedico rizzoli/osteosarcoma-2 protocol: an updated report. *J Clin Oncol*. 2000b;18(24):4016–27.
- Baker DL, et al. Outcome after reduced chemotherapy for intermediate-risk neuroblastoma. *N Engl J Med*. 2010;363(14):1313–23.
- Bardeesy N, et al. Anaplastic Wilms' tumour, a subtype displaying poor prognosis, harbours p53 gene mutations. *Nat Genet*. 1994;7(1):91–7.
- Barr FG, et al. Examination of gene fusion status in archival samples of alveolar rhabdomyosarcoma entered on the intergroup rhabdomyosarcoma study-III trial:

- a report from the Children's Oncology Group. *J Mol Diagn.* 2006;8(2):202–8.
- Beckwith JB. Precursor lesions of Wilms tumor: clinical and biological implications. *Med Pediatr Oncol.* 1993;21(3):158–68.
- Bhadri VA, et al. Hepatocellular carcinoma in children with Alagille syndrome. *J Pediatr Gastroenterol Nutr.* 2005;41(5):676–8.
- Biegel JA, et al. Germ-line and acquired mutations of INI1 in atypical teratoid and rhabdoid tumors. *Cancer Res.* 1999;59(1):74–9.
- Blohm ME, et al. Alpha 1-fetoprotein (AFP) reference values in infants up to 2 years of age. *Pediatr Hematol Oncol.* 1998;15(2):135–42.
- Bohdiewicz PJ, Gallegos E, Fink-Bennett D. Raccoon eyes and the MIBG super scan: scintigraphic signs of neuroblastoma in a case of suspected child abuse. *Pediatr Radiol.* 1995;25(Suppl 1):S90–2.
- Bokemeyer C, et al. Extragonadal germ cell tumors of the mediastinum and retroperitoneum: results from an international analysis. *J Clin Oncol.* 2002;20(7):1864–73.
- Bourdeaut F, et al. VIP hypersecretion as primary or secondary syndrome in neuroblastoma: a retrospective study by the Societe Francaise des Cancers de l'Enfant (SFCE). *Pediatr Blood Cancer.* 2009;52(5):585–90.
- Breneman JC, et al. Prognostic factors and clinical outcomes in children and adolescents with metastatic rhabdomyosarcoma—a report from the intergroup rhabdomyosarcoma study IV. *J Clin Oncol.* 2003;21(1):78–84.
- Bresler SC, et al. ALK mutations confer differential oncogenic activation and sensitivity to ALK inhibition therapy in neuroblastoma. *Cancer Cell.* 2014;26(5):682–94.
- Breslow NE, et al. End stage renal disease in patients with Wilms tumor: results from the National Wilms Tumor Study Group and the United States Renal Data System. *J Urol.* 2005;174(5):1972–5.
- Brodeur GM, et al. International criteria for diagnosis, staging, and response to treatment in patients with neuroblastoma. *J Clin Oncol.* 1988;6(12):1874–81.
- Brodeur GM, et al. Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. *J Clin Oncol.* 1993;11(8):1466–77.
- Brown J, et al. Pretreatment prognostic factors for children with hepatoblastoma—results from the International Society of Paediatric Oncology (SIOP) study SIOPEL 1. *Eur J Cancer.* 2000;36(11):1418–25.
- Bruder E, et al. Morphologic and molecular characterization of renal cell carcinoma in children and young adults. *Am J Surg Pathol.* 2004;28(9):1117–32.
- Byun BH, et al. Comparison of (18)F-FDG PET/CT and (99 m)Tc-MDP bone scintigraphy for detection of bone metastasis in osteosarcoma. *Skelet Radiol.* 2013;42(12):1673–81.
- Callaghan MU, Wong TE, Federici AB. Treatment of acquired von Willebrand syndrome in childhood. *Blood.* 2013;122(12):2019–22.
- Cash T, et al. Comparison of clinical features and outcomes in patients with extraskeletal versus skeletal localized Ewing sarcoma: a report from the Children's Oncology Group. *Pediatr Blood Cancer.* 2016;63(10):1771–9.
- Chen X, et al. Targeting oxidative stress in embryonal rhabdomyosarcoma. *Cancer Cell.* 2013;24(6):710–24.
- Chen X, et al. Recurrent somatic structural variations contribute to tumorigenesis in pediatric osteosarcoma. *Cell Rep.* 2014;7(1):104–12.
- Cohn SL, et al. The International Neuroblastoma Risk Group (INRG) classification system: an INRG Task Force report. *J Clin Oncol.* 2009;27(2):289–97.
- Crist W, et al. The third intergroup rhabdomyosarcoma study. *J Clin Oncol.* 1995;13(3):610–30.
- Crist WM, et al. Intergroup rhabdomyosarcoma study-IV: results for patients with nonmetastatic disease. *J Clin Oncol.* 2001;19(12):3091–102.
- Crompton BD, et al. The genomic landscape of pediatric Ewing sarcoma. *Cancer Discov.* 2014;4(11):1326–41.
- Cushing B, et al. Randomized comparison of combination chemotherapy with etoposide, bleomycin, and either high-dose or standard-dose cisplatin in children and adolescents with high-risk malignant germ cell tumors: a pediatric intergroup study—Pediatric Oncology Group 9049 and Children's Cancer Group 8882. *J Clin Oncol.* 2004;22(13):2691–700.
- Czauderna P, et al. Multicenter retrospective analysis of various primary pediatric malignant hepatic tumors—management in a series of 47 Polish patients (1985–1995). *Eur J Pediatr Surg.* 2001;11(2):82–5.
- Czauderna P, et al. Hepatocellular carcinoma in children: results of the first prospective study of the International Society of Pediatric Oncology group. *J Clin Oncol.* 2002;20(12):2798–804.
- Czauderna P, et al. The Children's Hepatic tumors International Collaboration (CHIC): novel global rare tumor database yields new prognostic factors in hepatoblastoma and becomes a research model. *Eur J Cancer.* 2016;52:92–101.
- Dark GG, et al. Surveillance policy for stage I ovarian germ cell tumors. *J Clin Oncol.* 1997;15(2):620–4.
- De Bernardi B, et al. Excellent outcome with reduced treatment for infants with disseminated neuroblastoma without MYCN gene amplification. *J Clin Oncol.* 2009;27(7):1034–40.
- Dehner LP. Gonadal and extragonadal germ cell neoplasia of childhood. *Hum Pathol.* 1983;14(6):493–511.
- Dexeus FH, et al. Genetic abnormalities in men with germ cell tumors. *J Urol.* 1988;140(1):80–4.
- Di Giannatale A, et al. Primary cutaneous and subcutaneous Ewing sarcoma. *Pediatr Blood Cancer.* 2015;62(9):1555–61.
- Diller L, et al. Germline p53 mutations are frequently detected in young children with rhabdomyosarcoma. *J Clin Invest.* 1995;95(4):1606–11.
- Dillon P, et al. A prospective study of nonrhabdomyosarcoma soft tissue sarcomas in the pediatric age group. *J Pediatr Surg.* 1992;27(2):241–4. discussion 244–5

- Dome JS, et al. Treatment of anaplastic histology Wilms' tumor: results from the fifth National Wilms' Tumor Study. *J Clin Oncol.* 2006;24(15):2352–8.
- Donaldson SS. Ewing sarcoma: radiation dose and target volume. *Pediatr Blood Cancer.* 2004;42(5):471–6.
- Donati D, et al. Osteosarcoma of the pelvis. *Eur J Surg Oncol.* 2004;30(3):332–40.
- Douglass EC, et al. Cisplatin, vincristine, and fluorouracil therapy for hepatoblastoma: a Pediatric Oncology Group study. *J Clin Oncol.* 1993;11(1):96–9.
- DuBois SG, et al. Comparative evaluation of local control strategies in localized Ewing sarcoma of bone: a report from the Children's Oncology Group. *Cancer.* 2015;121(3):467–75.
- Eaton KW, et al. Spectrum of SMARCB1/INI1 mutations in familial and sporadic rhabdoid tumors. *Pediatr Blood Cancer.* 2011;56(1):7–15.
- Eichenmuller M, et al. The genomic landscape of hepatoblastoma and their progenies with HCC-like features. *J Hepatol.* 2014;61(6):1312–20.
- El-Khoueiry AB, Melero I, Crocenzi TS, et al. Phase I/II safety and antitumor activity of nivolumab in patients with advanced hepatocellular carcinoma (HCC): CA209-040. Abstract. *J Clin Oncol.* 2015;33:PMID: 28147715.
- Eren E, et al. A rare cause of precocious puberty: hepatoblastoma. *J Clin Res Pediatr Endocrinol.* 2009;1(6):281–3.
- Federico SM, et al. Comparison of PET-CT and conventional imaging in staging pediatric rhabdomyosarcoma. *Pediatr Blood Cancer.* 2013;60(7):1128–34.
- Ferrari S, et al. Predictive factors of disease-free survival for non-metastatic osteosarcoma of the extremity: an analysis of 300 patients treated at the Rizzoli Institute. *Ann Oncol.* 2001;12(8):1145–50.
- Ferrari A, et al. Comparison of the prognostic value of assessing tumor diameter versus tumor volume at diagnosis or in response to initial chemotherapy in rhabdomyosarcoma. *J Clin Oncol.* 2010;28(8):1322–8.
- Frazier AL, et al. Revised risk classification for pediatric extracranial germ cell tumors based on 25 years of clinical trial data from the United Kingdom and United States. *J Clin Oncol.* 2015;33(2):195–201.
- Fuchs J, et al. Pretreatment prognostic factors and treatment results in children with hepatoblastoma: a report from the German Cooperative Pediatric Liver Tumor Study HB 94. *Cancer.* 2002;95(1):172–82.
- Geller JI, Dome JS. Local lymph node involvement does not predict poor outcome in pediatric renal cell carcinoma. *Cancer.* 2004;101(7):1575–83.
- Geller JI, et al. Characterization of adolescent and pediatric renal cell carcinoma: A report from the Children's Oncology Group study AREN03B2. *Cancer.* 2015;121(14):2457–64.
- German J. Bloom's syndrome. XX. The first 100 cancers. *Cancer Genet Cytogenet.* 1997;93(1):100–6.
- Gobel U, et al. Teratomas in infancy and childhood. *Med Pediatr Oncol.* 1998;31(1):8–15.
- Gobin YP, et al. Intra-arterial chemotherapy for the management of retinoblastoma: four-year experience. *Arch Ophthalmol.* 2011;129(6):732–7.
- Grant FD, Drubach LA, Treves ST. (18) F-fluorodeoxyglucose PET and PET/CT in pediatric musculoskeletal malignancies. *PET Clin.* 2010;5(3):349–61.
- Gratias EJ, et al. Association of chromosome 1q gain with inferior survival in favorable-histology Wilms tumor: a report from the Children's Oncology Group. *J Clin Oncol.* 2016;34(26):3189–94.
- Green DM. Diagnosis and management of malignant solid tumors in infants and children. Minneapolis, MN: MN Publishing; 1985. p. 129–86.
- Grimer RJ, et al. Osteosarcoma over the age of forty. *Eur J Cancer.* 2003;39(2):157–63.
- Grimer RJ, et al. Periosteal osteosarcoma—a European review of outcome. *Eur J Cancer.* 2005;41(18):2806–11.
- Grundy PE, et al. Loss of heterozygosity for chromosomes 1p and 16q is an adverse prognostic factor in favorable-histology Wilms tumor: a report from the National Wilms Tumor Study Group. *J Clin Oncol.* 2005;23(29):7312–21.
- Grundy PE, et al. Clinical significance of pulmonary nodules detected by CT and Not CXR in patients treated for favorable histology Wilms tumor on national Wilms tumor studies-4 and -5: a report from the Children's Oncology Group. *Pediatr Blood Cancer.* 2012;59(4):631–5.
- Gupta A, et al. Multifocal hepatic neoplasia in 3 children with APC gene mutation. *Am J Surg Pathol.* 2013;37(7):1058–66.
- Gurney JG, et al. Incidence of cancer in children in the United States. Sex-, race-, and 1-year age-specific rates by histologic type. *Cancer.* 1995;75(8):2186–95.
- Hamilton TE, et al. The management of synchronous bilateral Wilms tumor: a report from the National Wilms Tumor Study Group. *Ann Surg.* 2011;253(5):1004–10.
- Han G, et al. Amputation versus limb-salvage surgery in patients with osteosarcoma: a meta-analysis. *World J Surg.* 2016;40(8):2016–27.
- Hanks S, et al. Germline mutations in the PAF1 complex gene CTR9 predispose to Wilms tumour. *Nat Commun.* 2014;5:4398.
- Harris MB, et al. Treatment of metastatic osteosarcoma at diagnosis: a Pediatric Oncology Group Study. *J Clin Oncol.* 1998;16(11):3641–8.
- Heerema-McKenney A, et al. Congenital teratoma: a clinicopathologic study of 22 fetal and neonatal tumors. *Am J Surg Pathol.* 2005;29(1):29–38.
- Heifetz SA, et al. Immature teratomas in children: pathologic considerations: a report from the combined Pediatric Oncology Group/Children's Cancer Group. *Am J Surg Pathol.* 1998;22(9):1115–24.
- Hettmer S, et al. Anaplastic rhabdomyosarcoma in TP53 germline mutation carriers. *Cancer.* 2014;120(7):1068–75.

- Honeyman JN, et al. Detection of a recurrent DNAJB1-PRKACA chimeric transcript in fibrolamellar hepatocellular carcinoma. *Science*. 2014;343(6174):1010–4.
- Howlander N, Noone A, Krapcho M, et al. SEER cancer statistics review, 1975–2009. National Cancer Institute: Bethesda, MD; 2012.
- Huff V. Wilms tumor genetics. *Am J Med Genet*. 1998;79(4):260–7.
- Ikeda H, et al. Development of unfavorable hepatoblastoma in children of very low birth weight: results of a surgical and pathologic review. *Cancer*. 1998;82(9):1789–96.
- Indolfi P, et al. Renal cell carcinoma in children: a clinicopathologic study. *J Clin Oncol*. 2003;21(3):530–5.
- Johnson KJ, et al. Paediatric germ cell tumours and congenital abnormalities: a Children's Oncology Group study. *Br J Cancer*. 2009;101(3):518–21.
- Kaatsch P, et al. Pediatric germ cell tumors from 1987 to 2011: incidence rates, time trends, and survival. *Pediatrics*. 2015;135(1):e136–43.
- Kager L, et al. Skip metastases in osteosarcoma: experience of the Cooperative Osteosarcoma Study Group. *J Clin Oncol*. 2006;24(10):1535–41.
- Katzstein HM, et al. Hepatocellular carcinoma in children and adolescents: results from the Pediatric Oncology Group and the Children's Cancer Group intergroup study. *J Clin Oncol*. 2002;20(12):2789–97.
- Katzstein HM, Furman WL, Malogolowkin MH, Krailo MD, McCarville MB, Towbin AJ, Tiao GM, Finegold MJ, Ranganathan S, Dunn SP, Langham MR, McGahren ED, Rodriguez-Galindo C, Meyers RL. Upfront window vincristine/irinotecan treatment of high-risk hepatoblastoma: a report from the Children's Oncology Group AHEP0731 study committee. *Cancer*. 2017;123(12):2360–7. <https://doi.org/10.1002/encr.30591>.
- Kayton ML, et al. Experience with 31 sentinel lymph node biopsies for sarcomas and carcinomas in pediatric patients. *Cancer*. 2008;112(9):2052–9.
- Kim MS, et al. time dependency of prognostic factors in patients with stage II osteosarcomas. *Clin Orthop Relat Res*. 2007;463:157–65.
- Komura E, et al. Thrombopoietin in patients with hepatoblastoma. *Stem Cells*. 1998;16(5):329–33.
- Kopp LM, et al. Utility of bone marrow aspiration and biopsy in initial staging of Ewing sarcoma. *Pediatr Blood Cancer*. 2015;62(1):12–5.
- Kovar H, et al. Overexpression of the pseudoautosomal gene MIC2 in Ewing's sarcoma and peripheral primitive neuroectodermal tumor. *Oncogene*. 1990;5(7):1067–70.
- Labrune P, et al. Hepatocellular adenomas in glycogen storage disease type I and III: a series of 43 patients and review of the literature. *J Pediatr Gastroenterol Nutr*. 1997;24(3):276–9.
- Li FP, Fraumeni JF Jr. Rhabdomyosarcoma in children: epidemiologic study and identification of a familial cancer syndrome. *J Natl Cancer Inst*. 1969;43(6):1365–73.
- Liu AK, et al. Local control of metastatic sites with radiation therapy in metastatic Ewing sarcoma and rhabdomyosarcoma. *Pediatr Blood Cancer*. 2011;57(1):169–71.
- Llovet JM, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008;359(4):378–90.
- London WB, et al. Evidence for an age cutoff greater than 365 days for neuroblastoma risk group stratification in the Children's Oncology Group. *J Clin Oncol*. 2005;23(27):6459–65.
- Lopez-Terrada D, et al. Towards an international pediatric liver tumor consensus classification: proceedings of the Los Angeles COG liver tumors symposium. *Mod Pathol*. 2014;27(3):472–91.
- Maas SM, et al. Phenotype, cancer risk, and surveillance in Beckwith-Wiedemann syndrome depending on molecular genetic subgroups. *Am J Med Genet A*. 2016;170(9):2248–60.
- Mack JW, Grier HE. The day one talk. *J Clin Oncol*. 2004;22(3):563–6.
- Mahoney NR, et al. Pediatric horner syndrome: etiologies and roles of imaging and urine studies to detect neuroblastoma and other responsible mass lesions. *Am J Ophthalmol*. 2006;142(4):651–9.
- Maibach R, et al. Prognostic stratification for children with hepatoblastoma: the SIOPEL experience. *Eur J Cancer*. 2012;48(10):1543–9.
- Malek MM, et al. Review of outcomes of primary liver cancers in children: our institutional experience with resection and transplantation. *Surgery*. 2010;148(4):778–82. discussion 782–4
- Malempati S, et al. Rhabdomyosarcoma in infants younger than 1 year: a report from the Children's Oncology Group. *Cancer*. 2011;117(15):3493–501.
- Malogolowkin MH, et al. Germ cell tumors in infancy and childhood: a 45-year experience. *Pediatr Pathol*. 1990;10(1–2):231–41.
- Malogolowkin MH, et al. Complete surgical resection is curative for children with hepatoblastoma with pure fetal histology: a report from the Children's Oncology Group. *J Clin Oncol*. 2011;29(24):3301–6.
- Mann JR, et al. The United Kingdom Children's Cancer Study Group's second germ cell tumor study: carboplatin, etoposide, and bleomycin are effective treatment for children with malignant extracranial germ cell tumors, with acceptable toxicity. *J Clin Oncol*. 2000;18(22):3809–18.
- Marina NM, et al. Complete surgical excision is effective treatment for children with immature teratomas with or without malignant elements: a Pediatric Oncology Group/Children's Cancer Group Intergroup Study. *J Clin Oncol*. 1999;17(7):2137–43.
- Marina N, et al. Prognostic factors in children with extragonadal malignant germ cell tumors: a pediatric intergroup study. *J Clin Oncol*. 2006;24(16):2544–8.
- Marina NM, et al. Comparison of MAPIE versus MAP in patients with a poor response to preoperative chemotherapy for newly diagnosed high-grade

- osteosarcoma (EURAMOS-1): an open-label, international, randomised controlled trial. *Lancet Oncol.* 2016;17(10):1396–408.
- Maris JM, Matthay KK. Molecular biology of neuroblastoma. *J Clin Oncol.* 1999;17(7):2264–79.
- Mascarenhas L, et al. Pilot study of adding vincristine, topotecan, and cyclophosphamide to interval-compressed chemotherapy in newly diagnosed patients with localized ewing sarcoma: a report from the Children's Oncology Group. *Pediatr Blood Cancer.* 2016;63(3):493–8.
- Matthay KK, et al. Opsoclonus myoclonus syndrome in neuroblastoma a report from a workshop on the dancing eyes syndrome at the advances in neuroblastoma meeting in Genoa, Italy, 2004. *Cancer Lett.* 2005;228(1–2):275–82.
- Maurer HM, et al. The intergroup rhabdomyosarcoma study-II. *Cancer.* 1993;71(5):1904–22.
- Meyers RL. Tumors of the liver in children. *Surg Oncol.* 2007;16(3):195–203.
- Meyers PA, et al. High-dose melphalan, etoposide, total-body irradiation, and autologous stem-cell reconstitution as consolidation therapy for high-risk Ewing's sarcoma does not improve prognosis. *J Clin Oncol.* 2001;19(11):2812–20.
- Meyers RL, et al. Predictive power of pretreatment prognostic factors in children with hepatoblastoma: a report from the Children's Oncology Group. *Pediatr Blood Cancer.* 2009;53(6):1016–22.
- Meyers AB, et al. Hepatoblastoma imaging with gadoxetate disodium-enhanced MRI—typical, atypical, pre- and post-treatment evaluation. *Pediatr Radiol.* 2012;42(7):859–66.
- Meza JL, et al. Analysis of prognostic factors in patients with nonmetastatic rhabdomyosarcoma treated on intergroup rhabdomyosarcoma studies III and IV: the Children's Oncology Group. *J Clin Oncol.* 2006;24(24):3844–51.
- Milano GM, et al. Tumor lysis syndrome and neuroblastoma. *Med Pediatr Oncol.* 2003;41(6):592.
- Mosse YP, et al. Germline PHOX2B mutation in hereditary neuroblastoma. *Am J Hum Genet.* 2004;75(4):727–30.
- Mosse YP, et al. Identification of ALK as a major familial neuroblastoma predisposition gene. *Nature.* 2008;455(7215):930–5.
- Narod SA, et al. Congenital anomalies and childhood cancer in Great Britain. *Am J Hum Genet.* 1997;60(3):474–85.
- Newman EN, Jones RL, Hawkins DS. An evaluation of [F-18]-fluorodeoxy-D-glucose positron emission tomography, bone scan, and bone marrow aspiration/biopsy as staging investigations in Ewing sarcoma. *Pediatr Blood Cancer.* 2013;60(7):1113–7.
- Norris HJ, Zirkin HJ, Benson WL. Immature (malignant) teratoma of the ovary: a clinical and pathologic study of 58 cases. *Cancer.* 1976;37(5):2359–72.
- Nuchtern JG, et al. A prospective study of expectant observation as primary therapy for neuroblastoma in young infants: a Children's Oncology Group study. *Ann Surg.* 2012;256(4):573–80.
- Ognjanovic S, et al. Trends in childhood rhabdomyosarcoma incidence and survival in the United States, 1975–2005. *Cancer.* 2009;115(18):4218–26.
- Ognjanovic S, et al. Birth characteristics and the risk of childhood rhabdomyosarcoma based on histological subtype. *Br J Cancer.* 2010;102(1):227–31.
- Ognjanovic S, et al. Sarcomas in TP53 germline mutation carriers: a review of the IARC TP53 database. *Cancer.* 2012;118(5):1387–96.
- O'Neill AF, Towbin AJ, Krailo MD, Xia C, Gao Y, McCarville MB, Meyers RL, McGahren ED, Tiao GM, Dunn SP, Langham MR Jr, Weldon CB, Finegold MJ, Ranganathan S, Furman WL, Malogolowkin M, Rodriguez-Galindo C, Katzenstein HM. Characterization of pulmonary metastases in children with hepatoblastoma treated on Children's Oncology Group Protocol AHEP0731 (the treatment of children with all stages of hepatoblastoma): a report from the Children's Oncology Group. *J Clin Oncol.* 2017;35(30):3465–73. <https://doi.org/10.1200/JCO.2017.73.5654>.
- Ortega JA, et al. Randomized comparison of cisplatin/vincristine/fluorouracil and cisplatin/continuous infusion doxorubicin for treatment of pediatric hepatoblastoma: a report from the Children's Cancer Group and the Pediatric Oncology Group. *J Clin Oncol.* 2000;18(14):2665–75.
- Pakos EE, et al. Prognostic factors and outcomes for osteosarcoma: an international collaboration. *Eur J Cancer.* 2009;45(13):2367–75.
- Palculict TB, et al. Identification of germline DICER1 mutations and loss of heterozygosity in familial Wilms tumour. *J Med Genet.* 2016;53(6):385–8.
- Pappo AS, Pratt CB. Soft tissue sarcomas in children. *Cancer Treat Res.* 1997;91:205–22.
- Parham DM, Ellison DA. Rhabdomyosarcomas in adults and children: an update. *Arch Pathol Lab Med.* 2006;130(10):1454–65.
- Parham DM, et al. Nonrhabdomyosarcomatous soft tissue sarcomas of childhood: formulation of a simplified system for grading. *Mod Pathol.* 1995;8(7):705–10.
- Patel SS, et al. Milan criteria and UCSF criteria: a preliminary comparative study of liver transplantation outcomes in the United States. *Int J Hepatol.* 2012;2012:253517.
- Paulussen M, et al. Localized Ewing tumor of bone: final results of the cooperative Ewing's Sarcoma Study CESS 86. *J Clin Oncol.* 2001;19(6):1818–29.
- Pea M, et al. Apparent renal cell carcinomas in tuberculous sclerosis are heterogeneous: the identification of malignant epithelioid angiomyolipoma. *Am J Surg Pathol.* 1998;22(2):180–7.
- Peifer M, et al. Telomerase activation by genomic rearrangements in high-risk neuroblastoma. *Nature.* 2015;526(7575):700–4.
- Perilongo G, et al. Cisplatin versus cisplatin plus doxorubicin for standard-risk hepatoblastoma. *N Engl J Med.* 2009;361(17):1662–70.

- Perlman EJ. Pediatric renal tumors: practical updates for the pathologist. *Pediatr Dev Pathol.* 2005;8(3):320–38.
- Perlman EJ, et al. Hyperplastic perilobar nephroblastomatosis: long-term survival of 52 patients. *Pediatr Blood Cancer.* 2006;46(2):203–21.
- Pinto NR, et al. Advances in risk classification and treatment strategies for neuroblastoma. *J Clin Oncol.* 2015;33(27):3008–17.
- Popov SD, et al. Renal tumors in children aged 10–16 Years: a report from the United Kingdom Children's Cancer and Leukaemia Group. *Pediatr Dev Pathol.* 2011;14(3):189–93.
- Porteus MH, et al. Characteristics and outcome of children with Beckwith-Wiedemann syndrome and Wilms' tumor: a report from the National Wilms Tumor Study Group. *J Clin Oncol.* 2000;18(10):2026–31.
- Raney RB, et al. Results of the intergroup rhabdomyosarcoma study group D9602 protocol, using vincristine and dactinomycin with or without cyclophosphamide and radiation therapy, for newly diagnosed patients with low-risk embryonal rhabdomyosarcoma: a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. *J Clin Oncol.* 2011;29(10):1312–8.
- Rescorla FJ, et al. Surveillance after initial surgery for Stage I pediatric and adolescent boys with malignant testicular germ cell tumors: report from the Children's Oncology Group. *J Pediatr Surg.* 2015;50(6):1000–3.
- Rodriguez-Galindo C, et al. Analysis of prognostic factors in ewing sarcoma family of tumors: review of St. Jude Children's Research Hospital studies. *Cancer.* 2007;110(2):375–84.
- Roebuck DJ, et al. 2005 PRETEXT: a revised staging system for primary malignant liver tumours of childhood developed by the SIOPEL group. *Pediatr Radiol.* 2007;37(2):123–32. quiz 249–50
- Rogers PC, et al. Treatment of children and adolescents with stage II testicular and stages I and II ovarian malignant germ cell tumors: a pediatric intergroup study--Pediatric Oncology Group 9048 and Children's Cancer Group 8891. *J Clin Oncol.* 2004;22(17):3563–9.
- Rudnick E, et al. Opsoclonus-myooclonus-ataxia syndrome in neuroblastoma: clinical outcome and antineuronal antibodies-a report from the Children's Cancer Group Study. *Med Pediatr Oncol.* 2001;36(6):612–22.
- Ruteshouser EC, Huff V. Familial Wilms tumor. *Am J Med Genet C Semin Med Genet.* 2004;129C(1):29–34.
- Ruteshouser EC, Robinson SM, Huff V. Wilms tumor genetics: mutations in WT1, WTX, and CTNNB1 account for only about one-third of tumors. *Genes Chromosomes Cancer.* 2008;47(6):461–70.
- Sankar S, et al. Mechanism and relevance of EWS/FLI-mediated transcriptional repression in Ewing sarcoma. *Oncogene.* 2013;32(42):5089–100.
- Satge D, et al. Abnormal constitutional karyotypes in patients with neuroblastoma: a report of four new cases and review of 47 others in the literature. *Cancer Genet Cytogenet.* 2003;147(2):89–98.
- Schilling FH, et al. Neuroblastoma screening at one year of age. *N Engl J Med.* 2002;346(14):1047–53.
- Schleiermacher G, et al. Segmental chromosomal alterations have prognostic impact in neuroblastoma: a report from the INRG project. *Br J Cancer.* 2012;107(8):1418–22.
- Schmid I, et al. Sorafenib and cisplatin/doxorubicin (PLADO) in pediatric hepatocellular carcinoma. *Pediatr Blood Cancer.* 2012;58(4):539–44.
- Schultz KA, et al. Ovarian sex cord-stromal tumors, pleuropulmonary blastoma and DICER1 mutations: a report from the International Pleuropulmonary Blastoma Registry. *Gynecol Oncol.* 2011;122(2):246–50.
- Scott RH, et al. Syndromes and constitutional chromosomal abnormalities associated with Wilms tumour. *J Med Genet.* 2006;43(9):705–15.
- Servaes S, et al. Comparison of diagnostic performance of CT and MRI for abdominal staging of pediatric renal tumors: a report from the Children's Oncology Group. *Pediatr Radiol.* 2015;45(2):166–72.
- Shamberger RC, et al. Long-term outcomes for infants with very low risk Wilms tumor treated with surgery alone in National Wilms Tumor Study-5. *Ann Surg.* 2010;251(3):555–8.
- Sharp SE, et al. 123I-MIBG scintigraphy and 18F-FDG PET in neuroblastoma. *J Nucl Med.* 2009;50(8):1237–43.
- Shields CL, et al. The international classification of retinoblastoma predicts chemoreduction success. *Ophthalmology.* 2006;113(12):2276–80.
- Shimada H, et al. The International neuroblastoma pathology classification (the Shimada system). *Cancer.* 1999;86(2):364–72.
- Shimada H, et al. International neuroblastoma pathology classification for prognostic evaluation of patients with peripheral neuroblastic tumors: a report from the Children's Cancer Group. *Cancer.* 2001;92(9):2451–61.
- Siebel NL, Sun J, Anderson JR, et al. Outcome of clear cell sarcoma of the kidney (CCSK) treated on the National Wilms Tumor Study-5 (NWTS). Abstract. *J Clin Oncol.* 2006;24(Suppl 18):A-9000, 502s.
- Smith SC, et al. CIC-DUX sarcomas demonstrate frequent MYC amplification and ETS-family transcription factor expression. *Mod Pathol.* 2015;28(1):57–68.
- Spunt SL, et al. Risk-based treatment for nonrhabdomyosarcoma soft tissue sarcomas (MRSTS) in patients under 30 years of age: Children's Oncology Group study ARST0332. Abstract. *J Clin Oncol.* 2014;32(Suppl 15):A-10008.
- Strother DR, et al. Outcome after surgery alone or with restricted use of chemotherapy for patients with low-risk neuroblastoma: results of Children's Oncology Group study P9641. *J Clin Oncol.* 2012;30(15):1842–8.
- Sumazin P, et al. Genomic analysis of hepatoblastoma identifies distinct molecular and prognostic subgroups. *Hepatology.* 2016;65(1):104–21.
- Sun L, et al. Prognostic value of pathologic fracture in patients with high grade localized osteosarcoma: a

- systemic review and meta-analysis of cohort studies. *J Orthop Res.* 2015;33(1):131–9.
- Swartz MA, et al. Renal medullary carcinoma: clinical, pathologic, immunohistochemical, and genetic analysis with pathogenetic implications. *Urology.* 2002;60(6):1083–9.
- Tajiri H, et al. Reduction of hepatocellular carcinoma in childhood after introduction of selective vaccination against hepatitis B virus for infants born to HBV carrier mothers. *Cancer Causes Control.* 2011;22(3):523–7.
- Tanaka Y, et al. Gonadal mixed germ cell tumor combined with a large hemangiomatic lesion in a patient with Turner's syndrome and 45,X/46,X,+mar karyotype. *Arch Pathol Lab Med.* 1994;118(11):1135–8.
- Teshiba R, et al. Age-dependent prognostic effect by Mitosis-Karyorrhexis Index in neuroblastoma: a report from the Children's Oncology Group. *Pediatr Dev Pathol.* 2014;17(6):441–9.
- Tiao GM, et al. The current management of hepatoblastoma: a combination of chemotherapy, conventional resection, and liver transplantation. *J Pediatr.* 2005;146(2):204–11.
- Tirode F, et al. Genomic landscape of Ewing sarcoma defines an aggressive subtype with co-association of STAG2 and TP53 mutations. *Cancer Discov.* 2014;4(11):1342–53.
- Trobaugh-Lotrario AD, et al. Small cell undifferentiated variant of hepatoblastoma: adverse clinical and molecular features similar to rhabdoid tumors. *Pediatr Blood Cancer.* 2009;52(3):328–34.
- Walterhouse DO, et al. Shorter-duration therapy using vincristine, dactinomycin, and lower-dose cyclophosphamide with or without radiotherapy for patients with newly diagnosed low-risk rhabdomyosarcoma: a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. *J Clin Oncol.* 2014;32(31):3547–52.
- Wang N, Perkins KL. Involvement of band 3p14 in t(3;8) hereditary renal carcinoma. *Cancer Genet Cytogenet.* 1984;11(4):479–81.
- Wang LL, et al. Association between osteosarcoma and deleterious mutations in the RECQL4 gene in Rothmund-Thomson syndrome. *J Natl Cancer Inst.* 2003;95(9):669–74.
- Weigel BJ, et al. Intensive multiagent therapy, including dose-compressed cycles of ifosfamide/etoposide and vincristine/doxorubicin/cyclophosphamide, irinotecan, and radiation, in patients with high-risk rhabdomyosarcoma: a report from the Children's Oncology Group. *J Clin Oncol.* 2016;34(2):117–22.
- Wiener ES, et al. Controversies in the management of paratesticular rhabdomyosarcoma: is staging retroperitoneal lymph node dissection necessary for adolescents with resected paratesticular rhabdomyosarcoma? *Semin Pediatr Surg.* 2001;10(3):146–52.
- Williams SD, et al. Treatment of disseminated germ-cell tumors with cisplatin, bleomycin, and either vinblastine or etoposide. *N Engl J Med.* 1987;316(23):1435–40.
- de Wit R, Fizazi K. Controversies in the management of clinical stage I testis cancer. *J Clin Oncol.* 2006;24(35):5482–92.
- Wolden SL, et al. Indications for radiotherapy and chemotherapy after complete resection in rhabdomyosarcoma: a report from the Intergroup rhabdomyosarcoma studies I to III. *J Clin Oncol.* 1999;17(11):3468–75.
- Womer RB, West DC, Krailo MD, Dickman PS, Pawel BR, Grier HE, Marcus K, Sailer S, Healey JH, Dormans JP, Weiss AR. Randomized controlled trial of interval-compressed chemotherapy for the treatment of localized Ewing sarcoma: a report from the Children's Oncology Group. *J Clin Oncol.* 2012;30(33):4148–54. <https://doi.org/10.1200/JCO.2011.41.5703>.
- Wong FL, et al. Cancer incidence after retinoblastoma. Radiation dose and sarcoma risk. *JAMA.* 1997;278(15):1262–7.
- Woods WG, et al. Screening of infants and mortality due to neuroblastoma. *N Engl J Med.* 2002;346(14):1041–6.
- Wunder JS, et al. The histological response to chemotherapy as a predictor of the oncological outcome of operative treatment of Ewing sarcoma. *J Bone Joint Surg Am.* 1998;80(7):1020–33.
- Yanik GA, et al. Semiquantitative mIBG scoring as a prognostic indicator in patients with stage 4 neuroblastoma: a report from the Children's oncology group. *J Nucl Med.* 2013;54(4):541–8.
- Yu AL, et al. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. *N Engl J Med.* 2010;363(14):1324–34.
- Zsiros J, et al. Dose-dense cisplatin-based chemotherapy and surgery for children with high-risk hepatoblastoma (SIOPEL-4): a prospective, single-arm, feasibility study. *Lancet Oncol.* 2013;14(9):834–42.



Sabina Abidi

Introduction

Roughly 30–50% of severe and persistent psychiatric illnesses have their onset in childhood and adolescence (Girolamo et al. 2012). Psychiatric disorders are now revealed as one of the major contributors to the burden of disease in young people age 10–24 years and are now projected to be one of the five most common cause of morbidity, mortality and disability in young people (Gore et al. 2011). The overall prevalence of any psychiatric disorder with severe impairment and distress in adolescents is roughly 22% with most in fact meeting criteria for more than one disorder (Kessler et al. 2005). Psychiatric disorders that are specific to onset in childhood interfere with navigation of developmental milestones for the child and oftentimes significantly disrupt family dynamics and function leading to deterioration of protective factors. The childhood and adolescent age is a critical period of active synaptic pruning and maturation of brain circuitry and function and thus is significant not only in terms of the potential impact psychiatric symptoms can have on current functioning but also on the risk of future impairment. Youth often present help seeking to mental health services with functional impairment and distress secondary to a mixture

of subsyndromal symptoms that have yet to convert to meeting full criteria for diagnosis. This offers an opportune and exciting time to not only assist in managing symptoms with which youth and family present, but also offer indicated prevention to reduce the risk for conversion to more severe and chronic psychiatric outcomes in adulthood. A clinical staging framework of illness, often used in general medicine, proposes that illness symptoms exist on a continuum of severity with normal variants of experience on one end ranging to severe illness with associated morbidity and mortality on the other. The early intervention model purports that the emergence of early signs of mental concern may represent an opportunity to not only treat the current episode or presentation but also recognize that early states may represent modifiable risk factors to progression to later and more serious stages of illness. This concept is relatively new in child and adolescent psychiatry and offers a more optimistic outlook, supported by research on the potential for early intervention and treatment of psychiatric disorders (McGorry et al. 2007a, b).

Identifying a psychiatric diagnosis in children and particularly the adolescent not only requires the awareness of active brain development and acknowledgment that the impact of and symptoms themselves are fluid and subject to change over time but also accurate knowledge of the diagnostic criteria that must be met in full without which a diagnosis cannot be made. The recent fifth edition of the Diagnostic and Statistics

S. Abidi, M.D., F.R.C.P.C.
Department of Psychiatry, Dalhousie University,
Halifax, NS, B3K 6R8 Canada
e-mail: Sabina.Abidi@iwk.nshealth.ca

Manual of Mental Disorders (DSMV) appropriately emphasizes the dimensional perspective or continuum of symptom presentation and clinicians should familiarize themselves with this (or the most widely accepted diagnostic guide relevant to their population) to aid in clarifying diagnoses (American Psychiatric Association 2013). The dimensional perspective outlined in the DSMV differs from previous editions that had a more categorical approach which risks classifying pathologic normal variants of behavior and lowers the detection of atypical presentations that do not fit specific criteria as noted above. The DSMV adopts a more developmentally oriented approach conceptualizing all psychiatric disorders in a lifespan perspective and is organized as such. The new edition of the DSM equally emphasizes the need to consider other possible aetiologies of symptom presentation such as medical, medication-related, stress-induced or related, substance use, potential risk syndromes and comorbidities before making a diagnosis. Furthermore, essential to meeting diagnostic criteria is a noted change in function or impairment in navigating developmental milestones that persists and is directly associated with the symptoms presentation (Table 20.1). Due to the fluidity by which psychiatric symptoms can present in children and youth oftentimes directly influenced by both developmental stressors and environmental triggers, meeting full diagnostic criteria according to the DSMV is generally regarded as the threshold for making reliable and accurate psychiatric diagnoses, the first step to towards iden-

tifying and initiating evidence-based treatment recommendations.

Interviewing and assessing for child/adolescent psychiatric illness requires a vulnerability and honest curiosity on the part of the clinician. One must have a sharp awareness of the developmental, emotional, intellectual and social stage of the child or youth at the time as these impact the significance of the presenting symptom and its implication regarding illness identification. For example, a 5 year old child presenting with hallucinations may be a developmentally normal variant phenotype as compared to a 16 year old youth, where the symptom may be a marker of illness. Further, hallucinations in a 16 year old with the intellectual and emotional capacity of an 8 year old might carry a different significance. Moreover, cultural, spiritual and family beliefs and behaviors must all be factored in when attempting to clarify the significance of symptomatology. Symptoms must always be appreciated in the context within which they occur and in conjunction with collateral observations from family or primary carers or other sources with whom the patient spends time. The clinician must be curious and humble in the pursuit of possible illness presentations recognizing that more often than not, the thoughtful and comprehensive assessment and gathering of collateral will guide accurate conclusions and the most appropriate treatment recommendations to pursue. Adopting heightened sensitivity and awareness of possible illness presentations within the context of the family and remaining mindful of risk for potential worsening as the child ages is crucial to fostering stage-specific intervention decisions to maximize positive outcome.

Table 20.1 Points to consider when attempting to distinguish signs and symptoms of illness from normal variants of behavior

| |
|--|
| Is the symptom persistent |
| Is the symptom a significant change from baseline |
| Is the symptom inappropriate to the context (developmental/emotional/cognitive age) in which it occurs |
| Does the symptom cause social, academic, interpersonal and functional impairment |
| Does the symptom present in more than one setting or with more than one person |
| Is there any other identifiable etiology or cause for the symptom/change |

Changes in the DSMV for Child and Adolescent Psychiatric Disorders

The new edition of the DSM has reorganized its structure to better reflect the experiences of symptoms of illness in children and youth. The manual has adopted a lifespan approach to mental disorders reflected in the organisation of

Table 20.2 The new organisation of the DSM V is sequenced with the developmental lifespan in mind recognizing that vulnerabilities to illness can occur at any stage

| |
|--|
| Neurodevelopmental disorder |
| Schizophrenia spectrum and other psychotic disorders |
| Bipolar and related disorders |
| Depressive disorders |
| Anxiety disorders |
| Obsessive-compulsive and related disorders |
| Trauma- and stressor-related disorders |
| Dissociative disorders |
| Somatic symptom disorders |
| Feeding and eating disorders |
| Elimination disorders |
| Sleep-wake disorders |
| Sexual dysfunctions |
| Gender dysphoria |
| Disruptive, impulse control and conduct disorders |
| Substance use and addictive disorders |
| Neurocognitive disorders |
| Personality disorders |
| Paraphilic disorders |

Neurodevelopmental disorders typically diagnosed in childhood are first, followed by those with onset in adolescence and finally later life

disorders of childhood towards the beginning, those that tend to have onset in adolescence in the mid-section and those that present later in life towards the end (Table 20.2) (American Psychiatric Association 2013). In the effort to enhance early identification of illness-related symptoms and improve diagnostic accuracy the DSMV has integrated new disorders as well and some changes. Below are outlined a few of the recent changes that influence child and adolescent psychiatric care:

Neurodevelopmental Disorders

Diagnoses including attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), learning disorders, intellectual disability (ID) and motor and communication disorders fall under the new *neurodevelopmental disorders* category emphasizing a delay or deviation in brain development that influences symptoms presentation. The ASD diagnosis is a now a new

conceptualization encompassing the three previous diagnoses from the DSMIV edition (pervasive developmental disorder not otherwise specified, autistic disorder and Asperger's syndrome) as one single condition with symptom presentation that is thought to exist on a continuum of differing levels of severity.

Changes in age of onset of impairment for ADHD (from prior to age 7 to age 12) and lower diagnostic threshold reflects an attempt to decrease false negatives and capture a wider range of children impaired by the illness.

The previously termed mental retardation (MR) has been abandoned for the newer term intellectual disability (ID) due to a history of pejorative connotations with the MR label. Emphasis is placed on the requirement for more comprehensive patient assessment and measures of adaptive functioning *along with* IQ to meet diagnostic criteria.

Disruptive, Impulse-Control and Conduct Disorders

The criteria for oppositional defiant disorder (ODD) and conduct disorder (CD) have not changed substantially in the DSMV. However, requirement of increased duration, consistency and frequency of symptom criteria now exists to account for the fact that many behaviors associated with ODD in fact occur quite commonly in developing children and adolescents who do not have nor develop psychiatric illness. For example, for children under the age of 5, the behavior must now be identified on *most* days for a period of at least 6 months consecutively and consistently. Symptoms should also be pervasive across settings, as an indicator of severity.

Trauma and Stressor-Related Disorders

This is a new category outlining disorders that have as their core exposure to a traumatic or stressful event as an etiological factor leading to expression of the illness. Included are reactive

attachment disorder, disinhibited social engagement disorder, posttraumatic stress disorder (PTSD), acute stress disorder and adjustment disorders. While the diagnostic criteria for PTSD is relatively unchanged for adolescents and adults, DSMV now recognizes that preschool children (under age 6) are exposed to traumatic events and may manifest the symptoms of PTSD differently. The guide fosters enhanced awareness and recognition of symptoms by outlining a specific subtype for this age group with criteria more in keeping with their developmental stage and cognitive level.

Another recent change is the conceptualization of disinhibited social engagement disorder which shares with reactive attachment disorder the requirement for neglect (absence of adequate caregiving in childhood) as a causal factor, but the two differ in terms of life course, response to intervention and manifestation and are considered separate conditions as a result.

Depressive Disorders

Disruptive mood dysregulation disorder (DMDD) is a new diagnosis in the DSMV developed to more accurately represent children and adolescents who present with hyperarousal and severe, chronic non-episodic irritability with frequent temper outbursts. These children were often misidentified as having bipolar disorder, or the early stages of it, despite lack of traditional manic symptoms. Evidence from longitudinal studies suggests that these children and youth in fact tend to develop other psychiatric conditions such as major depressive disorder or anxiety disorder and not bipolar disorder. Family history data supports this finding further contradicting the previous assumption that severe and chronic irritability in children represents an alternative presentation or risk for bipolar disorder (see below for further discussion of DMDD).

Avoidant/Restrictive Food Intake Disorder (ARFID)

Pica, rumination disorder and the new diagnosis ARFID are now listed in the new Feeding and Eating disorders chapter. ARFID is a new diagnosis attempting to capture children and adolescents who suffer significant weight loss secondary to substantial restriction and experience consequent physiological and psychological distress but are distinct in that they lack body image preoccupation, drive for weight loss or thinness or fear of weight gain typically associated with anorexia or bulimia nervosa.

Research Criteria

Section III of the DSMV outlines conditions that are of clinical concern warranting further research and delineation. Pertinent to child and adolescent psychiatry is the recognition of non-suicidal self-injury (NSSI)—self harm without the intention of suicide- and internet gaming disorder as conditions of significant relevance to the population warranting further review. The attenuated psychosis syndrome (APS) is a new consideration underscoring the neurodevelopmental etiology of psychotic disorders highlighting the clinical at-risk (earliest) stage of illness onset that with further research may be reliably identifiable and a focus of intervention and possibly prevention.

Clinicians should familiarize themselves with the changes in the DSMV as they pertain to child/adolescent psychiatry. The following outlines some of the more common and impairing pediatric psychiatric disorders that oftentimes first present for care within a primary health care setting. Emphasis in this chapter is on those that are lifespan diagnoses, the course of which follow a continuum of phenotypic severity, namely ADHD, depression and bipolar disorder, anxiety disorders and psychotic spectrum disorders. Updates in regards to diagnosis and treatment are

reviewed as are any pertinent points of clinical concern that have arisen in the last decade in child/adolescent psychiatry.

Attention Deficit Hyperactivity Disorder (ADHD)

Prevalence

ADHD is one of the most prevalent psychiatric disorders in children under age 18 affecting about 3–4% of youth (Polanczyk et al. 2015). It is a neurodevelopmental disorder that has its onset in childhood and is characterized by at least 6 months of a persistent pattern of developmentally inappropriate impairing inattention and/or hyperactivity and impulsivity that result in functional impairment in multiple settings. A range of 50% and 80% of children have continued symptoms of ADHD into adolescence; in about 40%, symptoms continue into adulthood (Polanczyk et al. 2015; Bussing et al. 2010). Criteria as outlined in the DSMV include specifiers that capture how symptoms can manifest in older adolescents and adults recognizing the marked heterogeneity in presentations and that phenotypes are not necessarily stable over time.

Diagnosis

ADHD shows marked heterogeneity at clinical, etiological and pathophysiological levels making diagnosis based on a pattern of phenotype difficult. Furthermore, the clinical interview in conjunction with objective standardized scales¹ and

¹Standardized scales and screening tools for symptoms of ADHD are not required for diagnosis. Use however can assist clinicians in supporting a clinical diagnosis and monitoring efficacy of psychological and pharmacological interventions. Scales such as the Child Behavior Checklist–Attention Problem (CBCL-AP) scale, the Conners Rating Scale–Revised (CRS-R) and the SNAP [Swanson, Nolan and Pelham Teacher and Parent Rating Scale], and BASC [Behavior Assessment Scale for Children can be useful (Chang et al. 2016).

cognitive measures of attention, distractibility and impulsivity if indicated, are the main tools used for diagnosing ADHD. Interviews must be obtained from the patient combined with collateral from multiple sources including parents, teachers and other caregivers. Interviewing any one of these sources without the other is not a reliable means to ensuring symptoms are present in more than one setting and not due to another cause, e.g. medical, stress related, substance-induced. Oftentimes obtaining a psychoeducation or cognitive assessment if possible can assist in clarifying learning disabilities or deficits in cognitive function that could contribute or explain symptoms. Further, a comprehensive psychiatric assessment is important in identifying other potential causes for symptoms that might mimic ADHD such as anxiety, OCD, depression or psychosis. ADHD carries significant comorbidity with other illnesses namely autism spectrum disorder, communication and specific learning or motor disorders, intellectual disability, tic disorders, OCD and anxiety disorders making clarification of diagnosis difficult. Some children also have a temperamental phenotype marked by aggressiveness, irritability and mood lability. Recognition and intervention is imperative as untreated ADHD can lead to compounded negative outcomes in several life domains (Jensen and Steinhausen 2015; Taylor et al. 1996).

Treatment

Parent skills training, behavioral therapy, school adjustments and academic and school environment accommodations are first line of treatment (multisystemic therapy) particularly for children under the age of 6 (except for very severe complex cases where consultation with pediatric psychiatry colleagues and suggestions for pharmacotherapy might be warranted) but highly encouraged for young people of all ages in combination with medicine if warranted (Thapar 2016).

There is strong empirical support for the use of psychostimulants (methylphenidate, dexamethylphenidate, mixed amphetamine salts, dextroamphetamine, and lisdexamfetamine) as first line treatment for symptoms of ADHD. The combination of medicine with behavioral therapy can provide benefit with comorbid and associated symptoms as well as level of functioning (The MTA Cooperative Group 1999). All psychostimulants are either methylphenidate or amphetamine derivatives which among other things, enhance neurotransmission of dopamine. There is growing evidence for the use of non-stimulant formulations as augments or second line with slightly decreased efficacy. Of the non-stimulant medications, atomoxetine is a selective norepinephrine reuptake inhibitor; Clonidine and Guanfacine are selective alpha-adrenoceptor agonists (Thapar 2016; Hirota et al. 2014).

Generally, the response rate to psychostimulants for symptoms of ADHD is 60-70% with equivalent efficacy between the methylphenidate and amphetamine-based medications. At least 30% experience adverse effects and roughly 15% require a switch to an alternate medication as a result of side effects (Thapar 2016; Faraone 2009). There is no reliable patient profile that helps identify preferential response to one formulation or another thus selection among options is based on practical issues such as cost, dosing frequency and availability. There is no clear therapeutic dose window for stimulants; it is important to start at a low dose and titrate upwards every 1–3 weeks targeted to symptoms and tolerance of side effects. If one class of psychostimulant is ineffective, a trial of the alternate class is reasonable. For those with intolerant side effects a switch to a non-stimulant formulation or adjunctive use with lower stimulant doses is indicated. The effect sizes for guanfacine and clonidine as monotherapy are smaller. However use of these in combination with stimulants for those who are suboptimally treated with (or can only tolerate lower doses of) stimulants can be effective (Thapar 2016; Faraone 2009; Giles and Martini 2016). Clinicians need to be mindful however of the potential for increased side effects with polypharmacy.

All stimulant formulations have similar adverse effect profiles, the most common among which include delayed onset of sleep, appetite suppression

and weight loss, emotional lability and irritability (particularly in younger children or those with developmental delay). For some, a rebound lability and escalation of ADHD symptoms can be seen with wearing off of the medication that might warrant consideration of an alternate trial (Thapar 2016; Giles and Martini 2016). Considering strategies to manage side effects in the face of positive response to psychostimulants are important. Involving dietician colleagues to assist with managing intake and diet and monitoring growth and recommending good sleep hygiene techniques to manage insomnia assists in managing not only side effects but also symptoms of illness that worsen with lack of nutrition and sleep. Elevations in heart rate and blood pressure have also been associated with stimulant use. There is however as yet no evidence of increased risk for cardiac complication even in those with family history of cardiac disease secondary to psychostimulants (Correll et al. 2011). Despite this, good clinical practice dictates inquiry about family history of cardiac disease, congenital cardiac conditions and complications to identify at-risk children. Routine ECGs are not indicated however clinical indication may warrant consultation with cardiology colleagues prior to initiation of psychostimulant medication. Non stimulant medications differ in terms of side effects with less pronounced effects on sleep and appetite and reports of gastrointestinal distress, sedation and mood changes. As per other medications that affect serotonin metabolism, atomoxetine carries a boxed warning regarding a small risk of suicidal thinking that warrants psychoeducation and attention for the clinician, patient and family. Due to the effect of the alpha-agonists on cardiovascular system, monitoring of blood pressure and heart rate, particular if in combination with psychostimulants reflects good practice. For optimal outcome a combination of medication, psychoeducation and support plus behavioral management for the child along with parenting skills training² for the family is key.

²The Incredible Years (Kessler et al. 2012) is one example of a multicomponent parenting skills program. IY emphasizes opportunities for active involvement, reinforcement of positive behavior and setting clear limits all of which have proven successful in treating disruptive behaviors associated with ADHD in the family system.

Clinical Point

The diagnosis of ADHD, as per all psychiatric disorders often is based on reported symptoms alone; there are no biological tests. There is currently no evidence for increased population rates of ADHD despite societal opinion, yet the prescription rate of pharmacological intervention for ADHD across high income countries has increased in recent years (Giles and Martini 2016). Despite having clear-cut diagnostic criteria, there is risk of over diagnosis (and underdiagnosis) and inappropriate use of pharmacological intervention. Certainly this risk underscores the need for diligent and rigorous as well as patient expert assessment.

Of concern in terms of side effects is growth retardation secondary to psychostimulant and secondary appetite suppression. Monitoring of growth parameters is essential during treatment and if needed potential use of drug holidays to offset risk for impaired growth rates may be warranted. Psychostimulants are drugs of abuse certainly and prescribing clinicians need be wary of this particularly in youth and families at risk. In such cases use of non-stimulant formulations may be preferable; there is no evidence that use of stimulants for ADHD predisposes children/youth to addiction or concurrent disorders.

ADHD presentations for care are rarely simple; more often than not are complex with comorbidities and complicating factors. Consultation with colleagues in pediatric psychiatry is often warranted and welcomed to best clarify course of action that will optimize outcomes for the youth and family.

Depression

Prevalence

Depression has been identified as one of the leading causes of global disability by the World Health Organization (WHO) (Gore et al. 2011; World Health Organization 2009). Early identification and treatment in youth predicts a remission in 60–90% (Dunn and Goodyer 2006)

within the first year, however depression in childhood and adolescence is often the first episode of the illness that continues into adulthood with high rates of recurrence: follow-up studies report 50–70% within 5 years without effective intervention (March et al. 2004). Twenty-five percent of adolescents report subthreshold symptoms of depressive disorder that significantly impact emotional, social and academic functioning; at the same time the subsyndromal presentation carries increased risk for later development of the full blown disorder (Klein et al. 2009). Moreover, those who meet diagnostic criteria carry increased rate of comorbidities, substance misuse and physical health problems. In adolescents, suicide is often a consequence of depression and is the second leading cause of death for youth age 12–17 in North America. The prevalence for depression is lower in younger children as compared to adolescents but rises sharply around age 12; by age 18 the lifetime prevalence of a major depressive disorder reaches 20%; higher in girls (about 17%) than boys (about 7%) (Klein et al. 2009; Avenevoli et al. 2015).

Diagnosis

There are clear genetic underpinnings to depression which shows increasing heritability from childhood to adolescence; the biological correlates are increasingly being uncovered. Diagnosis is often complicated due to the clinical heterogeneity with which symptoms of depression can occur in children and youth, with multiple internal and external risk factors contributing to the presentation, the weight or clinical significance of which is individual and difficult to predict. Studies show that those with stronger familial risk may be inherently more sensitive to psychosocial risk factors or adversity contributing to risk for manifestation of symptoms via the gene-environment interplay (Thapar et al. 2012). Symptoms that might herald the onset of depression are outlined in Table 20.3 and are important to consider when screening. Standardized, reliable screening tools for depression in children and youth are widely available and useful in

Table 20.3 Symptoms that might warrant screening for depression in youth

| Symptom | What it might look like |
|---|---|
| Irritability/depressed mood | Short temper, new negativistic attitude, difficult interactions with peers, new onset substance use |
| Poor concentration and attention | Poor performance at school, decline in grades |
| Loss of interest | Withdrawal from previously enjoyed activities and peers, family |
| Anhedonia/loss of energy | Withdrawal, isolation, frequent absences |
| Insomnia/hypersomnia | Restlessness or fatigue |
| Guilt, low self-esteem, cognitive distortions | Crying, sadness, avoidance |
| Loss of appetite/increased appetite | Change in appearance, body habitus |
| Psychomotor retardation | Unable to perform assigned tasks |
| Thoughts of suicide | Isolation, avoidance, crying, self harm |

identifying those at risk³. Screening must be complimented by a thorough clinical assessment of the child or youth clarifying symptom presentation. The clinician should be aware of atypical symptoms of depression in the younger population and subclinical presentations recognizing that the symptoms are heterogeneous and fluid depending on the age and stage of the child. Assessment must also include including incorporating collateral information from caregivers and of particular importance, screening for risk for suicide.

³There are several screening tools available to assist in identifying risk for depression in children and adolescents. All have particular age groups and populations as targets and are well reviewed in the literature. Of import is utilization of the same tool in a repeated fashion that is clinically relevant and generalizable to the population and other respective clinicians and caregivers (National Collaborating Centre for Mental Health (UK)2005).

The most common differential diagnosis in children and youth is that the presentation of mood change is a developmentally normal response to an adverse childhood experience, trauma or grief. Most youth will experience sadness and have varying degrees of irritability and impaired vegetative symptoms in response to stressors. Of concern however is the fact that many youth who meet criteria for depression are missed. Major depressive disorder (MDD) is distinguished by the intensity of the presenting symptoms, the duration, and presence with other symptoms according to DSMV criteria along with a consistent and persistent level of impairment of functioning that outweighs that expected in response to the stressor. Furthermore, symptoms of depression can occur without identifiable environmental stressor.

Comorbidity is the norm for adolescents with depression the risk for which increases with severity of symptoms. Comorbidity complicates identification and treatment and impairs long term outcomes. Two-thirds have at least one comorbid psychiatric disorder and in 10–15%, two or more. Anxiety, ODD and substance use disorders are particularly common; almost 20% of adolescents with depression also meet diagnostic criteria for generalized anxiety disorder (Thapar et al. 2012; Angold and Costello 1993).

Suicide

Suicidal thoughts can be a manifestation of the depressed mood secondary to negative cognitive distortions that can occur. The risk for youth suicide is difficult to predict and despite societal opinion, the overall prevalence has not significantly increased in recent years. Suicide is uncommon in childhood but certainly the frequency of attempts increases post puberty into adolescence particularly among females. Roughly 16% of students between the ages of 14 and 18 years have considered suicide; 7.8% have attempted in one study (Centred for Disease Control and Prevention 2012). While attempts are twice as frequent in females, more males have

died by suicide than females (9.4/100,000 vs. 2.7/100,000). Data reveals that victims of suicide had often visited primary care or mental health care prior to the fatal attempt (Dilillo et al. 2015) emphasizing the need for screening for suicide risk at each office visit. Screening tools asking about factors that might confer increased risk for suicide in this population are available and useful (Shain 2007).

Both acute and chronic factors contribute and can be fluid in terms of their relevance over time and as the child ages. Chronic factors include a family history of suicide, past suicide attempts, chronic medical illness, and low socioeconomic status, among others. Acute factors include recent suicidal attempt, current ideation and plan, access to lethal means, current substance use, significant psychosocial stressors, and psychotic symptoms among others. It is imperative to screen for suicide risk with all pediatric and adolescent patients and be reassured that asking about suicide and associated safety planning is protective (Table 20.4) (Dilillo et al. 2015).

Table 20.4 Examples of factors associated with increased/reduced suicide risk

| Factors associated with increased suicide risk | Protective factors |
|--|--|
| Psychiatric illness (more than 60% meet criteria for depression) | Access to mental health care |
| Previous suicide attempt (20–30% will attempt again in the ensuing 2–4 years) | Positive stable support connections School Family Peers |
| Family dynamics/familiarity with suicide (stress, loss, member committed suicide) | Lack of access to means and substances |
| Substance abuse (alcohol intoxication significantly increases current risk) | Resilience—coping strategies, ability to overcome adversity |
| History of trauma, neglect, abuse (sexual/physical) | Help-seeking |
| Gender dysphoria | |
| Bullying (both bullies and victims) | |
| Safety of home environment (access to means, safety planning, supportive caregivers) | |

Treatment

Psychotherapy for depression aims to assist the youth in connecting their consequent mood to their life experiences and thoughts. Building resilience by strengthening awareness of this relationship and strategies or skills to modify perceptions about experiences can be preventative. Cognitive behavioral therapy (CBT) and interpersonal therapy (IPT) are the most widely studied for treatment of depression in youth and adults (Thapar et al. 2012; Weisz et al. 2006). For younger children and youth with less severe and more chronic mood symptoms, psychotherapy (CBT) can be very effective treatment. Combination treatment of antidepressant medication and evidence based psychotherapy proves to have some added treatment benefit as compared to placebo alone for the moderate-severely ill population and those who are treatment-resistant or do not respond to psychotherapy alone (March et al. 2004; Thapar et al. 2012; March and Vitiello 2009). Further though, one study found that for those where therapy was not feasible, even a switch from one SSRI to another can yield improvement in symptoms (March and Vitiello 2009; Brent et al. 2008).

Antidepressants in the form of selective serotonin uptake inhibitors (SSRI) have the most documented evidence of efficacy for treatment of depression in this population (Giles and Martini 2016), but in truth the evidence is still sparse. There are very few studies supporting utilization of other classes of medicines such as tricyclic antidepressants or mood stabilizers in the treatment of child/adolescent depression. In most trials, the response rate for SSRIs as antidepressants is about 60% in this population. There is limited evidence suggesting a stronger efficacy for one SSRI over another for depression. Thus, the choice of SSRI is determined by side effect profile, previous experience with medicine, pharmacodynamics of the medication and relative risk profile. Recommendations include starting at a low dose and tapering weekly to target symptoms and tolerability as effective dose is not related to weight. An adequate trial of an SSRI is 4–6 weeks at a therapeutic dose with consideration of a

switch to an alternate SSRI after a failed trial. Once effective treatment is established it is recommended medication be continued for 12 months before considering a discontinuation trial. There is some evidence supporting a longer term treatment benefit of combination psychotherapy, allowing for more successful medication discontinuation after 12 months (March et al. 2004).

Safety

Most side effects in youth treated with SSRIs are transient and generally well tolerated. Common side effects include gastrointestinal side effects such as nausea and dyspepsia as well as headaches, increased appetite and fatigue. Less frequent experiences include irritability, agitation, restlessness, insomnia, weight loss and affect instability. Rare but more troublesome side effects include sexual dysfunction, temperature dysregulation, bruxism and more severe GI distress. Rarely, SSRIs can induce a manic or hypomanic switch in youth with familial risk for bipolar disorder type I (Giles and Martini 2016; Strawn et al. 2015).

Clinical Point

SSRIs and Suicide Related Events

In 2004, the FDA reviewed results of a meta analysis of 24 clinical trials of nine different antidepressants in about 4000 pediatric patients. The cumulative risk for suicide-related thinking (thoughts of suicide, increased agitated thoughts related to hopelessness, worsening intent to self-harm) collected as spontaneous adverse events was 4% versus 2% with placebo (Hetrick et al. 2007). Further analysis of the data revealed no completed suicides in this population. Furthermore following a consequent nation-wide decrease in prescribing practice of SSRIs for depression in youth, there was identified an increased risk of death by suicide in untreated youth with depression as compared to those treated with antidepressants (March and Vitiello 2009; Hetrick et al. 2007; Bridge et al.

2007). It is important to note also the risk of increased suicide-related thoughts associated with initiation of psychotherapy (without medication) for depression is 25% in some studies (March and Vitiello 2009). There is a clear positive benefit to risk ratio of treating depression in youth with medication as required, particularly if in combination with psychotherapy. Nonetheless, educating and monitoring youth and families of the risk and the studies available is good clinical practice. It does appear that the risk for suicide related events is largely confined to trials on youth with depression (the risk is diminished for those taking SSRIs for anxiety, e.g. in OCD the number needed to harm (NNH) is 200) (Giles and Martini 2016; Correll et al. 2011); nonetheless, educating youth and families with anxiety or other illnesses for which SSRIs are being prescribed about the potential risk is recommended.

Long Term Effects of SSRIs and Youth

There are no studies completed assessing the potential long-term adverse effects of antidepressant use in youth with mood or anxiety disorders. It is important to discuss this lack of data with the youth and family and risk must be weighed against the potential risk of untreated illness on brain development. Following a period of stability (usually at least 12 months in remission) consideration of a slow taper with physician advice and eventual discontinuation if tolerated is warranted.

Non-suicidal Self-Injury (NSSI)

Non suicidal self-injury (NSSI) has been proposed as a possible separate diagnostic entity in section III of the DSMV (American Psychiatric Association 2013). Consensus agreement on definitions, however have not been agreed upon regarding self-harming behaviors. Research often uses the terms NSSI which refers to harmful behaviors without suicidal intent (cutting, burning, etc.) and self-directed harmful behaviors (SDH) which have suicidal intent (overdose, hanging) interchangeably. NSSI is not uncommon among adolescents, with lifetime prevalence rates of 4% and 7% for adolescent community

samples, increasing dramatically to roughly 50% for child and adolescent psychiatric samples (Muehlenkamp et al. 2012; Swannell et al. 2014). The prevalence decreases sharply into adulthood, possibly reflecting that this is a behavior specific to youth. Despite perception that NSSI lacks suicidal intent, the behavior has been described as strong risk factor for suicidality in adolescence (Andover et al. 2012), the association between which is still unclear. Research is focused on identifying possible predictors of risk associated with NSSI. Depressive symptomatology and associated distress, past NSSI or SDH, female gender and exposure to adversity for example may carry increased safety risk (Kessler et al. 2012). Clinicians should be aware of past history and current factors with which youth present in association with NSSI. Asking about intent for harm and reasons for behavior is of import in accurately determining the clinical relevance of NSSI in the moment and potential risk for future SDH in relation to this.

Anxiety

Prevalence

Childhood and adolescence is a key period for the development of symptoms of anxiety that can range from transient, self-limited symptoms to full-blown anxiety disorders. Anxiety is not typically pathological and is adaptive and protective in most cases. Anxiety becomes maladaptive however when subclinical symptoms begin to worsen, persist and interfere with functioning and certainly when symptoms present in situations that typically would not be anxiety-provoking. Difficulty arises in distinguishing between normal worries and fears of childhood and adolescence or specific to emotional and developmental stages, and those which cause significant distress impacting academic, social and emotional function. Anxiety disorders in childhood and adolescence as a group constitute the most prevalent mental disorder affecting roughly 15–20% of youth with a threefold female preponderance in adolescence (Kessler

et al. 2012; Beesdo et al. 2010). Despite the prevalence, most youth with anxiety disorders go unrecognized. There is considerable heterogeneity in the onset of the specific anxiety disorders with separation anxiety and social anxiety presenting commonly in early childhood while generalized anxiety disorder (GAD), panic disorder, and obsessive compulsive disorder (OCD) mostly emerging in adolescence. Oftentimes the symptoms of specific anxiety disorders co-occur; accumulating data suggests a pediatric anxiety disorder “triad” of separation anxiety, generalized anxiety and social anxiety reflecting similar trajectories, neurophysiology and response to treatment in these disorders (Kendall et al. 2010; McGuinness and Durand 2016). Identifying anxiety disorder as a psychiatric illness early is important as these can interfere with optimal growth and development and predict worsening or development of other anxiety disorders among other illnesses (ADHD, ODD, and depression) in adolescence and adulthood. Further, anxiety disorders carry high rates of comorbid illnesses such as substance use disorders and mood disorders and also risk for suicide.

Diagnosis

As with other psychiatric illnesses, the role of the caregivers and other support persons in other settings e.g. teachers, as integral informants during the assessment for anxiety disorders particularly in children is key. Oftentimes, the anxiety disorders, particularly the “triad”, but also separation anxiety and specific phobias are associated with avoidance (of anxiety) behaviors such as school refusal and selective mutism. Selective mutism appears in childhood, sometimes by the age of 4 and may be a variant of or predictive of development of social anxiety disorder in later years (McGuinness and Durand 2016).

Good clinical practice recommends screening for anxiety symptoms and carefully assessing for potential comorbid psychiatric and general medical conditions that can mimic anxiety. Distinguishing normal anxious responses

in childhood and adolescence from pathological responses is key as is identifying other potential internal or external factors or determinants that might have contributed to or assist in understanding the anxious response and symptomatology. Screening instruments are available and widely used to identify and monitor anxiety disorders in children and youth⁴ and should be used in conjunction with a comprehensive assessment interview with the young person and family (March et al. 1997; Birmaher et al. 1999).

Trauma in childhood and adolescence is a prevalent cause of development of anxiety disorders in children and adolescents. The lifetime prevalence of posttraumatic stress disorder (PTSD) is about 9.2% in the general population; many children and youth likely experience subthreshold symptoms of PTSD that carry significant risk for impairment if unrecognized (McGuiness and Durand 2016). As noted above the DSMV now recognizes that preschool children, in the face of trauma may manifest the symptoms of PTSD and have specified criteria to foster reliable identification of this presentation.

Anxiety heritability is estimated as high as 50% which when combined with environmental factors which might include parenting styles (modeling), exposure to traumatic events leading to a fear response and chronic risk factors (familial risk) plays a role in the genesis of the disorders. The temperament of the child reflected in early childhood behavior may further predict anxiety disorder development. Anxiety disorders often co-occur as noted in children and youth but may also morph in terms of phenotype over time depending on the developmental and emotional age of the person (Kessler et al. 2012; Beesdo et al. 2010; Kendall et al. 2010; McGuiness and Durand 2016).

⁴The Multidimensional Anxiety Scale for Children (MASC), and the Screen for Child Anxiety and Related Emotional Disorders (SCARED) are examples of tools designed to monitor anxiety symptoms in youth with good psychometric properties (March et al. 1997; Birmaher et al. 1999).

Treatment

Cognitive behavioral therapy is highly regarded as first line treatment with strong evidence base for anxiety disorders in this population. Mild severity of symptoms respond very well to CBT. CBT is most successful in this population if combined with a behavioral component of introducing graded exposure to the anxiety-provoking stimulus or thoughts. Furthermore, development of coping skills and relaxation strategies to assist children in exposure to anxiety provoking stimuli is key. Finally, psychoeducation for both the child but also the parent/caregiver is also helpful for younger children particularly. Education enhances caregivers' awareness of their own behaviors and anxious responses that might enable avoidance behaviors in their children. Parenting style is determined as one of the most important environmental factors contributing to anxiety disorder development in children and youth. More specifically, overly critical over protective approaches have been associated with pathological anxiety in children and can be a focus of intervention. For example assisting parents to be aware and learn to regulate their own emotional response to their child's fear can enhance a child's ability to cope in anxiety-provoking situations. Strong empirical evidence supports CBT plus parent education and training in this way as first line intervention for anxiety disorders in this population (Giles and Martini 2016; McGuiness and Durand 2016; Walkup et al. 2008).

Moderate to severe symptoms of anxiety that are more impairing and do not respond to psychotherapy alone have been shown to respond very well to combination pharmacotherapy and psychotherapy. Strong evidence based data demonstrates up to 80% improvement in symptomatology (World Health Organization 2009; McGuiness and Durand 2016; Rynn et al. 2015) with combination therapy in this population. Anxiety disorders with comorbid psychiatric conditions and certainly those that are treatment resistant benefit from both a psychotherapeutic and pharmacological approach to treatment by virtue of severity of symptoms.

SSRIs are commonly used both on and off-label in treatment of anxiety disorders in children and youth with good clinical practice emphasizing their use first line. Multiple medications from the SSRI class have good evidence for efficacy in treating anxiety disorders including obsessive compulsive disorder (OCD) as compared to placebo (Pediatric OCD Treatment Study (POTS) Team 2004). Fluoxetine and Sertraline have good evidence base for use in treating anxiety and often choice is dictated by adverse effects and history (Correll et al. 2011; Rynn et al. 2015; Pediatric OCD Treatment Study (POTS) Team 2004).

Benzodiazepines have not been shown to be efficacious in the treatment of anxiety disorders in youth as single agents. Case reports do exist demonstrating benefit of short-term benzodiazepine for extreme anxiety symptoms particularly during progression of or a switch among SSRI options. Clinicians need be mindful of added adverse effects and potential for dependence in using this class of medication. Evidence for the use of atypical antipsychotics or buspirone (often used to treat anxiety in adults) in treating anxiety in the child/youth population is lacking (Giles and Martini 2016; Correll et al. 2011; Strawn et al. 2015).

Trauma-focused CBT is the mainstay of treatment for PTSD in children and youth. Data is unfortunately lacking in terms of effective pharmacological management of symptoms of childhood/adolescent PTSD. SSRIs have been identified in case reports as acceptable options for augmentation of psychotherapy but there is less evidence for this as compared to other anxiety disorders potentially due to lack of studies in the younger population. This is in sharp contrast to research in the adult population that strongly supports use of SSRIs for PTSD (McGuiness and Durand 2016).

Clinical Point

Obsessive Compulsive Disorder (OCD)

OCD is an illness marked by intrusive thoughts and compulsive behaviors that previously fell within the category of anxiety disorders. In the

DSMV it is listed in its own chapter under OCD and related disorders and has added specifiers qualifying varying levels of insight into the content of the thoughts and behaviors reflecting the continuum of severity of the illness and heterogeneity of presentation depending on age and developmental stage.

OCD is prevalent (1–2%) in the younger population but oftentimes goes undetected especially in children. OCD is highly heritable with a risk of 12% in first degree relatives with a more severe manifestation of the symptoms in those with familial risk (McGuiness and Durand 2016). CBT with the exposure-response prevention (ERP) component is first line treatment for mild-moderate symptoms of OCD. Antidepressant medication (SSRIs) is recommended as adjunctive treatment to CBT for moderate to severe cases. The evidence for combination therapy as opposed to monotherapy is strong for other anxiety disorders as well as OCD with relatively low numbers needed to treat (NNT) at 3 and 6 respectively (Correll et al. 2011; Strawn et al. 2015; Pediatric OCD Treatment Study (POTS) Team 2004). Moreover, for those who were initially treated with SSRIs in one study with only partial response, augmentation with OCD-specific (exposure based) brief (12 weeks) CBT provided a superior treatment response as compared to medication alone or medication plus nonspecific CBT strategies (Giles and Martini 2016; Correll et al. 2011; McGuiness and Durand 2016).

Bipolar Disorder

Prevalence

The prevalence of bipolar disorder is difficult to ascertain in the pediatric population due to a heterogeneous clinical presentation in youth (including unipolar mania, mania with depression, brief hypomanias, and chronic mood lability). Overall the prevalence of bipolar spectrum disorders (bipolar I, II, cyclothymic disorder) across ages is about 1.7–2.5% with about two thirds experiencing their first mood episode before age 18 (Cosgrove et al. 2013). For this update, focus

is primarily on bipolar I disorder. There has been a marked increase in diagnosis of bipolar I disorder in North America, particularly in the US in recent years, reasons for which are unclear. It is surmised that this is secondary to an increasing problem of over diagnosis in this area of the world (as increase prevalence has not been observed internationally). Certainly under diagnosing bipolar disorder can lead to prognostic consequences, worsening frequency and severity of the mood episodes and consequent prolonged impairment. Over diagnosis may be due to clinician misidentification of symptom overlap of bipolar disorder with symptoms of disruptive behavior disorders such as ADHD, conduct disorder and oppositional defiant disorder. Disruptive mood dysregulation disorder (DMDD) is a new DSMV diagnosis developed in response to this very issue and in hopes to decrease the risk of misidentification and false positives and consequent exposure to adverse effects of pharmacotherapy such as antipsychotics and mood stabilizers (Leibenluft 2011) (see below and Table 20.5).

Diagnosis

Bipolar I disorder (BD) is a serious and persistent psychiatric disorder. Early onset BD is associated with a more severe presentation and neurocognitive deficits relative to peers. Youth with BD may be less likely to develop adequate social skills,

and are at increased risk for comorbid disorders. However, if recognized early and with appropriate treatment the trajectory of BD may be significantly improved. The illness is marked by extreme episodic mood states, depression and at least one episode of mania (Cosgrove et al. 2013; Van Meter et al. 2016). DSMV criteria requires the mood states, to persist for up to 14 days for depression and 5 for mania with the onset of the episodes being a marked change in presentation from baseline. For example, pathological elevated or euphoric mood, persistent insomnia without need for sleep and disinhibition with hyper sexuality are specific to the manic phase of bipolar disorder. Furthermore, symptoms such as grandiosity and elation must be inappropriate to the context and unprovoked. Irritability as a symptom of bipolar disorder is difficult to clarify and confirm. Irritability is a manifestation of many other psychiatric illnesses in youth including depression, anxiety, ADHD, CD and OCD. Irritability in association with bipolar disorder must be episodic, connected to the mood state and again a change from baseline (in between extreme mood states). Moreover, irritability alone even if episodic does not meet the threshold for diagnosis. It is generally accepted that symptoms heralding onset of bipolar I disorder exist on a continuum or dimensional scale however as yet recognition of risk for or signs of new onset bipolar disorder in youth can be difficult (Cosgrove et al. 2013; Singh et al. 2014).

Table 20.5 Distinguishing DMDD from bipolar I disorder

| Features associated with DMDD | Features associated with BD I |
|---|---|
| Must present between age 6–18. Symptoms must have onset by age 10; cannot be diagnosed outside of this age range for the first time | Rare in childhood, onset peaks in early 20s–30s with early onset cases in adolescence |
| Prevalence between 2% and 5% in childhood; decreases to 0.8–1.1% in older youth | Prevalence stable about about 1% in young adulthood; rare in childhood |
| Symptoms must be present for 1 year; no period greater than 3 months symptoms free | Episodic, must meet criteria for manic episodes, are unprovoked |
| Chronic, unremitting irritability with or without severe explosive outburst (3/week) | Episodes of mania ± depression, may have baseline normal mood without irritability |
| No psychosis | May have symptoms of psychosis in the extremes of mood |
| Usually associated with development of a unipolar mood disorder | Presentation associated with the development of chronic bipolar mood disorder |

Depression is often the first symptom of pediatric Bipolar disorder with 20% of youth with MDD experiencing manic episodes by adulthood. Risk factors for developing bipolar disorder identified in the younger population include: family history, acute onset of major depressive disorder, psychotic features with severe depression and psychomotor retardation. Further atypical depressive features such as hypersomnia, hyperphagia, low energy and antidepressant mood destabilization or inefficacy may also predict later conversion to bipolar disorder. It appears that youth with MDD that later develop bipolar depression are more severe in initial presentation of low mood, more anhedonic, have an earlier age of onset and lower functioning than youth with unipolar depressive disorder (Cosgrove et al. 2013; Van Meter et al. 2016; Singh et al. 2014; Chang 2009).

Treatment

Lithium and a select few of the atypical antipsychotics are approved as first line treatment in the pediatric population for acute mania and bipolar I disorder maintenance treatment. Treatment of and utilization of other mood stabilizers in this population is both on and off-label; involvement of colleagues in child psychiatry can be useful. Lithium has been proven to be efficacious in treatment of bipolar I disorder in children and youth with symptoms of acute mania. There is growing evidence for efficacy of Lamotrigine in treating the depressive phase of pediatric bipolar disorder as monotherapy and in combination. Data however on other mood stabilizers including atypical antipsychotics, Oxcarbazepine, Gabapentin and Topiramate are limited (Giles and Martini 2016; Cosgrove et al. 2013).

Safety

All mood stabilizers carry adverse effects and potential for chronic medical complications. For example, Lamotrigine is associated with a rare risk of fatal cutaneous reactions such as Stevens

Johnson syndrome. Divalporex is associated with polycystic ovarian syndrome with associated symptomology. Carbamazepine is at higher risk for drug-drug interactions by virtue of induction of the hepatic CP450 isoenzyme system. Diligence and awareness of and monitoring strategies for potential adverse events and risk associated with these medications in children and youth is essential.

Lithium adverse effects commonly can include weight gain, acne, psoriasis, polydipsia, polyuria, and sedation, gastrointestinal distress with nausea, pain and diarrhea. Hypothyroidism, ataxic gait and tremor and nephrogenic diabetes insipidus are rarer. Baseline investigations of renal function, thyroid indices, electrolytes and complete blood count are recommended with routine monitoring (Giles and Martini 2016; Cosgrove et al. 2013).

Clinical Point

DMDD encompasses children age 6–18 with mood dysregulation that is reflected in a presentation of persistent, irritable and angry mood with recurrent temper outbursts that occur before the age of 10. Evidence from longitudinal studies suggests that these children and youth tend to develop other psychiatric conditions such as major depressive disorder or anxiety disorder and not bipolar I disorder. Family history data supports this finding further contradicting the previous assumption that severe and chronic irritability in children/adolescents represents an alternative presentation or risk for bipolar disorder (Leibenluft 2011; Van Meter et al. 2016; Tang and Pinsky 2015). Further longitudinal studies are underway to better understand the underpinnings of this disorder.

Schizophrenia and Other Psychotic Spectrum Disorders

Prevalence

The WHO has ranked psychosis as third among the most disabling conditions in youth worldwide (Gore et al. 2011). The prevalence of schizophrenia

and other psychotic spectrum disorders is between 1–1.5% with about 18–30% of cases with onset before the age of 18, particularly in males. The average age of onset in males is between 17–21 years. Rarely, schizophrenia presents in childhood in 1.6–1.9 per 100,000 children under age 12 (Gillberg 2001; Thomsen 1996). At this age, it is difficult to clarify the diagnosis and by virtue of the heterogeneous presentation, is often misidentified as autistic spectrum disorder. Childhood onset schizophrenia carries a more severe prognosis with most experience treatment refractory symptoms and longstanding impairment. Early onset psychotic disorders (onset between ages 12–18) are associated with impairments in social, emotional and occupational function by virtue of the cluster of functions affected by the illness symptoms. Schizophrenia follows a variable course with one-third to forty percent of cases achieving functional recovery (Clemmensen et al. 2012). Recent advances in the field of early intervention for psychosis and the development of multidisciplinary specialized early psychosis programs however has fostered early identification of those both a risk for psychosis and in the earliest phase of identifiable symptoms of the disorder. A more optimistic approach to recovery is attainable in youth whose illness is identified and treated early.

Diagnosis

The term ‘psychosis’ refers to the group of psychotic disorders characterized by hallucinations or delusions and experiences that alter perception, thoughts, emotionality and behavior all of which can markedly impair the trajectory of social, emotional and physical health of a young person. Psychosis includes schizophrenia but also schizoaffective disorder, schizophreniform disorder and delusional disorder. In the DSMV, criteria used to diagnose schizophrenia are relatively the same as in adults bearing in mind youth with schizophrenia often have a more severe form of illness symptoms, more cytogenetic abnormalities and potentially more neurodevelopmental abnormalities (Clemmensen et al. 2012). Recent work in the field has identified a

prodromal stage of the illness marked by attenuated symptoms that cause distress and impairment yet do not reach psychotic disorder threshold. The prodrome is a retrospective diagnosis as symptoms overlap with other psychiatric illnesses and presentations at this age; however work is actively ongoing to elicit diagnostic tools to help identify youth in this phase and initiate indicated prevention as warranted (Yung et al. 2008). At this time diagnostic criteria must be met before initiating treatment with antipsychotic medication.

Treatment

Schizophrenia and psychotic spectrum disorders are severe and persistent neurodevelopmental illnesses. Collaboration with pediatric psychiatry colleagues regarding symptoms management is helpful. Antipsychotic medications are the mainstay of pharmacological treatment of the symptoms of psychosis. Older antipsychotics or first generation (FGA) which act via direct blockade at the dopamine receptor (such as Chlorpromazine or Haloperidol) while approved for treatment in adolescents with psychosis have generally been replaced with second generation antipsychotics (SGA) due to concern regarding movement disorder effects such as extrapyramidal side effects (EPSE), parkinsonism and dystonia. The SGAs block D2 receptors as well but primarily via reciprocal block of serotonin receptors and lower receptor occupancy. Studies show no efficacy difference between FGAs and SGAs in treating the symptoms of psychosis (with the exception of Clozapine) yet in the last two decades, the SGAs are more widely prescribed when available. Clozapine is an SGA that has demonstrated superior efficacy for children and adolescents with schizophrenia. Clozapine however cannot be prescribed without evidence of two failed trials of antipsychotics and requires specific monitoring due to its propensity, albeit rare for potentially life threatening side effects of agranulocytosis and leukopenia (Schimmelmann et al. 2013; Pisano et al. 2016).

Family support and psychoeducation has demonstrated efficacy in reducing relapse rates and rehospitalisation in adolescents with schizophrenia. Individual cognitive behavioral therapy has limited evidence however psychosocial rehabilitation interventions with peer support modalities can be helpful particularly in the first episode of psychosis (Yung et al. 2008).

Clinical Point

Psychotic Experiences and Other DSMV Disorders

It is important to recognize that symptom domains for psychosis can differ depending on age and stage of development, and can potentially be a manifestation of multiple diagnostic categories. Most children and who report psychotic symptoms do not have schizophrenia or another psychotic disorder. Children and youth's interpretation of internal and external perceptual experiences can be influenced greatly by factors such as intellect and emotional maturity in the face of exposure to developmental stressors, environmental triggers, cultural dynamics and family belief systems. The perception of a psychotic experience can be a normal variant for very young children and indeed in isolation is relatively common and clinically benign in adolescents, occurring in 15–20% in some studies (Lachman 2014; Scott et al. 2006). Furthermore, the perception of a psychotic experience may be the manifestation of other medical or psychiatric etiologies such as primary mood or anxiety disorders. Simultaneously, clinicians need be aware that many adults with schizophrenia report the initial onset of symptoms prior to the age 18 before diagnostic criteria were met (Schimmelmann et al. 2013), making the interpretation of the clinical significance of the psychotic experience in childhood and adolescence complex.

The lifetime prevalence of a psychotic experience that does not go on to develop into a psychotic disorder in 10–20% (Scott et al. 2006). Severe depression or anxiety (often social anxiety disorder, generalized anxiety disorder and

PTSD) can present with perceptual abnormalities in children and youth often congruent in content to the context of the primary illness. In these cases, the experiences usually present only in the face of triggers related to the primary disorder. OCD is an illness that in youth can manifest as the perception of auditory hallucinations. Sometimes the OCD thoughts are described as “voices” by youth who comprehend the experience as external to the self. Further, some youth lack insight into the etiology of their OCD thoughts and compulsions and in turn qualify for the specifier of OCD “with poor/delusional insight”, new in the DSMV. Children with ASD can often also present with psychotic experiences that are inherent to the illness itself and not predictive of increased risk for a psychotic disorder. Youth with depression oftentimes will report auditory hallucinations that mimic their negative cognitive distortions. It is extremely important to distinguish the etiology of the psychotic experience as the longer term implications and approach to treatment are significantly different. Treatment modalities for example for anxiety or depression (CBT for instance) can target the psychotic experiences as a cognitive distortion and support the youth in reframing the experience in the context of the primary illness. Further, if warranted antidepressants (SSRIs) can prove helpful. The heterogeneous presentation of psychotic experiences as a manifestation of other psychiatric illnesses (Yung et al. 2008; Lachman 2014) in youth underscores the value of conducting a thorough comprehensive assessment in order to identify the other clinical correlates of psychotic experiences and avoid misattributing their presence to a primary psychotic disorder or worse, treating the child inappropriately as a result.

Clinical Point 2

Atypical Antipsychotics: Issue for Consideration

Overall, literature on the use of antipsychotics in children and youth is limited with the best evidence for use of these medications for schizophrenia and bipolar I disorder (Pisano et al. 2016).

Despite this, in the last decade there has been a significant increase in the prescription of SGAs for more than the symptoms of psychotic or bipolar disorder in pediatric and adolescent patients. SGAs are often prescribed for irritability and aggression in autism spectrum disorder or intellectual disability, Tourettes' disorder, mood disorder, conduct disorder and eating disorders. Unfortunately polypharmacy with more than one SGA is also common despite lack of evidence supporting this practice (Olfson et al. 2015). Several recent studies have raised significant concerns regarding the adverse effects of SGAs and the potential risk for iatrogenic secondary metabolic syndrome (weight gain/obesity, hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, hyperinsulinism and hypertension). These potential adverse effects are more frequent in children and youth and also include hyperprolactinemia, cardiovascular effects such as prolonged QTc intervals, and neuromotor adverse effects (dystonias, EPSEs, parkinsonism and akathisia) (Giles and Martini 2016; Schimmelmann et al. 2013; Pisano et al. 2016). Recommendations for monitoring of SGAs were put forth by both the Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA) and the American Academy of Child and Adolescent Psychiatry (AACAP) (Pringsheim et al. 2001; American Academy of Child and Adolescent Psychiatry 2011) strongly supporting preventative baseline and periodic measures of indices related to risk of morbidity and mortality associated with prescription of SGA (Fig. 20.1). Despite this, national monitoring programs do not exist and many prescribers of SGAs do not adhere to recommendations. Consequently the adverse events from SGA use lead to many pediatric emergency room visits and negative outcomes.

Antipsychotics and Aggressive Behavior

Randomized control trials do demonstrate positive results (with small to moderate effect sizes) from risperidone and aripiprazole compared to placebo in decreasing irritability and aggression

in pediatric patients with ASD, lower intellectual function and in fewer studies children with ADHD and conduct disorder. Of particular import is the finding that Risperidone *plus* parent training leads to a greater reduction of maladaptive behaviors than medication alone in these populations and often lead to requirement of lower doses of Risperidone. Furthermore, the treatment effects are limited to aggression; the core deficits of the primary disorder are not affected by these medicines (Giles and Martini 2016; Pisano et al. 2016). Long term benefit of antipsychotic use in these children is not substantiated and thus regular re-evaluation of prescribing practice with ongoing attention towards evidence for use is crucial.

Adverse Effect Profile of SGAs

Weight Gain and Obesity

The risk for weight gain with use of SGAs is remarkable—highest for Olanzapine and Clozapine followed by Risperidone, Quetiapine, Aripiprazole and Ziprasidone. The risk for weight gain is higher in the younger population and is not always dose dependent. For those more vulnerable to adverse effects of medication such as children with ASD, the weight increase can be significant, with drug-naïve patients presenting with the highest risk in some studies. Of note, in one study examining the effects of maintenance vs discontinuation of Risperidone in children, neither those who discontinued Risperidone nor those who switched to another SGA lost their body fat mass incurred secondary to Risperidone, indicating that the metabolic risks associated with SGAs may be chronic in some (Giles and Martini 2016; Pisano et al. 2016; Calarge et al. 2014; Prinsheim et al. 2011).

Diabetes

The rapid weight gain secondary to SGAs is sometimes paralleled by an increased risk for diabetes mellitus type 2 (DM2). Moreover research identifies that SGAs are associated with insulin dysregulation independent of weight gain. Youth with type 1 diabetes prescribed SGAs were

| Monitoring Safety of Second Generation Antipsychotics (SGA) in Children | | | | | | | | |
|---|---|---------|---|---------|---------|-------------------|----------|--|
| Patient Name: | | | Gender: | | | DOB (YYYY/MM/DD): | | |
| SGA Medication: olanzapine (Zyprexa) | | | Target Symptoms (e.g. tics, rage, psychosis): | | | | | |
| Parameter | Pre-Treatment Baseline | 1 Month | 2 Month | 3 Month | 6 Month | 9 Month | 12 Month | |
| General Information: | | | | | | | | |
| Assessment Date (YYYY/MM/DD): | | | | | | | | |
| Patient Age at Assessment: | | | | | | | | |
| Daily Dose of olanzapine: | mg | mg | mg | mg | mg | mg | mg | |
| Physical Examination Maneuvers: | | | | | | | | |
| Height (cm) | | | | | | | | |
| Height percentile ¹ | Round to nearest 5, 10, 25, 50, 75, 90, or 95 %ile | | | | | | | |
| Weight (kg) | | | | | | | | |
| Weight percentile ¹ | Round to nearest 5, 10, 25, 50, 75, 90, or 95 %ile | | | | | | | |
| BMI (kg/m ²) ¹ | | #DIV/0! | #DIV/0! | #DIV/0! | #DIV/0! | #DIV/0! | #DIV/0! | |
| BMI percentile ¹ | Use CDC calculator to calculate value ¹ | | | | | | | |
| Waist Circumference (at level of umbilicus) (cm) | | | | | | | | |
| Waist Circumference percentile ² | >90, or round to nearest 10, 25, 50, 75, or 90 %ile | | | | | | | |
| Systolic Blood Pressure (mm Hg) | | | | | | | | |
| Systolic Blood Pressure percentile ³ | Provide range (<50, 50-90, 90-95, 95-99, or ≥99) | | | | | | | |
| Diastolic Blood Pressure (mm Hg) | | | | | | | | |
| Diastolic Blood Pressure percentile ³ | Provide range (<50, 50-90, 90-95, 95-99, or ≥99) | | | | | | | |
| Neurological Examination: | | | | | | | | |
| Neurological Exam completed? ⁴ | | | | | | | | |
| Neurological Exam Normal or Abnormal? | | | | | | | | |
| Laboratory Evaluations: | | | | | | | | |
| Test | Normal Values | | | | | | | |
| Fasting Plasma Glucose ⁵ | ≤ 6.1 mmol/L | 5 | | | 5 | 5 | 5 | |
| Fasting Insulin ⁶ | ≤ 100 pmol/L | 6 | | | 6 | 6 | 6 | |
| Fasting Total Cholesterol ⁷ | < 5.2 mmol/L | | | | | | 7 | |
| Fasting LDL-C ⁷ | < 3.35 mmol/L | | | | | | 7 | |
| Fasting HDL-C ⁷ | ≥ 1.05 mmol/L | | | | | | 7 | |
| Fasting Triglycerides ⁷ | < 1.5 mmol/L | | | | | | 7 | |
| AST ⁸ | | | | | | | 8 | |
| ALT ⁸ | | | | | | | 8 | |
| Prolactin ^{9, 10} | | | | | | 10 | 10 | |
| Amylase ¹¹ | | 11 | 11 | 11 | 11 | 11 | 11 | |
| Other (e.g. A1C, OGTT, etc.): <i>Please List</i> | | | | | | | | |
| Physician Initials: | | | | | | | | |

Fig. 20.1 Example of monitoring protocol suggested by Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA) obtained from <http://comesguideline.org/information-for-doctors> (accessed 29 June 2016)

found to have poorer glycemic control and higher HbA1c levels than placebo (Pisano et al. 2016; Lachman 2014; Prinsheim et al. 2011).

Dyslipidemia

Increased triglyceride and cholesterol levels can occur early in the course of treatment of children and youth with SGAs and may precede or be independent of weight gain as well as secondary to obesity. Aripiprazole and Ziprasidone seem to cause less dyslipidemias than the other SGAs

however long term data is lacking (Lachman 2014; Prinsheim et al. 2011).

Movement Disorders

The risk for extrapyramidal symptoms (EPSE: chronic or acute dystonia, parkinsonism, tardive dyskinesia and akathisia) is lower with SGA use as compared to FGA use but not absent. Children and adolescents, particularly those who are drug naïve, are more vulnerable to EPSEs. There is a higher risk for movement

disorders with risperidone, aripiprazole (akathisia), and olanzapine as compared to placebo; whereas quetiapine and clozapine seem to be more neutral. Other factors such as younger age, comorbid substance misuse, polypharmacy, previous history of EPSEs can further contribute to risk (Lachman 2014; Prinsheim et al. 2011).

Other adverse effects of SGAs as noted can include hyperprolactinemia, cardiovascular adverse effects, and neuroleptic malignant syndrome (NMS), a potentially fatal adverse reaction marked by elevated CPK, muscle rigidity, hyperthermia, autonomic dysfunction, confusion and leukocytosis (Lachman 2014).

The potential for serious adverse events with antipsychotic use emphasizes the need for diagnostic diligence and evidence for efficacy of antipsychotic use in children and youth. If SGAs are needed, utilization of monitoring strategies and standardized scales to monitor for involuntary movements⁵ is useful (Guy 1976). A thorough review of medications, history of substance use, medical history and history of adverse effects to medications, especially antipsychotics is required. Consultation with child/adolescent psychiatry colleagues when considering prescription of antipsychotics can be helpful. Regardless, prescription of antipsychotics should not be chronic unless indicated by the presentation.

Substance Related Disorders in Children and Adolescents

Prevalence

Substance Use Disorders (SUD) is one of the most common mental health disorders with a lifetime prevalence of 35% with more than 30% of SUD onset in adolescence. About 50% of 12th graders in the US have used at least one illicit substance in their lifetime with the most commonly reported substances being alcohol, tobacco

and cannabis. The lifetime prevalence of substance abuse and dependence in adolescents ranges from 3.3% in 15 year olds to almost 10% in 17–19 year olds. More than 60% of older adolescents with SUD had another psychiatric disorder. Substance use is rare in childhood and increases significantly after age 12 (Centred for Disease Control and Prevention 2012; Schulden et al. 2009).

SUD impacts all facets of a child's life interfering with all spheres of development. Substance use can worsen the prognosis for many comorbid psychiatric illnesses, some by potentially reducing the effectiveness of medicines, leading to poor prognosis. Comorbidity is the rule rather than the exception with SUD (Jackson et al. 2000).

Diagnosis

The continuum of substances use ranges from non-users, to experimental or casual users to those with substance use disorders. The diagnosis is primarily made via clinical interview as well as signs of toxidromes on physical exam in moderate-severe cases. The DSMV divides the disorders into SUD (which includes combined criteria for substance abuse and dependence—previously separated in DSMIV) and substance induced disorders including both intoxication and withdrawal syndromes specific to the substance.

Risk for SUD is dependent on the developmental stages of the child or adolescent, e.g. peer pressure during may be more a powerful factor in adolescence than childhood. Community factors such as drug availability and societal tolerance for drug use are also significant. Certainly stressors in the child's life such as school transitions are risk factors as is exposure to caregivers who abuses drugs and ineffective parenting styles. Other factors such as history of trauma, neglect and abuse, low self-esteem, aggression or comorbid externalizing disorders (ODD, CD) may also play a role (Jackson et al. 2000; Collins et al. 2016; Stone et al. 2012).

All children over age 9 should be screened for substance use (younger patients for any accidental

⁵The Abnormal Involuntary Movement Scale (AIMS) (Guy 1976) is, among others, a useful tool to monitor for neuromotor adverse effects secondary to antipsychotic use.

use) at every health visit. Tools such as the CRAFFT screen are widely used with good reliability and psychometric properties (Knight et al. 2002). For more severe cases consultation with child/adolescent psychiatry colleagues may be helpful to help evaluate for addiction or dependence, comorbid psychiatric disorders and suggestions for treatment.

Treatment

Treatment methodologies and timing for same in adolescents depends on the severity and circumstance of the use. Mild or casual use may benefit from brief intervention—support, advice, education, counseling and monitoring. Further, the stage at which the adolescent is regarding readiness to change patterns of use is key to determining treatment steps. Developing a therapeutic alliance with the youth is crucial in determining these factors. Several modes of psychotherapy have been evaluated with some evidence for success such as motivational interviewing, CBT, IPT, group therapy to motivate and support youth on their path to recovery, help build social skills, enhance distress tolerance and reach a point of desire towards harm reduction and possibly abstinence.

For more severe cases, a youth may consider detoxification, involving physician assistance to help stabilize the youth from the withdrawal effects of the substances. During detox and potentially after the youth may benefit from medicines to assist with the detox process and/or facilitate motivation and reduction of cravings/dependence in the attempt to reduce use (Collins et al. 2016). A multidisciplinary approach following the youth and family throughout the treatment process promotes optimum treatment success.

Clinical Point

Marijuana is the most commonly used drug among North American adolescents (American Academy of Pediatrics, Committee on Substances Abuse and Committee on Adolescence 2015).

There is currently no evidence supporting the use of medicinal marijuana or pharmaceutical cannabinoids for psychiatric symptoms in pediatric populations and yet it is often prescribed. Marijuana has been identified to have potential negative consequences with both short and long term use in adolescents. Learning difficulties secondary to impaired motivation, decreased concentration and attention span have been reported. Further, impairment in judgment, reaction time, and motor control have been documented potentially negatively affecting function such as driving, sports, and daily activities. There is strong evidence demonstrating the potential negative effect of cannabinoid exposure to the developing brain increasing predisposition risk for psychiatric illness or sequela such as psychosis. Moreover the younger the exposure to marijuana the increased likelihood drug addiction might develop in adulthood (MacDonald and Pappas 2016; Committee on Substance Abuse, Committee on Adolescence 2015). The American Academy of Pediatrics (AAP) strongly opposes marijuana use in the pediatric and adolescent population 0–21 years (Committee on Substance Abuse, Committee on Adolescence 2015).

Clinical Point 2

Cannabis and Psychosis

In the last decade a substantial amount of research has demonstrated a strong association between increased risk for psychotic disorders, particularly schizophrenia and exposure to cannabinoids in those with a familial risk for schizophrenia. Adolescents with regular cannabis use double the risk for reporting psychotic symptoms or being diagnosed with schizophrenia in adulthood. Cannabis use has been shown to increase morbidity (compared with other drugs and alcohol) and confer a poorer prognosis on those with schizophrenia contributing to altered psychosocial function, cognitive impairment, poor response to medication and nonadherence and increased rates of rehospitalisation (Committee on Substance Abuse, Committee on Adolescence 2015; Fergusson et al. 2003;

Radhakrishnan et al. 2014). For youth with a family history of schizophrenia or other psychotic outcomes, counseling against cannabis use is essential referring to the specific risk and not just reduction of harm in general.

Conclusion

Most psychiatric illnesses that present in childhood and adolescence are neurodevelopmental in nature, the symptoms of which exist on a continuum of severity and impact on functioning. The manifestation of phenotypes may be contingent on exposure to risks factors related to illness that influence a child's vulnerability to illness development. The childhood and adolescent period is an exciting time for clinicians working in the field in terms of the potential for earliest identification of psychiatric illness and implementation of stage-specific interventions that may simultaneously reduce risk for poor outcomes. Familiarizing oneself with the most up to date information and concepts in this rapidly developing field is essential. Clinicians need to adopt a curious and transparent approach with youth and families presenting for care. Engaging the youth, their families as well as expert colleagues in child/adolescent psychiatry and utilizing all available information including the most current evidence to collaboratively make reliable diagnostic and treatment decisions will ultimately help to foster optimum outcome for patients.

References

- American Academy of Child and Adolescent Psychiatry. Practice parameters for the use of atypical Antipsychotic medications in children and adolescents. 2011. https://www.aacap.org/App_Themes/AACAP/docs/practice_parameteres/atypical_antipsychotic_medicaitons_web.pdf.
- American Academy of Pediatrics, Committee on substances abuse and committee on adolescence. Technical report: the impact of marijuana policies on youth: clinical, research and legal update. *Pediatrics*. 2015;135(3).
- American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5 edn (DSM-V). Washington, DC: American Psychiatric Publishing; 2013.
- Andover MS, Morris BW, Wren A, Bruzzese ME. The occurrence of non-suicidal self-injury and attempted suicide among adolescents: distinguishing risk factors and psychosocial correlates. *Child Adolesc Psychiatry Ment Health*. 2012;6:11.
- Angold A, Costello EJ. Depressive comorbidity in children and adolescents: empirical, theoretical, and methodological issues. *Am J Psychiatry*. 1993;150:1779–91.
- Avenevoli S, Swendson J, He J, et al. Major depression in the national comorbidity survey—adolescent supplement: prevalence, correlates, and treatment. *J Am Acad Child Adolesc Psychiatry*. 2015;54:37–44.e2.
- Beesdo K, Pine DS, Lieb R, Wittchen H-U. Incidence and risk patterns of anxiety and depressive disorders and categorization of generalized anxiety disorder. *Arch Gen Psychiatry*. 2010;67(1):47–57.
- Birmaher B, Brent DA, Chiappetta L, Bridge J, Monga S, Baugher M. Psychometric properties of the screen for child anxiety related emotional disorders (SCARED): a replication study. *J Am Acad Child Adolesc Psychiatry*. 1999;38(10):1230–6.
- Brent D, Emslie G, Clarke G, et al. Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: the TORDIA randomized control trial. *JAMA*. 2008;299:901–13.
- Bridge JA, Yengar S, Salary CB, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. *JAMA*. 2007;63:332–9.
- Bussing R, Mason DM, Bell L, et al. Adolescent outcomes of childhood attention-deficit/hyperactivity disorder in a diverse community sample. *J Am Acad Child Adolesc Psychiatry*. 2010;49:595–605.
- Calarge CA, Nicol G, Schlechte JA, Burns TL. Cardiometabolic outcomes in children and adolescents following discontinuation of long term risperidone treatment. *J Child Adolesc Psychopharmacol*. 2014;24:120–9.
- Centred for Disease Control and Prevention. Youth risk behavior surveillance – United States. *MMWR*. 2012;61:11–2.
- Chang KD. Diagnosing bipolar disorder in children and adolescents. *J Clin Psychiatry*. 2009;70(11):e41. <https://doi.org/10.4088/JCP.8125tx7c>.
- Chang LY, Wang MY, Tsai PS. Diagnostic accuracy of rating scales for attention-deficit/hyperactivity disorder: a meta-analysis. *Pediatrics*. 2016;137(3):1–15.
- Clemmensen L, Vernal DL, Steinhausen HC. A systematic review of the long-term outcome of early onset schizophrenia. *BMC Psychiatry*. 2012;12:150.
- Collins GA, McAllister MS, Adury K. (2016) Drug abuse and addiction. Cleveland Clinic Centre for Continuing Education Lyndhurst, OH. <http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/psychiatry-psychology/drug-abuse-and-addiction/>. Accessed 25 June 2016.
- Committee on Substance Abuse, Committee on Adolescence. The impact of marijuana policies on youth: clinical, research, and legal update. *Pediatrics*. 2015;135(3):584–7. <https://doi.org/10.1542/peds.2014-4146>.

- Correll CU, Kratochvil CJ, Marcj JS. Developments in pediatric psychopharmacology: focus on stimulants, antidepressants and antipsychotics. *J Clin Psychiatry*. 2011;72:655–70.
- Cosgrove VE, Roybal D, Chang KD. Bipolar depression in pediatric populations: epidemiology and management. *Pediatr Drugs*. 2013;15(2):83–91.
- Dilillo D, Mauri S, Mantegazza C, Fabiano V, Mameli C, Zucotti GV. Suicide in pediatrics: epidemiology, risk factors, warning signs and the role of the pediatrician detecting them. *Ital J Pediatr*. 2015;41:49. <https://doi.org/10.1186/s13052-015-0153-3>.
- Dunn V, Goodyer IA. Longitudinal investigation into childhood- and adolescence- onset depression: psychiatric outcome in early adulthood. *Br J Psychiatry*. 2006;188:216–22.
- Faraone SV. Using meta-analysis to compare the efficacy of medication for attention-deficit/hyperactivity disorder in youth. *P T*. 2009;34:678–94.
- Fergusson DM, Horwood LJ, Swain-Campbell NR. Cannabis dependence and psychotic symptoms in young people. *Psychol Med*. 2003;33(1):15–21.
- Giles LL, Martini R. Challenges and promises of pediatric psychopharmacology. *Acad Pediatr*. 2016;16:508–18.
- Gillberg C. Epidemiology of early onset schizophrenia. In: Remschmidt H, editor. *Schizophrenia in children and adolescents*. Cambridge: Cambridge University Press; 2001. p. 43–59.
- Girolamo G, Dagani J, Purcell R, Cocchi A, McGorry PD. Age of onset of mental disorders and use of mental health services: needs, opportunities and obstacles. *Epidemiol Psychiatr Sci*. 2012;21:47–57.
- Gore FM, Bloem PJN, Patton GC, Ferguson J, Joseph V, Coffey C, Sawyer SM, Mathers CD. Global burden of disease in young people aged 10–24 years: a systematic analysis. *Lancet*. 2011;377(9783):2093–102.
- Guy W. *Abnormal Involuntary Movement Scale (AIMS)*. ECDEU assessment manual for psychopharmacology, revised. Rockville, MD: National Institute of Mental Health. Psychopharmacology Research Branch; 1976. 1976:534–537 NIMH. DHEW Pub. No (ADM)
- Hetrick S, Merry S, McKenzie J, Sindahl P, Proctor M. Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents. *Cochrane Database Syst Rev*. 2007;3:CD004851.
- Hirota T, Schwartz S, Correll CU. Alpha-2 agonists for attention deficit/hyperactivity disorder in youth: a systematic review and meta-analysis of monotherapy and add-on trials to stimulant therapy. *J Am Acad Child Adolesc Psychiatry*. 2014;53:153–73.
- Jackson KM, Sher KJ, Wood PK. Trajectories of concurrent substance use disorders: a developmental, typological approach to comorbidity. *Alcohol Clin Exp Res*. 2000;24:902–13.
- Jensen CM, Steinhausen H-C. Comorbid mental disorders in children and adolescents with attention-deficit/hyperactivity disorder in a large nationwide study. *Atten Defic Hyperact Disord*. 2015;7:27–38.
- Kendall PC, Compton SN, Walkup JT, et al. Clinical characteristics of anxiety disordered youth. *J Anxiety Disord*. 2010;24(3):36–5.
- Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62:593–602.
- Kessler RC, Petukhova M, Sampson NA, Zaslavsky AM, Wittchen HU. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. *Int J Methods Psychiatr Res*. 2012;21(3):169–84.
- Klein DN, Shankman SA, Lewinsohn PM, et al. Subthreshold depressive disorder in adolescents: predictors of escalation to full-syndrome depressive disorders. *J Am Acad Child Adolesc Psychiatry*. 2009;48:703–10.
- Knight JR, Sherritt L, Shrier LA, Harris SK, Chang G. Validity of the CRAFFT substance abuse screening test among adolescent clinic patients. *Arch Pediatr Adolesc Med*. 2002;156:607–14.
- Lachman A. New developments in diagnosis and treatment update: Schizophrenia/first episode psychosis in children and adolescents. *J Child Adolesc Mental Health*. 2014;26(2):109–24.
- Leibenluft E. Severe mood dysregulation, irritability and the diagnostic boundaries of bipolar disorder in youth. *Am J Psychiatry*. 2011;168(2):129–42.
- MacDonald K, Pappas K. Why not pot? A review of the brain-based risks of cannabis. *Innov Clin Neurosci*. 2016;13(3-4):13–22.
- March JS, Vitiello B. Clinical messages from the treatment for adolescents with depression study (TADS). *Am J Psychiatry*. 2009;166:1118–23.
- March JS, Parker JD, Sullivan K, Stallings P, Conners CK. The Multidimensional Anxiety Scale for Children (MASC): factor structure, reliability, and validity. *J Am Acad Child Adolesc Psychiatry*. 1997;36(4):554–65.
- March J, Silva S, Petrycki S, et al. Treatment for adolescents with depression study (TADS) team. fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for adolescents with depression study (TADS) randomized controlled trial. *JAMA*. 2004;292:807–20.
- McGorry PD, Purcell R, Hickie IB, Jorm AF. Investing in youth mental health is a best buy. *Med J Aust*. 2007a;187(Suppl. 7):S5.
- McGorry PD, Purcell R, Hickie IB, Yung AR, Pantelis C, Jackson HJ. Clinical staging: a heuristic model for psychiatry and youth mental health. *Med J Aust*. 2007b;187(Suppl. 7):S40–2.
- McGuinness TM, Durand SC. Update on anxiety disorder in childhood and adolescence. *J Psychosoc Nurs Ment Health Serv*. 2016;54(6):25–8.
- Muehlenkamp JJ, Claes L, Havertape L, Plener PL. International prevalence of adolescent non-suicidal self-injury and deliberate self-harm. *Child Adolesc Psychiatr Ment Health*. 2012;6:10.
- National Collaborating Centre for Mental Health (UK). *Depression in Children and Young People: Identification and Management in Primary, Community and Secondary Care*. Leicester: British Psychological Society; 2005. (NICE Clinical Guidelines, No. 28.)

- Olfson M, King M, Schoenbaum M. Treatment of young people with antipsychotic medications in the United states. *JAMA Psychiat*. 2015;72:867–74.
- Pediatric OCD Treatment Study (POTS) Team. Cognitive behavior therapy, sertraline, and their combination for children and adolescents with obsessive-compulsive disorder: the pediatric OCD treatment study (POTS) randomized controlled trial. *JAMA*. 2004;292:1969–76.
- Pisano S, Catone G, Veltri S, et al. Update on the safety of second generation antipsychotics in youths: a call for collaboration among pediatricians and child psychiatrists. *Ital J Pediatr*. 2016;42:51. <https://doi.org/10.1186/s13052-016-0259-2>.
- Polanczyk GV, Salum G, Sugaya LS, et al. Annual research review: a meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. *J Child Psychol Psychiatry*. 2015;56:345–65.
- Pringsheim T, Panagiotopoulos C, Davidson J, Ho J. Evidence based recommendations for monitoring safety of second generation antipsychotics in children and youth. *J Can Acad Child Adolesc Psychiatry*. 2001;3:1–2.
- Prinsheim T, Lam D, Ching H, Patten S. Metabolic and neurological complications of second generation Antipsychotic use in children: a systematic review and meta-analysis of randomized controlled trials. *Drug Saf*. 2011;34:651–68.
- Radhakrishnan R, Wilkinson ST, D'Souza DC. Gone to pot – a review of the association between cannabis and psychosis. *Front Psych*. 2014;5:54.
- Rynn MA, Walkup JT, Compton SN. Child/adolescent anxiety multimodal study: evaluating safety. *J Am Acad Child Adolesc Psychiatry*. 2015;54(3):180–90.
- Schimmelmann BG, Schmidt SJ, Carbon M, Correll CU. Treatment of adolescents with early-onset schizophrenia spectrum disorders: in search of a rational, evidence-informed approach. *Curr Opin Psychiatry*. 2013;26:219–30.
- Schulden JD, Thomas YF, Compton WM. Substance abuse in the United States: findings from recent epidemiologic studies. *Curr Psychiatry Rep*. 2009;11:353–9.
- Scott J, Chant D, Andrews G. Psychotic-like experiences in the general community: the correlates of CIDI psychosis screen items in an Australian sample. *Psychol Med*. 2006;36:231–8.
- Shain BN. Suicide and suicide attempts in adolescents. *Pediatrics*. 2007;120(3):669–76.
- Singh MK, Ketter T, Chang KD. Distinguishing bipolar disorder from other psychiatric disorders in children. *Curr Psychiatry Rep*. 2014;16:516. <https://doi.org/10.1007/s11920-014-0516-2>.
- Stone AL, Becker LG, Huber AM, Catalano RF. Review of risk and protective factors of substance use and problem use in emerging adulthood. *Addict Behav*. 2012;37(7):747–75.
- Strawn JR, Welge JA, Wehry AM, et al. Efficacy and tolerability of antidepressants in pediatric anxiety disorders: a systematic review and meta-analysis. *Depress Anxiety*. 2015;32:149–57.
- Swannell SV, Martin GE, Page A, Hasking P, St John NJ. Prevalence of nonsuicidal self-injury in non-clinical samples: systematic review, meta-analysis and meta-regression. *Suicide Life Threat Behav*. 2014;44:273–303.
- Tang MH, Pinsky EG. Mood and affect disorders. *Pediatr Rev*. 2015;36(2):52–63.
- Taylor E, Chadwick O, Heptinstall E, et al. Hyperactivity and conduct problems as risk factors for adolescent development. *J Am Acad Child Adolesc Psychiatry*. 1996;35:1213–26.
- Thapar A, Cooper M. Attention deficit hyperactivity disorder. *Lancet*. 2016;387:1240–50.
- Thapar A, Collishaw S, Pine DS, Thapar AK. Depression in adolescence. *Lancet*. 2012;379(9820):1056–67.
- The MTA Cooperative Group. Multimodal treatment study of children with ADHD. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry*. 1999;56:1073–86.
- Thomsen PH. Schizophrenia with childhood and adolescent onset—a nationwide register-based study. *Acta Psychiatr Scand*. 1996;94:187–93.
- Van Meter AR, Burke C, Youngstrom EA, et al. The bipolar prodrome: meta-analysis of symptom prevalence prior to initial or recurrent mood episodes. *J Am Acad Child Adolesc Psychiatry*. 2016;55(7):543–55.
- Walkup JT, Albano AM, Piacentini J, et al. Cognitive behavioral therapy, sertraline or a combination in childhood anxiety. *N Engl J Med*. 2008;359:2753–66.
- Weisz JR, McCarty CA, Valeri SM. Effects of psychotherapy for depression in children and adolescents: a meta-analysis. *Psychol Bull*. 2006;132:132–49.
- World Health Organization. Global health risks: mortality and burden of disease attributable to selected major risks. Geneva: World Health Organization; 2009.
- Yung AR, Nelson B, Stanford C. Validation of “prodromal” criteria to detect individuals at ultra high risk of psychosis: 2 year follow-up. *Schizophr Res*. 2008;105:10–7.



Roberta A. Berard and Ronald M. Laxer

Introduction

Pediatric Rheumatology is a rapidly evolving field. There have been many exciting advances in the recognition, diagnosis and management of autoimmune and autoinflammatory conditions over recent years. In addition, pediatric musculoskeletal complaints are very common in children presenting to general practitioners, pediatricians and orthopedic surgeons which mandates a good foundation of knowledge in the common inflammatory and non-inflammatory conditions by age group for timely, appropriate and evidence-based assessments. This chapter will focus on an update in a few key areas in Pediatric Rheumatology. Advances in the assessment of the pediatric musculoskeletal (MSK) complaints for the general practitioner, the diagnosis and management of juvenile idiopathic arthritis (JIA), non-inflammatory MSK causes of pain, macrophage activation

syndrome and advances in the most common autoinflammatory diseases (periodic fever syndromes) will be discussed and reviewed.

Musculoskeletal Assessment Tool: The pGALs—Pediatric Gait, Arms, Legs, and Spine (Foster et al. 2006)

Musculoskeletal problems are common presenting complaints of children and youth to health care practitioners. This may include clinicians working in family practice, emergency medicine, orthopedics, pediatrics or adult rheumatology in addition to nurse practitioners delivering primary care. A Canadian study published in 2012 examined the annual prevalence of healthcare contacts for MSK complaints using administrative data. One in eight children in Ontario make physician visits in a year for MSK complaints (122.1 per 1000 children). The majority of visits are for injury and related conditions (63.2 per 1000), arthritis (27.7 per 1000), bone and spinal conditions (14.2 per 1000) and congenital anomalies (3 per 1000). The majority of children presented to primary care physicians (74.4%), orthopedic surgeons (22.3%) and pediatricians (10.1%) (Gunz et al. 2012).

The majority of MSK disorders in children are benign, self-limited and often trauma-related, clearly not always requiring a subspecialist referral. MSK symptoms can also be the presenting features of Juvenile Idiopathic Arthritis (JIA),

R.A. Berard (✉)

Division of Rheumatology, Department of Paediatrics, Children's Hospital, London Health Sciences Centre, Western University, 800 Commissioners Road East, London, N6A5W9 Ontario, ON, Canada
e-mail: roberta.berard@lhsc.on.ca

R.M. Laxer, M.D.C.M., F.R.C.P.C

Division of Rheumatology, The Hospital for Sick Children, Department of Paediatrics and Medicine, University of Toronto, 555 University Avenue, Toronto, M5G 1X8 Ontario, ON, Canada
e-mail: ronald.laxer@sickkids.ca

but also of more life-threatening conditions like malignancy, infection, vasculitis and non-accidental injury. Inflammatory arthritis can also be seen in association with other chronic diseases in pediatrics such as inflammatory bowel disease (IBD), psoriasis, and immune deficiency.

Several studies have highlighted the lack of confidence that doctors have in their pediatric MSK clinical skills and knowledge (Myers et al. 2004; Jandial et al. 2009). Given the prevalence of MSK complaints, clinicians require skills to effectively triage patients and when appropriate to refer to a subspecialist. In many conditions, including JIA, there is a reported delay in referral to specialist care. It is likely that the delay in access to care has an adverse impact on long-term clinical outcomes (Foster et al. 2010). There have been considerable efforts to raise awareness of JIA, including educational strategies such as the pGALS and e-resources as outlined below.

A detailed MSK physical examination should include growth parameters and vital signs. The presence of fever should alert the clinician to more severe conditions requiring urgent treatment (e.g. septic arthritis). On general examination, clues to the underlying diagnosis include rash (psoriasis, viral exanthema, autoimmune), iritis (IBD or enthesitis-related arthritis), and hepatosplenomegaly/lymphadenopathy suggestive of malignancy. The MSK examination should include a review of all joints and examination of gait but with a focus on the affected joints. Joint abnormalities can be subtle and therefore looking for asymmetrical changes can often be helpful (except in symmetric disease). Additionally, regional muscle wasting indicates chronicity of the problem. In contrast to adults where the majority of diagnoses can be made by history, in pediatric patients, the history is often provided by an observer and may be vague with non-specific complaints. It is certainly not uncommon to find joint involvement that has not been mentioned as

part of the presenting complaint (Goff et al. 2012).

The pGALS (Fig. 21.1) is an evidence-based approach to basic pediatric MSK assessment and is aimed at the non-specialist in pediatric MSK medicine to be able to discern normal from abnormal. The components of the pGALS are essentially the same as the adult GALS (Doherty et al. 1992) with a few additional maneuvers as original testing of the GALS in the pediatric patients missed significant abnormalities in the foot and ankles, wrists and temporomandibular joints. The pGALS has excellent sensitivity (97–100%) to detect abnormalities, it is quick to do (taking an average of 2 min), and incorporates simple maneuvers that are used in clinical practice (Foster et al. 2006). The pGALS was validated in school-aged children but can be successfully performed in younger ambulatory children. However, the examiner must take an opportunistic approach given the cooperation level and attention span of the child.

There should be a low threshold to perform the pGALS in the context of a patient with MSK complaints. It is particularly relevant in the following clinical scenarios: unwell child with pyrexia, child with a limp, delay or regression of motor milestones, child with chronic disease with known association with MSK presentations (such as inflammatory bowel disease), and the “clumsy” child in the absence of neurological disease (Foster and Jandial 2013). The pGALS should also be performed when the history is suggestive of inflammatory disease, such as joint swelling or stiffness, particularly morning or post-inactivity (e.g. long car rides), and/or altered function (e.g. play, handwriting skills, and regression of milestones).

The pGALS was developed to identify inflammatory disease but has been shown to be effective in identifying other joint problems (e.g. orthopedic problems involving the hip, scoliosis,

Fig. 21.1 (a–c) The pGALS musculoskeletal screen (From Foster HE, Jandial S. pGALS—a screening examination of the musculoskeletal system in school-aged children. Reports on the Rheumatic Diseases (Series 5),






Hands on 15: Arthritis Research Campaign; 2008. P. 4–6. Copyright © Arthritis Research Campaign; with permission)



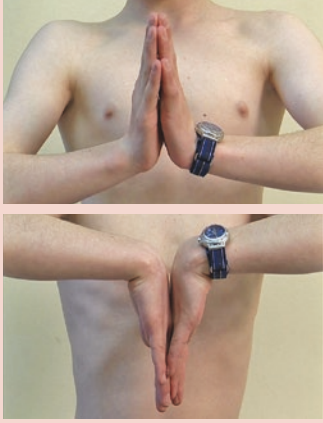


a

The pGALS musculoskeletal screen

Screening questions

- Do you (or does your child) have any pain or stiffness in your (their) joints, muscles or back?
- Do you (or does your child) have any difficulty getting yourself (him/herself) dressed without any help?
- Do you (or does your child) have any problem going up and down stairs?

| FIGURE | SCREENING MANOEUVRES (Note the manoeuvres in bold are additional to those in adult GALS ²) | WHAT IS BEING ASSESSED? |
|---|---|---|
|  | <p>Observe the child standing (from front, back and sides)</p> | <ul style="list-style-type: none"> • Posture and habitus • Skin rashes – e.g. psoriasis • Deformity – e.g. leg length inequality, leg alignment (valgus, varus at the knee or ankle), scoliosis, joint swelling, muscle wasting, flat feet |
|  | <p>Observe the child walking and 'Walk on your heels' and 'Walk on your tiptoes'</p> | <ul style="list-style-type: none"> • Ankles, subtalar, midtarsal and small joints of feet and toes • Foot posture (note if presence of normal longitudinal arches of feet when on tiptoes) |
|  | <p>'Hold your hands out straight in front of you'</p> | <ul style="list-style-type: none"> • Forward flexion of shoulders • Elbow extension • Wrist extension • Extension of small joints of fingers |
|  | <p>'Turn your hands over and make a fist'</p> | <ul style="list-style-type: none"> • Wrist supination • Elbow supination • Flexion of small joints of fingers |
|  | <p>'Pinch your index finger and thumb together'</p> | <ul style="list-style-type: none"> • Manual dexterity • Coordination of small joints of index finger and thumb and functional key grip |

| b FIGURE | SCREENING MANOEUVRES | WHAT IS BEING ASSESSED? |
|---|--|--|
|  | <p>'Touch the tips of your fingers'</p> | <ul style="list-style-type: none"> • Manual dexterity • Coordination of small joints of fingers and thumbs |
|  | <p>Squeeze the metacarpophalangeal joints for tenderness</p> | <ul style="list-style-type: none"> • Metacarpophalangeal joints |
|  | <p>'Put your hands together palm to palm' and 'Put your hands together back to back'</p> | <ul style="list-style-type: none"> • Extension of small joints of fingers • Wrist extension • Elbow flexion |
|  | <p>'Reach up, "touch the sky"' and 'Look at the ceiling'</p> | <ul style="list-style-type: none"> • Elbow extension • Wrist extension • Shoulder abduction • Neck extension |
|  | <p>'Put your hands behind your neck'</p> | <ul style="list-style-type: none"> • Shoulder abduction • External rotation of shoulders • Elbow flexion |




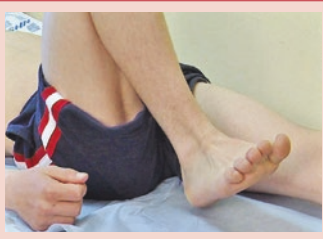


| C | FIGURE | SCREENING MANOEUVRES | WHAT IS BEING ASSESSED? |
|---|---|--|-------------------------|
|  | <p>'Try and touch your shoulder with your ear'</p> | <ul style="list-style-type: none"> • Cervical spine lateral flexion | |
|  | <p>'Open wide and put three (<i>child's own</i>) fingers in your mouth'</p> | <ul style="list-style-type: none"> • Temporomandibular joints (and check for deviation of jaw movement) | |
|  | <p>Feel for effusion at the knee (patella tap, or cross-fluctuation)</p> | <ul style="list-style-type: none"> • Knee effusion (small effusion may be missed by patella tap alone) | |
|  | <p>Active movement of knees (flexion and extension) and feel for crepitus</p> | <ul style="list-style-type: none"> • Knee flexion • Knee extension | |
|  | <p>Passive movement of hip (knee flexed to 90°, and internal rotation of hip)</p> | <ul style="list-style-type: none"> • Hip flexion and internal rotation | |
|  | <p>'Bend forwards and touch your toes?'</p> | <ul style="list-style-type: none"> • Forward flexion of thoraco-lumbar spine (and check for scoliosis) | |

Fig. 21.1 (continued)

Table 21.1 Normal variants in gait patterns and leg alignment

| |
|---|
| 1. Habitual toe walking is common in young children up to 3 years |
| 2. Intoeing can be due to: <ul style="list-style-type: none"> • Persistent femoral anteversion (characterized by child walking with patellae and feet pointing inwards and is common between ages of 3–8 years) • Internal tibial torsion (characterized by child walking with patella facing forward and toes pointing inwards and is common from onset of walking to 3 years) • Metatarsus adductus (characterized by a flexible “C shaped” lateral border of the foot and most resolve by 6 years). |
| 3. Bow legs (genu varus) are common from birth to early toddler, often with out-toeing (maximal at approximately 1 year of age), and most resolve by 18 months |
| 4. Knock knees (genu valgus) are common and are often associated with in-toeing (maximal at approximately 4 years of age) and most resolve by age of 7 years |
| 5. Flat feet —most children have a flexible foot with normal arch on tiptoeing and resolve by 6 years |
| 6. Crooked toes —most resolve with weight bearing |

Normal variants: indications for referral

- Persistent changes (beyond the expected age ranges)
- Progressive/asymmetrical changes
- Short stature or dysmorphic features
- Painful changes with functional limitations
- Regression or delayed motor milestones
- Abnormal joint examination elsewhere
- Suggestion of neurological disease/developmental delay

Data from Foster, H. E. & Jandial, S. pGALS – paediatric Gait Arms Legs and Spine: a simple examination of the musculoskeletal system. *Pediatric Rheumatology Online Journal* **11**, 44, 2013

and hypermobility). The key to an appropriate interpretation of the pGALS is knowledge of normal movements of joints in different age groups, variability in gait, leg alignment, and normal motor milestones (Table 21.1). These normal variants are a common cause of parental concern and often can be addressed with explanation and reassurance.

The pGALS is an essential clinical skill to be acquired at a minimum, by all medical students as part of undergraduate training and incorporated in the training of other clinicians (such as nurse practitioners) to facilitate assessments and timely

referrals to specialist care as needed. Details of teaching and performing the pGALS are available on the following free educational resource: (<http://www.arthritisresearchuk.org/health-professionals-and-students/video-resources/pgals.aspx>). The same working group has also developed an online evidence based interactive learning tool and information resource for education in pediatric musculoskeletal medicine (Smith et al. 2016). Pediatric Musculoskeletal Matters (www.pmmonline.org). This learning tool was designed to target medical students and primary care doctors, however the content is certainly relevant to pediatricians and other clinicians involved in the care of pediatric patients. The site is an excellent resource with learning modules, a guide to the investigations and management of common MSK complaints, case based teaching and problem list by anatomic sites.

Update on Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children, affecting about 1 in 1000 children worldwide (Hayward and Wallace 2009). JIA is an umbrella term describing a group of arthritides of unknown etiology lasting more than 6 weeks with onset in children younger than 16 years of age (Petty et al. 2004). There are seven categories of JIA (Table 21.2). An accurate diagnosis of JIA

Table 21.2 Juvenile idiopathic arthritis categories

| Category | Key features |
|------------------------------|---|
| Systemic arthritis | Fever, rash, serositis, adenopathy, hepatosplenomegaly |
| Oligoarthritis | 4 or fewer joints |
| Polyarthritis, RF- | 5 or more joints, RF- |
| Polyarthritis, RF+ | 5 or more joints, RF+ |
| Psoriatic arthritis | Psoriasis, nail pits, dactylitis, family history of psoriasis |
| Enthesitis-related arthritis | Enthesitis, acute uveitis, sacroiliitis, HLA-B27 |
| Undifferentiated | Fit into one or more criteria or satisfy criteria for none |

RF rheumatoid factor

depends on the history and physical examination. The presence of a positive anti-nuclear antibody (ANA) or rheumatoid factor (RF) is neither necessary nor sufficient to make a diagnosis of JIA. (Malleson et al. 2010) Early referral is essential to reduce morbidity in terms of effect on normal growth and development, pain and quality of life. As well, it is clear that earlier treatment can improve outcomes in terms of time to and rate of achieving remission (Albers et al. 2009; Broughton and Armon 2012).

In years past, it has been a common misbelief that children with arthritis outgrow the disease in the adolescent years. Multiple long-term outcome studies published early in this century report relatively poor outcomes even for the “mildest” cases (i.e. those with oligoarthritis). A Canadian multicenter retrospective cohort study reported that at age 16, there was only a 50% percent probability of remission (defined here as 2 years off medications and no disease activity). At the time of the study, those patients >16 years of age had a high probability of active disease (62–94% depending on category) in their thirties and forties (Oen 2002).

Over the last 15 years, tremendous advances have occurred in the treatment of JIA primarily with the use of biologic therapies. More recent data from a Canadian longitudinal outcomes study (Research on Arthritis in Canadian Children Emphasizing Outcomes: ReACCh-Out) suggests better outcomes in terms of rate and time to achieving remission in the short term (2 year data reported); however, collection of longer-term data is ongoing.

As in other chronic illnesses of childhood, the treatment of JIA must include a multidisciplinary team approach. In all cases, the goal of treatment is complete remission and normal physical and social/emotional development. Particularly with newer medications available, this end point is achievable for the majority of patients. Physical and occupational therapy are essential in the management of JIA. These therapies improve range of motion and mobility thereby ideally preventing permanent disability. The therapists can also provide exercise guidelines to encourage children to be physically active within the limits

of their abilities. Physical activity is encouraged and is safe and important for children with JIA.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used frequently, in particular for the treatment of oligoarthritis patients and as an adjunct for pain and stiffness in polyarthritis patients. The most common side effects are nausea and/or vomiting. Naproxen and indomethacin are available in liquid form for younger children who cannot swallow pills. Use of NSAIDs is appropriate before review with a pediatric rheumatologist. Corticosteroid use is limited to bridging therapy while DMARDs reach their therapeutic effect. Corticosteroids are particularly helpful in polyarthritis and systemic JIA; however, they do not induce remission and given the potential side effects, exposure should be limited. Particular attention to bone health and calcium and vitamin D supplementation should be paid for any patient on prolonged oral corticosteroid use. Intra-articular corticosteroid injections can induce inactive disease when used as a monotherapy or in conjunction with methotrexate. Triamcinolone hexacetonide is the preferred compound.

The main synthetic DMARD used is methotrexate either by subcutaneous injection or orally once weekly. The most common side effects are nausea and vomiting for which anti-emetics are often used with variable effect. Other side effects include fatigue, mouth ulcers and potentially liver toxicity or bone marrow suppression. Monitoring blood work including liver enzymes and a complete blood count should be performed every 3 months (more frequently when the medication is initiated). Folic acid is given with methotrexate and is thought to assist with gastrointestinal side effects such as ulcers, nausea and transaminitis. Leflunomide and sulfasalazine are also used with similar (no fatigue or mouth ulcers) side-effect profiles. None of these medications are safe for use in pregnancy.

The biologic DMARDs include the tumour necrosis factor (TNF) inhibitors (etanercept, adalimumab, infliximab), interleukin (IL) inhibitors (IL-1Ra-Anakinra, IL-1 β -canakinumab, and IL-6-tocilizumab), T-cell co-stimulatory modulator (abatacept), and B-cell inhibitor (rituximab). In

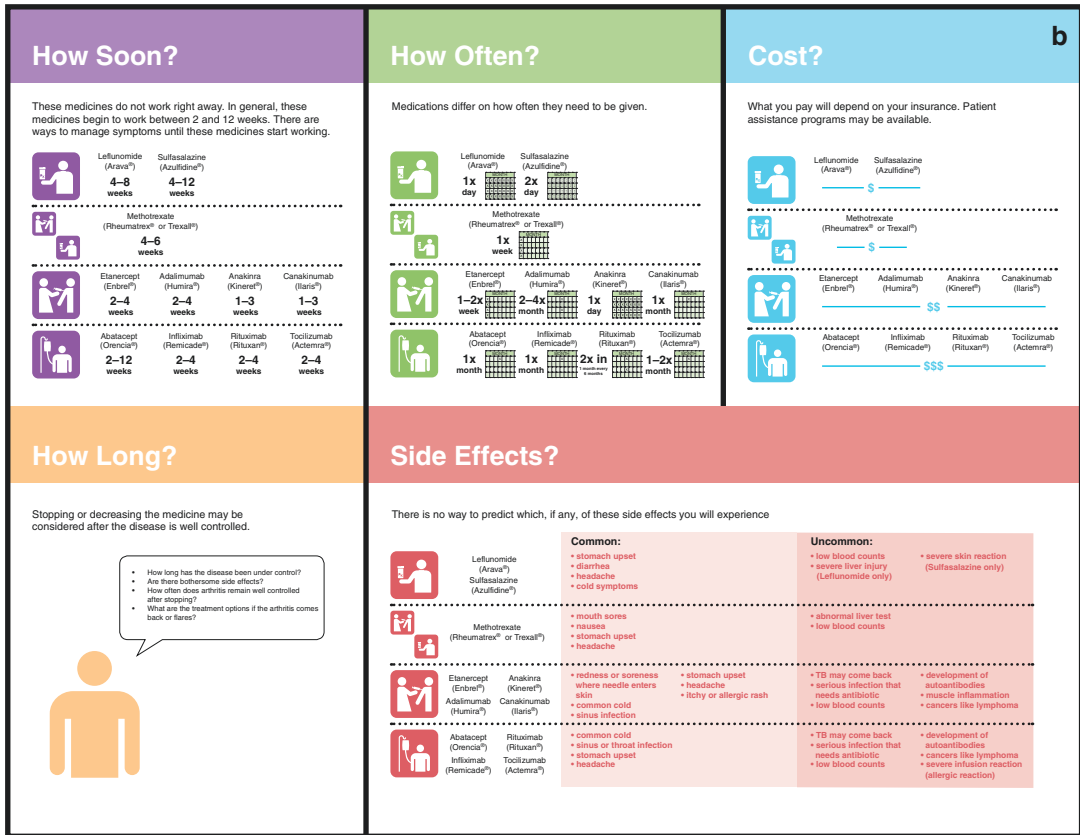


Fig. 21.2 (continued)

every 3 months for the young (<4 years at onset of disease), female, ANA-positive oligoarthritis patients. Morbidity from uveitis includes cataracts, glaucoma, band keratopathy and loss of vision. Visual outcome has improved over the past 20 years; most children have a relatively good prognosis if the disorder is detected and treated early. However, uveitis in childhood (including JIA) remains a leading cause of loss of vision and blindness worldwide (10–15%).

A team approach to surveillance for and prevention of complications of JIA and its treatment is essential. The following considerations in the management of JIA highlight the importance of a team approach: adherence to uveitis screening guidelines, necessary laboratory monitoring for medications, vaccine counseling (live vaccines prohibited while on immunosuppression and annual influenza vaccine encouraged), monitor-

ing for growth disturbances (particularly leg length discrepancy and growth abnormalities of the mandible), screening and awareness of adolescent issues (mental health, sexual activity, and alcohol use due to the potential for liver toxicity and teratogenicity associated with the most commonly used DMARD, methotrexate).

A change in the treatment paradigm for JIA, including an early introduction of synthetic DMARDs and biologic DMARDs has remarkably improved the outcomes for patients. The goals of therapy to achieve remission, minimize medication toxicity, maximize function, optimize growth and development and improve quality of life are achievable. Multinational collaborative efforts addressing issues of incorporation of genetic and immunologic data to develop outcome based classification systems and personalized treatment plans, and the timing of initiation

and cessation of biologic therapies, are central and ongoing areas of study to further the advances in the management of children with JIA.

Update on Non-inflammatory Musculoskeletal Pain

Musculoskeletal pain is one of the most common presenting symptoms to health care practitioners. Benign limb pain of childhood (growing pains), hypermobility, overuse syndromes, malignancy and pain amplification syndromes are the most commonly seen non-inflammatory causes. An excellent comprehensive review on this topic was published in 2012 and is suggested for further information (Weiser 2012).

Growing pains, which is a misnomer, usually occur outside of major growth spurt periods, with an onset between 4 and 10 years of age. Growing pains are characterized by a deep aching, crampy pain in the thighs or shins bilaterally. They usually occur at night causing nocturnal awakenings. The pain occurs mostly in the calves with a peak intensity of 10–15 min that slowly resolves over an hour. Massage, heat and/or analgesia with ibuprofen or acetaminophen may be helpful. Typically symptoms resolve by the morning and children are asymptomatic during the day. There are symptom free periods between the episodes from days to weeks. Few studies exist looking at the long-term outcome of this condition. Five-year follow up results suggest resolution in about half of the patients but the remainder have persistent complaints into adulthood (Uziel et al. 2010).

Chronic pain syndromes and pain symptoms can often be more debilitating and difficult to treat than inflammatory disease. Many children with chronic MSK pain do not have an identifiable cause. The prevalence of chronic MSK pain is variable. One-third of school-age children reported pain lasting longer than 6 months, more than half of which was described as MSK pain (Roth-Isigkeit et al. 2005). Pain syndromes frequently start following an inciting injury or illness, but also seem to be related to emotional stress such as the loss of a loved one or moving house. After onset, the pain either stays localized

or spreads diffusely. The patients can develop significant disability to the point of becoming immobile and unable to function physically. Additionally, the pain can lead to social withdrawal, missed school days, and isolation.

There are regional and diffuse pain amplification syndromes. The classic regionalized pain syndrome is complex regional pain syndrome Type I (CRPS1 or reflex sympathetic dystrophy). This entity is characterized by chronic pain involving a peripheral extremity, often following an injury that leads to immobilization. The main clinical features are pain and allodynia (a painful response to a normally innocuous stimulus), edema, changes in skin blood flow leading to discoloration, and/or abnormal sweating in the region of pain secondary to sympathetic dysfunction. Motor impairment (e.g. weakness) can also be seen. With exclusion of other conditions that could lead to the degree of pain and dysfunction (infection, malignancy, fracture), the treatment involves intense physiotherapy with manipulation of the extremity with the goal of restoring function. Desensitization with manual therapy as well as heat/cold therapy is a mainstay of treatment. Mirror box therapy is a novel specialized approach to the treatment of CRPS1 that has shown promising results in terms of pain reduction (Cacchio et al. 2009). This technique uses visual feedback as a substitute for inappropriate proprioceptive feedback with the understanding that pain in this syndrome may be induced by a mismatch between proprioceptive feedback and motor action.

Juvenile fibromyalgia is characterized by generalized MSK aches at ≥ 3 sites for ≥ 3 months in the absence of underlying conditions or causes, and with normal laboratory tests. The physical examination shows ≥ 5 tender points (areas of tenderness occurring in muscle, muscle-tendon junction, bursa, or fat pads). It is associated with fatigue, poor sleep, chronic anxiety, chronic headaches, and irritable bowel syndrome. Conversion symptoms are also not uncommon. Onset of the illness may be triggered by a change in physical activity due to injury or chronic illness. Often there is a family history of pain and a pain role model in the family. The pathogenesis is

complex and likely related to abnormal pain processing and central amplification.

Effective treatment is through a multidisciplinary approach with the goal to focus on pain control but also on regaining function and returning to regular daily activities. The three P's of pain management are pharmacological, physical and psychological and includes education, sleep hygiene, exercise, physiotherapy, cognitive behavioral therapy for management of stress and pain triggers. As the primary care provider seeing these patients, it is important to limit investigations and referrals to other specialists once the diagnosis is clear. Additional excellent online resources for patients, families and care providers are www.stopchildhoodpain.org and www.rsd.org.

Macrophage Activation Syndrome

Macrophage activation syndrome (MAS) is a potentially life-threatening complication of rheumatic diseases (particularly systemic JIA) characterized by activation of T cells and macrophages, leading to an overwhelming inflammatory response. Complete understanding of the pathophysiology is lacking but it is clear that the dysfunctional immune response is similar to that seen in other forms of hemophagocytic lymphohistiocytosis (HLH). MAS is classified as an acquired cause of HLH, along with other acquired causes such as infection, endogenous tissue damage (e.g. sepsis) and malignancy; whereas, in primary HLH, the causes are genetic or immunodeficiency related.

MAS can be a complication of a known case of systemic JIA (sJIA) but can also be the initial presentation of the disease. The incidence of MAS in sJIA is unknown but it is estimated that around 10% of children develop overt MAS. It is abundantly clear that MAS occurs much more commonly than thought, more recent data suggests that up to 30–40% of patients with sJIA will develop subclinical or MAS in a milder form (Behrens et al. 2007). Kawasaki disease (KD) and systemic lupus erythematosus (SLE) are also associated with MAS but not as frequently as sJIA. A set of classification criteria for MAS

complicating sJIA has been proposed (Ravelli et al. 2016).

The main clinical manifestations of MAS are sustained fever (compared with the quotidian fever of sJIA), hepatosplenomegaly, anemia, liver function abnormalities, rash, coagulopathy, and central nervous system dysfunction (lethargy, irritability, disorientation, headache, seizure or coma). Laboratory features suggestive of MAS include falling white blood cell count and platelets, falling erythrocyte sedimentation rate (secondary to hypofibrinogenemia), significantly increased ferritin level (>5000–10,000 ng/ml generally but should at least consider the diagnosis when the ferritin is >1000 ng/ml), elevated transaminases, hypertriglyceridemia, hypofibrinogenemia, elevated lactate dehydrogenase (LDH), elevated d-dimers, and evidence of hemophagocytosis on bone marrow aspirate (positive only in 60%) (Minoia et al. 2014). Although the ESR decreases, the C-reactive protein level continues to increase in worsening MAS (Petty et al. 2016). Elevated markers of T cell activation, including soluble IL-2 receptor alpha chain and soluble CD137, have good sensitivity. They are helpful in detecting subclinical disease and following response to treatment (Bleesing et al. 2007); however, they are challenging to access given that are only performed in specialized laboratories.

A prolonged fever is defined as a single illness in which duration of fever exceeds that expected for the clinical diagnosis (e.g. >10 days for a viral URI) (Long 2005). The most common rheumatic causes of prolonged fever are KD, sJIA, systemic lupus erythematosus (SLE) and acute rheumatic fever (ARF). However, MAS must be considered in this context particularly because the presentation is often acute and may be severe with rapid development of multiorgan failure that requires the admission of the patient to the intensive care unit (Petty et al. 2016). In the context of a patient with prolonged fever a rheumatic cause should be considered in the presence of the following: isolated fever >5 days in young infant (<6 months), presence of arthritis/arthritis, presence of a rash, presence of serositis, presence of cytopenias, culture negative sepsis, and/or recurrent and periodic episodes of fever (see Autoinflammatory disease below).

Early diagnosis and aggressive management of MAS are necessary to avoid significant morbidity and mortality. High-dose corticosteroids and supportive care are the first-line therapies; intravenous immunoglobulin and anakinra are also frequently used (particularly in MAS complicating sJIA) as well as cyclosporine and etoposide.

Autoinflammatory Disease (Periodic Fever syndromes)

The autoinflammatory (AID) conditions are caused by dysregulation in the innate immune system (e.g. neutrophils, monocytes/macrophages). Typically, the AID are characterized by recurrent episodes of fever, systemic inflammation, multi-system involvement and possible end-organ damage. Periodic fever syndromes, the former term for this group of diseases, is not adequate because most syndromes are not truly periodic, and fever is not a necessary feature. The definition of a periodic fever is recurring episodes of illness for which fever is the cardinal feature, and other associated symptoms are similar and predictable, and the duration is days to weeks, with intervening intervals of weeks to months of complete well being (Long 2005). The main causes of periodic fever in childhood are outlined in Table 21.3.

The AIDs often presents a diagnostic challenge to clinicians. Fever is a very common presenting symptom to health care professionals, the cause of which is rarely an AID. With multiple febrile illnesses, the child is often evaluated by several practitioners, leading to a delay in consideration of an AID as the cause for the symptoms. The key to making the diagnosis is a careful history and physical examination. Important features to consider narrowing the diagnosis of AID are the following: age at onset of the recurrent febrile episodes, ethnicity, family history, attack triggers, fever duration and periodicity, clinical manifestations, and response to therapy. Investigations should be done when the patient is having an episode and also when well (Table 21.4). In a typical AID, elevated inflammatory markers are present with an attack but normal blood work is seen when the patient is

Table 21.3 Differential diagnosis of periodic fever in childhood

| | |
|---------------------------|---|
| Infectious disease | <ul style="list-style-type: none"> • Recurrent upper respiratory tract infections • Urinary tract infections • Viral infections (EBV, Parvovirus B19, HSV1 and HSV2) • Bacterial infections (Borrelia, Brucella, Salmonella, tuberculosis, Yersinia) • Parasitic disease (malaria, toxoplasmosis) |
| Congenital immune defects | <ul style="list-style-type: none"> • Primary immunodeficiencies • Cyclic neutropenia |
| Fever syndromes | <ul style="list-style-type: none"> • Familial Mediterranean fever • Cryopyrin associated periodic syndromes • Tumour necrosis factor receptor associated periodic syndrome • Mevalonate kinase deficiency (includes Hyper-IgD syndrome) • PFAPA • Periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) |
| Neoplastic disease | <ul style="list-style-type: none"> • Acute lymphoblastic leukemia • Acute myeloid leukemia • Lymphoma (Pel Epstein fever) |
| Autoimmune | <ul style="list-style-type: none"> • Systemic lupus erythematosus • Systemic JIA • Vasculitis |
| Granulomatous | <ul style="list-style-type: none"> • Blau syndrome • Early onset sarcoidosis • Crohn disease |

Adapted from Federici S and Gattorno M. A practical approach to the diagnosis of autoinflammatory disease in children. *Best Pract Res Clin Rheumatol* **28**, 263–276, 2014

well. If an AID is suspected, a fever and symptom diary should be performed for at least 6 months with consideration of referral to a pediatric rheumatologist. Apart from familial Mediterranean fever (FMF), no validated diagnostic criteria are available (Yalcinkaya et al. 2009). There is an evidence-based diagnostic score that has been developed for the identification of patients at a higher risk of carrying a causative mutation in one of the genes associated with a periodic fever syndrome (Gattorno et al. 2008).

Table 21.4 Approach to periodic fevers

| History | Physical examination |
|--|---|
| <ul style="list-style-type: none"> • Duration of febrile episodes, regular or irregular and intervals • Associated symptoms • Full review of systems • Ill contacts • Travel history • Pets • History of unpasteurized dairy, uncooked meat, etc. • Family and past medical history: <ul style="list-style-type: none"> Ethnicity, consanguinity Diseases in family: renal transplants, hearing loss, early deaths, amyloidosis • Past medical history: appendectomy, hearing loss | <ul style="list-style-type: none"> • Vital signs, growth parameters • Head and neck exam—mouth sores, pharyngitis, cervical adenopathy • Rash • Signs of serositis • Hepatosplenomegaly • Other adenopathy • Joint abnormalities • Need to do full physical examination |

Investigations

- Complete blood count (CBC)
- Liver enzymes (AST, ALT) and Albumin
- ESR, CRP
- Renal function
- Immunoglobulins G,A,M
- Urinalysis (urine protein)
- Immunoglobulin D
- When indicated:
- Blood culture
- Viral testing, e.g. NP swab
- Urine culture
- If travel history, consider malaria smears
- Tuberculin skin test
- Imaging as directed by physical exam
- Serum amyloid A (done only in specialized laboratories)

MVKD mevalonate kinase deficiency

There is need to raise awareness of these conditions to decrease the delay in the time to referral to a specialist in order to reduce associated morbidity and to prevent any potential organ damage. With a better understanding of the disease pathogenesis for many of the AID, there has been an improvement in the diagnostic tests and therapeutic options for these patients. The features of the most common hereditary autoinflammatory disease (familial Mediterranean fever)

and the most common cause of periodic fevers (periodic fever, aphthous stomatitis, pharyngitis, and adenitis—PFAPA) will be reviewed. For a full review of the AID, see 2012 paper by Hashkes and Toker (Hashkes and Toker 2012) and 2014 paper by Federici and Gattorno (Federici and Gattorno 2014).

Familial Mediterranean Fever

FMF was the first described (1945; Siegal 1949) and is the most common hereditary AID; it is inherited in an autosomal recessive manner. It has been linked to a genetic mutation in the *MEFV* gene encoding pyrin. There is an ethnic predilection in Sephardic Jews, Arabic, Turkish and Armenian populations. It is increasingly recognized in Ashkenazi Jews, Greeks and Italians and Japanese (Ben-Chetrit and Touitou 2009).

FMF usually presents in childhood with 80% of patients presenting prior to 10 years of age and 90% by 20 years. The attacks are typically 12–72 h in duration and can occur at variable intervals from every few days to every few months. Severe abdominal pain (caused by peritonitis), often mimicking appendicitis, accompanies fever in most patients. Pleuritis can occur in up to one-third of patients. Monoarthritis and rash (erysipelas-like rash on the shins and the dorsum of the feet) are additional characteristic clinical features. Headaches related to aseptic meningitis may occur. In children younger than 5 years of age, recurrent fever may be the only feature (Padeh et al. 2010).

If left untreated, FMF can lead to renal failure secondary to amyloidosis. There appears to be a genotype-phenotype correlation with more severe disease and amyloidosis occurring in patients with the M694V, M694I and M680I mutations (Gershoni-Baruch et al. 2003). Although an autosomal recessive condition, 30% of patients who are diagnosed with definite FMF by clinical criteria lack one or even two mutations, especially patients from Western Europe or the United States. There may be mutation or polymorphisms in genes other than *MEFV* gene impacting on the development of FMF or the severity of the disease. Further understanding of

the pathogenesis of FMF has led to new therapeutic options. An appreciation of the interaction of the pyrin protein with the inflammasome, which is responsible for activation of inflammatory processes and promotes the maturation the proinflammatory cytokine IL-1 β , has led to the discovery of the role of IL-1 as the key cytokine driving the FMF attacks.

Colchicine is the mainstay of treatment for FMF which completely prevents attack in at least 60–70% of patients with an additional 20–30% having a partial response; only about 5% are considered non-responders. In colchicine failures, IL-1 inhibitors can be used. Serum amyloid A (SAA) may be helpful in monitoring treatment efficacy. Ongoing debate exists both on how to manage asymptomatic patients with homozygous mutations and also on which asymptomatic relatives of patients with genetically proven FMF should genetic testing be performed.

Periodic Fever, Aphthous Stomatitis, Adenitis and Pharyngitis (PFAPA)

Periodic fever aphthous stomatitis, adenitis, and pharyngitis (PFAPA) is the most common AID in childhood with onset typically before the age of 5 (most frequently age 2–3). PFAPA is the only true “periodic” AID with attacks occurring every 3–6 weeks (parents can very often predict the day of the attack). Parents/patients report a glassy-eyed look and feeling unwell several hours before the onset of the attack. Pharyngitis is the most commonly report symptom associated with the fever, occurring in >90% of patients. Bacterial throat swabs are repeatedly normal. Cervical lymphadenopathy occurs in 60–80% and aphthous stomatitis in 40%. However, the full triad only occurs in 25% (Tasher et al. 2006). It is not uncommon for patients to also complain of headache, abdominal pain, nausea, vomiting, arthralgias, and myalgia. The diagnostic criteria proposed by Thomas et al. (Thomas et al. 1999) include regular recurring fevers with an early age of onset (<5 years of age), constitutional symptoms in the absence of an upper respiratory infection with at least 1 the 3 criteria list above,

completely asymptomatic between episodes, normal growth and development, and exclusion of cyclic neutropenia.

The pathogenesis of PFAPA is multifactorial and possibly includes infection and abnormal host immune responses, characterized by cytokine dysfunction. There is a strong familial clustering suggesting a potential genetic origin but no consistent mutations or polymorphisms have been identified that are relevant to the disease etiology. Variants in the inflammasome related genes, such as *NLRP3* and *MEFV* (pyrin) have been detected, which suggests an oligenic or polygenic etiology. In one study nearly half of PFAPA patients (38/84) had a positive family history for recurrent fever and 10 of those had been diagnosed with PFAPA (Cochard et al. 2010).

A proposed “diagnostic test” in PFAPA is the dramatic response to one dose of prednisone (1–2 mg/kg) given at the onset of the attack; a positive response is typically seen within a few hours. With prednisone therapy, the intervals between the attacks may shorten. Studying the efficacy of therapy in PFAPA is challenging given the lack of diagnostic criteria (leading to inclusion of patients in studies that do not have PFAPA) and the natural history to outgrow this condition. Response to prednisone therapy is likely complete in 80–90% (Ter Haar et al. 2013), occasionally a second dose is required 24 h later. Tonsillectomy (with or without adenoidectomy) is curative in the majority of patients with a meta-analysis showing complete resolution in 83% (95% confidence interval, 77–89%) (Garavello et al. 2011). Tonsillectomy may be an option for those needing frequent dosing of corticosteroids or those patients with a marked negative impact on quality of life. A recent Cochrane review on this use of tonsillectomy for PFAPA concluded that children who had had surgery were about four times more likely to be free of PFAPA symptoms from the point of surgery until the end of the follow-up period for the study than those children treated with medical therapy (Burton et al. 2014).

Although there is no known risk for the development of amyloidosis or other long-term

sequelae, this relatively common AID has significant morbidity, including absence at school/daycare, work days missed for parents/other caregivers, and frequent clinical symptoms. Morbidity is one of the main reasons for treatment. The frequency and severity of attacks tends to decrease with time and most will outgrow this condition during the second decade of life.

Summary

There have been significant advances in our understanding of the etiopathogenesis for many of the rheumatic diseases, with ensuring impressive additions to the armamentarium of treatment options for rheumatic disease. Particularly for JIA, treating to remission of disease is an achievable target and ultimately finding a cure for the disease is at the forefront of research agendas. The major objectives for the pediatric rheumatology community are to increase awareness of the relatively uncommon pediatric rheumatic conditions and to educate and empower community practitioners with skills to confidently assess MSK complaints and appropriately triage referrals to specialist care when needed. Certainly in JIA, earlier referral and treatment has been linked to improved outcomes in terms of disease control and quality of life. With increasing awareness of the AIDs, previously undiagnosed children have been identified and now receive care. There still exist a delay in time to referral to specialist care and shortening this gap has the potential to reduce morbidity and potentially improve outcomes overall.

References

- Albers HM, et al. Time to treatment as an important factor for the response to methotrexate in juvenile idiopathic arthritis. *Arthritis Rheum.* 2009;61:46–51. <https://doi.org/10.1002/art.24087>.
- Behrens EM, Beukelman T, Paessler M, Cron RQ. Occult macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis. *J Rheumatol.* 2007;34:1133–8.
- Ben-Chetrit E, Touitou I. Familial mediterranean Fever in the world. *Arthritis Rheum.* 2009;61:1447–53. <https://doi.org/10.1002/art.24458>.
- Bleesing J, et al. The diagnostic significance of soluble CD163 and soluble interleukin-2 receptor alpha-chain in macrophage activation syndrome and untreated new-onset systemic juvenile idiopathic arthritis. *Arthritis Rheum.* 2007;56:965–71. <https://doi.org/10.1002/art.22416>.
- Broughton T, Armon K. Defining juvenile idiopathic arthritis remission and optimum time for disease-modifying anti-rheumatic drug withdrawal: why we need a consensus. *Paediatr Drugs.* 2012;14:7–12. <https://doi.org/10.2165/11595980-000000000-00000>.
- Burton MJ, Pollard AJ, Ramsden JD, Chong LY, Venekamp RP. Tonsillectomy for periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome (PFAPA). *Cochrane Database Syst Rev.* 2014;9:CD008669. <https://doi.org/10.1002/14651858.CD008669.pub2>.
- Cacchio A, De Blasis E, Necozone S, di Orio F, Santilli V. Mirror therapy for chronic complex regional pain syndrome type 1 and stroke. *N Engl J Med.* 2009;361:634–6. <https://doi.org/10.1056/NEJMc0902799>.
- Cassidy J, et al. Ophthalmologic examinations in children with juvenile rheumatoid arthritis. *Pediatrics.* 2006;117:1843–5. <https://doi.org/10.1542/peds.2006-0421>.
- Cochard M, et al. PFAPA syndrome is not a sporadic disease. *Rheumatology.* 2010;49:1984–7. <https://doi.org/10.1093/rheumatology/keq187>.
- Doherty M, Dacre J, Dieppe P, Snaith M. The ‘GALS’ locomotor screen. *Ann Rheum Dis.* 1992;51:1165–9.
- Federici S, Gattorno M. A practical approach to the diagnosis of autoinflammatory diseases in childhood. *Best Pract Res Clin Rheumatol.* 2014;28:263–76. <https://doi.org/10.1016/j.berh.2014.05.005>.
- Foster HE, Jandial S. pGALS – paediatric Gait Arms Legs and Spine: a simple examination of the musculoskeletal system. *Pediatr Rheumatol Online J.* 2013;11:44. <https://doi.org/10.1186/1546-0096-11-44>.
- Foster HE, Kay LJ, Friswell M, Coady D, Myers A. Musculoskeletal screening examination (pGALS) for school-age children based on the adult GALS screen. *Arthritis Rheum.* 2006;55:709–16. <https://doi.org/10.1002/art.22230>.
- Foster H, Rapley T, May C. Juvenile idiopathic arthritis: improved outcome requires improved access to care. *Rheumatology.* 2010;49:401–3. <https://doi.org/10.1093/rheumatology/kep347>.
- Garavello W, et al. Tonsillectomy in children with periodic fever with aphthous stomatitis, pharyngitis, and adenitis syndrome. *J Pediatr.* 2011;159:138–42. <https://doi.org/10.1016/j.jpeds.2010.12.014>.
- Gattorno M, et al. A diagnostic score for molecular analysis of hereditary autoinflammatory syndromes with periodic fever in children. *Arthritis Rheum.* 2008;58:1823–32. <https://doi.org/10.1002/art.23474>.

- Gershoni-Baruch R, et al. The contribution of genotypes at the MEFV and SAA1 loci to amyloidosis and disease severity in patients with familial Mediterranean fever. *Arthritis Rheum.* 2003;48:1149–55. <https://doi.org/10.1002/art.10944>.
- Goff I, Rowan A, Bateman BJ, Foster HE. Poor sensitivity of musculoskeletal history in children. *Arch Dis Child.* 2012;97:644–6. <https://doi.org/10.1136/archdischild-2011-300853>.
- Gunz AC, Canizares M, Mackay C, Badley EM. Magnitude of impact and healthcare use for musculoskeletal disorders in the paediatric: a population-based study. *BMC Musculoskelet Disord.* 2012;13:98. <https://doi.org/10.1186/1471-2474-13-98>.
- Hashkes PJ, Toker O. Autoinflammatory syndromes. *Pediatr Clin N Am.* 2012;59:447–70. <https://doi.org/10.1016/j.pcl.2012.03.005>.
- Hayward K, Wallace CA. Recent developments in anti-rheumatic drugs in pediatrics: treatment of juvenile idiopathic arthritis. *Arthritis Res Ther.* 2009;11:216. <https://doi.org/10.1186/ar2619>.
- Heiligenhaus A, et al. Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis. *Rheumatol Int.* 2012;32:1121–33. <https://doi.org/10.1007/s00296-011-2126-1>.
- Jandial S, Myers A, Wise E, Foster HE. Doctors likely to encounter children with musculoskeletal complaints have low confidence in their clinical skills. *J Pediatr.* 2009;154:267–71. <https://doi.org/10.1016/j.jpeds.2008.08.013>.
- Long SS. Distinguishing among prolonged, recurrent, and periodic fever syndromes: approach of a pediatric infectious diseases subspecialist. *Pediatr Clin N Am.* 2005;52:811–35. <https://doi.org/10.1016/j.pcl.2005.02.007>.
- Lovell DJ, et al. Measuring process of arthritis care: a proposed set of quality measures for the process of care in juvenile idiopathic arthritis. *Arthritis Care Res.* 2011;63:10–6. <https://doi.org/10.1002/acr.20348>.
- Malleson PN, Mackinnon MJ, Sailer-Hoeck M, Spencer CH. Review for the generalist: the antinuclear antibody test in children – when to use it and what to do with a positive titer. *Pediatr Rheumatol Online J.* 2010;8:27. <https://doi.org/10.1186/1546-0096-8-27>.
- Minoia F, et al. Clinical features, treatment, and outcome of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a multinational, multicenter study of 362 patients. *Arthritis Rheumatol.* 2014;66:3160–9. <https://doi.org/10.1002/art.38802>.
- Myers A, et al. More ‘cries from the joints’: assessment of the musculoskeletal system is poorly documented in routine paediatric clerking. *Rheumatology.* 2004;43:1045–9. [https://doi.org/10.1093/rheumatology/keh245\[pil\]](https://doi.org/10.1093/rheumatology/keh245[pil]).
- Oen K. Long-term outcomes and predictors of outcomes for patients with juvenile idiopathic arthritis. *Best Pract Res Clin Rheumatol.* 2002;16:347–60.
- Padeh S, et al. Familial Mediterranean fever in children presenting with attacks of fever alone. *J Rheumatol.* 2010;37:865–9. <https://doi.org/10.3899/jrheum.090687>.
- Petty RE, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol.* 2004;31:390–2.
- Petty R, Laxer R, Lindsey C, Wedderburn L. *Textbook of pediatric rheumatology.* 7th ed. Amsterdam: Elsevier; 2016.
- Ravelli A, et al. Classification Criteria for Macrophage Activation Syndrome Complicating Systemic Juvenile Idiopathic Arthritis: A European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaboration. *Arthritis Rheum.* 2016;68(3):566–76.
- Roth-Isigkeit A, Thyen U, Stoven H, Schwarzenberger J, Schmucker P. Pain among children and adolescents: restrictions in daily living and triggering factors. *Pediatrics.* 2005;115:e152–62. <https://doi.org/10.1542/peds.2004-0682>.
- Siegal S. Benign paroxysmal peritonitis. *Gastroenterology.* 1949;12:234–47.
- Smith N, et al. Paediatric musculoskeletal matters (pmm)—collaborative development of an online evidence based interactive learning tool and information resource for education in paediatric musculoskeletal medicine. *Pediatr Rheumatol Online J.* 2016;14:1. <https://doi.org/10.1186/s12969-015-0062-4>.
- Tasher D, Somekh E, Dalal I. PFAPA syndrome: new clinical aspects disclosed. *Arch Dis Child.* 2006;91:981–4. <https://doi.org/10.1136/adc.2005.084731>.
- Ter Haar N, et al. Treatment of autoinflammatory diseases: results from the Eurofever Registry and a literature review. *Ann Rheum Dis.* 2013;72:678–85. <https://doi.org/10.1136/annrheumdis-2011-201268>.
- Thomas KT, Feder HM Jr, Lawton AR, Edwards KM. Periodic fever syndrome in children. *J Pediatr.* 1999;135:15–21.
- Uziel Y, Chapnick G, Jaber L, Nemet D, Hashkes PJ. Five-year outcome of children with “growing pains”: correlations with pain threshold. *J Pediatr.* 2010;156:838–40. <https://doi.org/10.1016/j.jpeds.2009.11.078>.
- Weiser P. Approach to the patient with noninflammatory musculoskeletal pain. *Pediatr Clin N Am.* 2012;59:471–92. <https://doi.org/10.1016/j.pcl.2012.03.012>.
- Yalcinkaya F, et al. A new set of criteria for the diagnosis of familial Mediterranean fever in childhood. *Rheumatology.* 2009;48:395–8. <https://doi.org/10.1093/rheumatology/ken509>.

Index

- A**
- Abdominal pain, 275–276, 299
- Abdominal trauma, 93, 102, 244
- ABLE trial, 317
- Abnormal Involuntary Movement Scale (AIMS), 532
- Abusive head trauma, 97
- Acetaminophen, 236
- Acquired aplastic anemia, 325
- Acquired epileptic aphasia, 446–447
- Acquired hyperthyroidism, 261–266
- Acquired hypothyroidism, 261
- Acute acetaminophen (APAP) toxicity, 295
- Acute kidney injury (AKI)
- definition, 398–399
 - epidemiology, 400
 - etiology, 399–400
 - indications and timing of RRT, 400–401
 - prognosis, 401
 - treatment, 400
- Acute liver failure (ALF), *see* Pediatric acute liver failure (ALF)
- Acute lung injury (ALI), 122
- Acute lymphoblastic leukemia (ALL)
- genetic features, 464
 - aneuploidy, 464–465
 - genomic profile, 466
 - structural alterations, 465
 - immunophenotype, 461–462
 - immunotherapy, 470–471
 - antibody conjugates, 471
 - bispecific antibodies, 471–472
 - engineered T cells, 472–473
 - moving novel therapies into frontline treatment, 473
 - precision medicine therapies, 470–471
 - prognostic factors
 - clinical features, 462–463, 466
 - early response to therapy, 463–464
 - treatment for childhood, 466–467
 - CNS-directed therapy, 467–468
 - hematopoietic stem cell transplantation, 468
 - novel therapy approaches, 468–473
 - risk-adapted therapy, 467
- Acute pancreatitis (AP), 299, 301
- Acute renal failure (ARF), 398
- Acute respiratory distress syndrome (ARDS), 122
- Acute urinary tract infection, 393
- Acute viral bronchiolitis, 331
- bronchodilators, 332–333
 - diagnosis, 332
 - feeding and hydration, 334
 - hypertonic saline, 333
 - oxygen management, 334–335
 - prevention, 335
 - suctioning, 333–334
- AD, *see* Atopic dermatitis (AD)
- Addiction, 519, 533
- Adenosine deaminase (ADA), 375
- ADHD, *see* Attention deficit hyperactivity disorder (ADHD)
- Adjunctive steroid therapy, 230
- Adolescence
- cognitive changes, 3
 - confidentiality, 5–8
 - development, 1–3
 - early adolescence, 1
 - emotional changes, 4
 - healthcare, 31, 33
 - late adolescence, 1
 - middle adolescence, 1
 - patient interviewing, 5–7
 - prolonged adolescence, 1–2
 - psychosocial changes, 4
 - resources for patients, 13
 - substance use, 8
- Adrenal cortisol, 252, 253
- Adrenal insufficiency (AI)
- etiology, 251–252
 - investigations, 252–253
 - primary, 251
 - secondary, 251
 - symptoms, 252
 - treatment, 253–254
- Adrenocortical carcinoma, 504–505
- Adrenocorticotropin (ACTH), 251
- Adult height therapy, 257
- Age of blood, 317–318
- Aggression
- antipsychotics and, 530
- ASD, 215
- AI, *see* Adrenal insufficiency (AI)

- AID, *see* Autoinflammatory disease (AID)
- Air entrapment, 233
- Airway management
 pediatric emergency medicine, 223
 transport team, 233
 trauma, 239
- AKI, *see* Acute kidney injury (AKI)
- Alert, verbal, pain, unresponsive (AVPU) scale, 241
- ALF, *see* Acute liver failure (ALF)
- Alfa-fetoprotein (AFP), 500
- Allergic rhinitis, 49
- Alpha-thalassemia, 316
- Alport syndrome, 373
- Alprolix®, 322
- ALPS, *see* Autoimmune lymphoproliferative syndrome (ALPS)
- ALTE, *see* Apparent life-threatening event (ALTE)
- Alveolar RMS, 497
- Ambulatory blood pressure monitoring (ABPM), 404
- American Academy of Pediatrics (AAP), 10
- American College of Critical Care Medicine (ACCM), 228–230
- American College of Medical Genetics (ACMG), 374
- American Heart Association, 66
- Aminocaproic acid, 23
- Aminosalicilate (ASA), 280
- Amplatz device, 73
- Analgesia, in procedural pain, 423
- Anaphylaxis
 clinical presentation, 52–53
 definition, 51–52
 diagnosis, 53–54
 epidemiology, 52
 management, 54–55
 sign and symptom, 51
- Anemia, 15
 aplastic, 325–326
 iron-deficiency (*see* Iron-deficiency anemia)
- Aneuploidy, 464
- Anogenital examination, 106
- Antibiotic Stewardship, 355–357
- Antibody conjugates, 471
- Anticoagulation therapy, 323–324
- Anticonvulsants, 15
- Antidepressant, 521
- Antihistamine, 55
- Antipsychotics, 529
- Anti-tissue transglutaminase (TTG), 272
- Anxiety
 ASD, 216–217
 diagnosis, 523–524
 prevalence, 523
 treatment, 524–525
- Aplastic anemia, 325
- Apparent life-threatening event (ALTE), 338, 339
- Applied behavioral analysis (ABA), 214
- ARDS, *see* Acute respiratory distress syndrome (ARDS)
- ARF, *see* Acute renal failure (ARF)
- ARFID, *see* Avoidant/restrictive food intake disorder (ARFID)
- ARIPI trial, 317
- Aromatase inhibitors, 257
- Array comparative genomic hybridization (aCGH), 369
- Arrhythmias, 66
- ASD, *see* Autism spectrum disorder (ASD)
- Askin tumor, 493
- Assisted reproductive technique (ART), 431
- Asunra®, 316
- Atopic dermatitis (AD)
 calcineurin inhibitors in, 48–49
 food allergy risk with, 47–48
 updates in, 45–46
- Atrial septal defects (ASDs), 62, 64, 73
- Atrioventricular septal (canal) defects (AVSDs), 62
- Atropine, 225
- Attention deficit hyperactivity disorder (ADHD), 110, 215, 515
 clinical point, 519
 diagnosis, 517
 prevalence, 517
 treatment, 517–518
- Attenuated psychosis syndrome (APS), 516
- Atypical hemolytic uremic syndrome (aHUS), 405
- Auditory brainstem response (ABR), 419
- Autism and Developmental Disabilities Monitoring (ADDM) Network, 208
- Autism Diagnostic Observation Schedule 2nd Edition (ADOS-2), 213
- Autism spectrum disorder (ASD), 387, 433, 515
 ADHD, 215
 anxiety, 216
 assessment/evaluation, 212–213
 behavioral intervention, 214
 biomedical interventions, 214–215
 causes, 209–210
 DCD, 217
 definition, 207–208
 dyspraxia, 217
 gastrointestinal disorders, 216
 genetics, 210–211
 intellectual disability, 217
 investigations, 213–214
 irritability/aggression, 215–216
 prevalence, 208–209
 risk-factors, 210
 seizures, 216
 sleep problems, 217
 tics and Tourette syndrome, 218
 treatment options for, 214
- Autoimmune lymphoproliferative syndrome (ALPS), 319, 324–325
- Autoinflammatory disease (AID), 548–549
- Autosomal dominant polycystic kidney disease (ADPKD), 405, 406
- Avoidant/restrictive food intake disorder (ARFID), 516
- Axial skeletal tumors, 496

B

- Bacteremia
 - epidemiology, 338
 - time to blood culture positivity, 338
 - urinary tract infection, 337
- Bag mask ventilation (BMV), 224, 225
- B-ALL, 461, 462
 - clinical features, 462–463, 466
 - CNS-directed therapy, 467–468
 - genetic features, 464–466
 - hematopoietic stem cell transplantation, 468
 - immunotherapy, 470–473
 - moving novel therapies into frontline treatment, 473
 - novel therapy approaches, 468–473
 - precision medicine therapies, 470–471
 - risk-adapted therapy, 467
- Balloon enteroscopy, 303
- Basic life support (BLS) algorithm, 124
- Bayley Scales of Infant Development, 64
- Benign epilepsy with centro temporal spikes (BECTS), 450
- Benign familial infantile seizure (BFIS), 443
- Benign familial neonatal seizure (BFNS), 442–443
- Benign familial neonatal-infantile seizure (BFNIS), 443
- Benign neonatal sleep myoclonus (BNSM), 457
- Beta-thalassemia, 316
- Bidentate chelator, 316
- Biliary atresia, 287
- Bioinformatics, 119
- Bipolar disorder (BD)
 - diagnosis, 526
 - prevalence, 525–526
 - safety, 527
 - treatment, 527
- Bispecific antibodies, 471
- Bispecific T-cell engagers (BiTE), 471
- Bleeding disorder, *see* Hemophilia
- Blinatumomab, 471
- Bone marrow replacement, 461
- Bone mineral density (BMD), 14
- Bone tumors
 - epidemiology and genetic predisposition, 493–494
 - histology and molecular profile, 494
 - pathophysiology, 493–494
 - staging, 494–496
 - symptoms, 494
 - treatment and outcomes, 496–497
- Bortezomib, 468–469
- Breastfeeding, 429
 - benefits, 416, 417
 - contraindications, 416
 - supplement with, 416–417
- Breathing, transport team, 233
- Brief resolved unexplained event (BRUE), 339–341
- Bronchiolitis, 331–335
- Bronchodilators, 332
- Bruising, child maltreatment, 89
 - cause of, 93

- differential diagnosis, 91
 - documentation of physical findings, 92
 - history, 91
 - physical examination, 92
 - testing for occult injuries, 93
- Burns, 103–105
- C**
- Calcineurin inhibitors, 48
- Canadian Cardiac Disease in Pregnancy (CARPREG) registry, 66
- Canadian College of Medical Genetics (CCMG), 374
- Cannabis, 533
- Capnography, 118–119
- Carcinoma, hepatocellular, 502
- Cardiac computed tomography (CT), 72
- Cardiac MRI, 69–71
- Cardiac output (CO), 229
- Cardiopulmonary resuscitation (CPR), 99, 123, 225–226
- Cardioversion, 226
- CAR-expressing T cells, 472
- Catecholaminergic polymorphic ventricular tachycardia (CPVT), 75, 76
- Catheter based interventions, 72–73
- Catheter-associated blood stream infections (CLABSI), 128
- cCMV, *see* Congenital CMV (cCMV)
- Celiac disease
 - definition, 271
 - diagnosis, 272
 - epidemiology, 271
 - genetics and risk factor, 271–272
 - pathogenesis, 271
 - treatment, 272
- Cell culture cytotoxicity neutralization assay (CCNA), 354
- Central line associated infection (CLABSI), 286
- Central precocious puberty (CPP), 258
- Central venous catheter (CVC), 342
- Centrosome, 406
- Cervical intraepithelial neoplasia (CIN), 349
- CHD, *see* Congenital heart disease (CHD)
- Chemical dependency professional (CDP), 12
- Child maltreatment
 - abdominal trauma, 101–103
 - bruising, 89–91
 - cause of, 93
 - differential diagnosis, 91
 - documentation of physical findings, 92
 - history, 91–92
 - physical examination, 92
 - testing for occult injuries, 93
 - burns, 103–104
 - differential diagnosis, 104
 - documentation, 104–105
 - history, 104
 - medical testing, 105

- Child maltreatment (*cont.*)
 physical examination, 104
 definition, 84
 discharge and follow-up, 109
 emergency contraception, 109
 fractures, 93–94
 cause of, 96
 differential diagnosis, 94–95
 history, 95
 medical testing, 95–96
 physical examination, 95
 head and spine injuries, 97–98
 cause of, 101
 differential diagnosis, 98–99
 history, 99–100
 medical testing, 100–101
 physical examination, 100
 HIV post exposure prophylaxis, 109
 identifying, 86
 neglect, 109
 physical abuse, 89
 physical injuries
 developmental history, 87
 documentation, 89
 general approach, 86
 history, 87–88
 non-judgemental and supportive style, 88
 physical examination, 88–89
 risk factors, 87
 psychosocial support, 109
 sexual abuse and assault
 documentation, 107
 forensic evidence collection, 108
 history, 106
 interpretation of findings, 107
 physical examination, 106–107
 timing of examination, 105–106
 sexually transmitted infections, 108–109
 terminology, 85–86
 United States, 83
- Child-centred approach, 236
 Childhood absence epilepsy (CAE), 450–451
 Children’s Hospital of Eastern Ontario pain scale, 235
 Children’s Oncology Group (COG) MRD assay, 463
 Chimeric antigen receptor (CAR), 472
 Chlamydia, 108
 Choosing Wisely®, 344
 Chromosomal karyotyping, 448
 Chromosomal microarray (CMA), 213, 369–371, 448
 Chromosome variant, 370
 Chronic kidney disease (CKD), 401
 estimation GFR, 402
 progression, marker, 402–403
 Chronic lymphocytic thyroiditis, 261
 Chronic pain syndrome, 546
 Chronic pancreatitis, 301
 Ciliopathies, 406
 Circulation
 hemorrhage, 240
 transport team, 233
- Cirrhosis, 293
 CKD, *see* Chronic kidney disease (CKD)
 Clinical genetics, 369–370
 Clinical-decision support tools, 119
 Clofarabine, 469
Clostridium difficile infection (CDI), 353–355
 CMA, *see* Chromosomal microarray (CMA)
 CNS-directed therapy, acute lymphoblastic leukemia, 467
 CNV, *see* Copy number variant (CNV)
 Coagulopathy, 320
 Coarctation of the aorta (CoA), 62
 Cofactor therapy, 385
 Colchicine, 550
 Cold shock, 227, 228, 230
 Colonoscopy, 303
 Compensated shock, 226
 Complex regional pain syndrome Type I (CRPS1), 546
 Conduct disorder (CD), 515
 Congenital adrenal hyperplasia (CAH), 251, 252
 Congenital anomalies of the kidney and urinary tract (CAKUT), 408
 Congenital cardiac disease, 421
 Congenital CMV (cCMV) infection, 359–360
 Congenital heart disease (CHD)
 cardiac CT, 72
 cardiac MRI, 69–70
 catheter based interventions, 72–74
 echocardiography, 71
 epidemiology, 61–62
 exercise in, 65
 genetic syndrome, 64
 heart transplantation, 63
 late outcomes, 62–63
 mortality rate, 61, 63
 neonatal oximetry screening, 68
 neurodevelopmental outcomes in, 63–65
 pregnancy in, 66–68
 quality of life in, 65
 survival rates for, 61
 termination rates, 61
 WHO Class I/IV, 67
 Congenital hypothyroidism, 259–261
 Constipation, 274, 276
 Continuous antibiotic prophylaxis (CAP), 395
 Continuous EEG (cEEG) monitoring, 119
 Continuous renal replacement therapy (CRRT), 401
 Contraception
 conversation, 13
 decision-making, 14–15
 eligibility for various methods, 13–14
 emergency contraception, 16–18
 LARC, 15
 non-LARC option, 16
 options to teens, 15
 Copper intrauterine device (IUD), 17
 Copy number variant (CNV), 210, 370
 Cornell Assessment for Pediatric Delirium (CAPD), 121
 Coronary artery abnormalities, 66
 Corticosteroid therapy, 230, 280

- Corticotropin-releasing hormone (CRH), 251
 Cortisol, 252, 253
 CPP, *see* Central precocious puberty (CPP)
 CPR, *see* Cardiopulmonary resuscitation (CPR)
 CRAFFT screening, 11, 533
 Craniopharyngioma, 252
 Critical congenital heart disease (CCHD), 68, 421
 Cross-Canada Anaphylaxis Registry (C-CARE), 52
 Crushing head trauma, 99
 Culture-negative sepsis, 227
 Cyberbullying, 28
 CYP2D6 polymorphisms, 236
 Cytokine release syndrome (CRS), 471
 Cytopenia, 325
 Cytotoxic agents, 468–470
- D**
- Decompensated shock, 226
 Deferasirox, 316
 Deferiprone, 316
 Defibrillation, 225
 Delirium, 121
 Denys-Drash and Fraiser syndrome, 490
 Depression, 14, 516
 clinical point, 522–523
 diagnosis, 519–520
 prevalence, 519
 safety, 522
 Desferal[®], 316
 Desferrioxamine, 316
 Developmental coordination disorder (DCD), 217
 Dextrose gel, 428
 Diabetes mellitus, 14, 530–531
 Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V), 25, 28, 457, 513–517, 520, 522, 524–526, 529, 532
 Diaper dermatitis, 418
 Diarrhea, 273
 DIC, *see* Disseminated intravascular coagulation (DIC)
 Digital rectal exam (DRE), 241
 Dilated cardiomyopathy (DCM), 75
 Disability
 GCS, 241
 transport team, 234
 Disease-modifying therapy for IEM, 385
 Disorders of sexual development (DSD), 24
 Disruptive mood dysregulation disorder (DMDD), 516, 526
 Disseminated intravascular coagulation (DIC), 240, 319–321
 DNA-based tests, 384, 421
 Domestic violence, 84
 Dravet syndrome, 443, 446
 Dronabinol, 9
 Duchenne muscular dystrophy, 371
 Dysbiosis, 210
 Dyserythropoiesis, 316
 Dyslipidemia, 531
 Dysmorphic syndrome, 386
 Dyspraxia, 217
- E**
- Early infantile epileptic encephalopathy (EIEE), 443
 Early myoclonic encephalopathy (EME), 444
 Early T cell precursor (ETP) ALL, 462
 Early-onset sepsis (EOS), 424
 Echocardiography, CHD, 71
 Eculizumab, 406
 Edible marijuana, 9
 Educational neglect, 110
 EGD, *see* Esophagogastroduodenoscopy (EGD)
 E-learning, 129
 Elimination diet, 43
 Eloctate[®], 321
 Embryonal tumors, 497
 Emergency contraception (EC), 16, 109
 Emergency medical services (EMS), 232, 234
 Emergency Triage Assessment at Treatment (ETAT), 128
 Emerging genetic technology, 448–449
 Emollients, 46
 Emotional development, 139, 141, 144, 147, 152, 156, 160, 165, 170, 174, 179, 184, 188, 193, 198
 Emotional neglect, 110
 Encephalopathy, epileptic, 447, 451
 Endoscopic retrograde cholangiopancreatography (ERCP), 303
 Endoscopy, 301
 Engineered T cells, 472
 Enquiring about Tolerance (EAT) study, 44
 Enteroscopy, balloon, 303
 Environmental peanut exposure (EPE), 48
 Enzyme immunoassay (EIA), 354
 Enzyme replacement therapy (ERT), 380
 EOS, *see* Early-onset sepsis (EOS)
 Eosinophilic esophagitis (EoE)
 management, 270
 diet, 270
 dilation, 271
 drug, 270–271
 pathogenesis, 269
 presentation, 269–270
 therapy, 270
 Epigenetics, 134
 Epilepsy, 440
 diagnosis, 441
 focal, 441
 Epileptic aphasia, 446
 Epileptic encephalopathy, 443, 447, 451
 Epileptic seizures, 439
 Epileptic syndrome, 452
 Epileptogenic lesion, 441
 Epinephrine, 54
 ERCP, *see* Endoscopic retrograde cholangiopancreatography (ERCP)
 Esophagogastroduodenoscopy (EGD), 301, 302
 Etonogestrel (ENG) implant, 17
ETV6-RUNX1 (TEL-AML1) gene fusion, 465

- European Registry on Pregnancy and Cardiac Disease (ROPAC) registry, 66
- European Society of Human Genetics (ESHG), 374
- Evans syndrome, 319
- Ewing sarcoma, 493, 495
- Exercise, in CHD, 65–66
- Exjade[®], 316
- Extracorporeal Liver Assist Device (ELAD), 299
- Extracorporeal membrane oxygenation (ECMO), 415
- Extragenital tumors, 501
- Extrauterine growth failure, 432
- Extremely preterm infant (EPT), 430
- Ex utero intrapartum treatment (EXIT), 416
- Eye injury, 99
- Eye tumors, 504
- F**
- Familial Mediterranean fever (FMF), 549–550
- Family history (FHx)
- fracture, 95
 - physical injuries, 87
- Feminizing hormones, 26
- Fentanyl, 236
- Ferriprox[®], 316
- Fetal growth, 254
- Fetal teratomas, 500
- FGID, *see* Functional gastrointestinal disorder (FGID)
- Fibrolamellar HCC, 503
- Filaggrin (FLG), 46–47
- Fine motor development, 139, 142, 146, 150, 154, 158, 163, 168, 173, 177, 181, 186, 190, 195, 200
- Fluid Expansion as Supported Therapy (FEAST) trial, 127
- Fluid resuscitation, 240
- Fluorescence in situ hybridization (FISH), 465
- FMF, *see* Familial Mediterranean fever (FMF)
- Focal epilepsy, 441
- Focal segmental glomerulosclerosis (FSGS), 405
- Focal seizure, 441, 444
- Focused assessment of sonography in trauma (FAST), 241, 242
- Food allergy
- clinical presentation, 41
 - diagnosis, 42–43
 - management, 42–43
 - pathophysiology, 40
 - physical examination, 42
 - prevalence, 39
 - prevention and new research, 44–45
 - risk factors, 40–41
 - risk with atopic dermatitis, 47–48
 - Western lifestyle, 40
- Food protein-induced enterocolitis syndrome (FPIES), 41
- Foreign body ingestion, 301
- Fractures, child maltreatment, 93
- cause of, 96
 - differential diagnosis, 94
 - history, 95
 - medical testing, 95
 - physical examination, 95
- Functional constipation (FC), 274, 276
- Functional diarrhea, 273–274
- Functional gastrointestinal disorder (FGID), 272–273
- G**
- Gastroesophageal reflux disease (GERD), 267, 268, 417
- Gastrointestinal bleeding, 301–303
- Gastrointestinal disorder, 216, 273
- Gastroschisis, 284
- GCTs, *see* Germ cell tumors (GCTs)
- Gender dysphoria (GD), 211
- management of, 26
 - referral and treatment, 25–26
- Gender expression, 25
- Gender identity, 25
- Gender identity disorder (GID), 211
- Gene panel, 373
- Gene therapy, 375
- Generalized epilepsy with febrile seizures plus (GEFS+), 445–446
- Genetic disease management, 375
- Genetic syndrome, 64, 66, 386
- Genetic testing, in pediatric cardiology, 74
- Genomic technology, 466
- Germ cell tumors (GCTs)
- histology and molecular profile, 500–501
 - staging, 501
 - symptoms, 500
 - treatment and outcomes, 501–502
- Germline mutations, 493
- Gestational age (GA), 431
- Gestational alloimmune liver disease (GALD), 296
- Glasgow Coma Scale (GCS)
- disability, 241
 - transport team, 234
- Glomerular disease, 396–398, 405–406
- Glomerular filtration rate (GFR), 402
- Glomerulonephritis, 396
- Glomerulonephritis (GN)
- clinical manifestation, 397
 - diagnosis, 397
 - epidemiology, 397
 - management, 397–398
 - prognosis, 398
- Glucocorticoid, 251, 253
- Glucocorticoid (steroid)-resistant nephrotic syndrome, 405
- Glucose monitoring, 428
- Glycemic control, 125
- Gonadotropin-releasing hormone (GNRH), 257
- Gonorrhea, 108
- Gore Septal Occluder device, 73
- GPO-L-ONE[®], 316
- Graft-versus-host disease (GVHD), 468
- Grastek[®], 50
- Gross motor development, 139, 142, 145, 149, 154, 158, 162, 167, 172, 176, 182, 187, 191, 196, 201

- Group B *Streptococcus* (GBS), 338
 Growing pain, 546
 Growth failure, 255–256
 Growth hormone, 256–257
 Gut dysbiosis, 210
- H**
- Hair removal, 26
 Hashimoto's thyroiditis, 261
 Head and spine injuries, child maltreatment, 97
 cause of, 101
 differential diagnosis, 98
 history, 99
 medical testing, 100
 physical examination, 100
 Head injury, 93
 Healthcare, 31
 Hear screening program, 419
 Heart failure, 62
 Heart transplantation, 63
 Heavy menstrual bleeding (HMB), 18–19
 additional treatment considerations, 23–24
 evaluation, 19–20
 history of, 19–21
 internal exam, 21
 laboratory and imaging studies, 22
 management, 21–22
 medical options for, 22–23
 physical exam, 21
 testing, 21–22
 HEEADSSS mnemonic, 5
 Hematology, 126
 Hematopoietic stem cell transplantation (HSCT), 380,
 382, 465, 468
 Hemoglobin (Hb) disorder, 315
 Hemoglobinopathy, 314
 Hemophagocytic lymphohistiocytosis (HLH), 547
 Hemophilia
 gene therapy, 322–323
 treatment, 321
 FIX-albumin fusion, 322
 FIX-Fc fusion, 322
 FVIII with pegylated liposomes, 322
 FVIII-Fc fusion, 321
 pegylated FIX, 322
 Hemorrhage
 circulation, 240
 fluid resuscitation, 240
 Hemostasis, 324
 Hepatic encephalopathy (HE), 296
 Hepatitis, viral, 292
 Hepatitis B vaccine, 109
 Hepatitis B virus (HBV), 293
 Hepatitis C virus (HCV), 293–294
 Hepatoblastoma (HB), 502
 Hepatocellular carcinoma (HCC), 293, 502
 Hepatocellular carcinoma not otherwise specified (HCC
 NOS), 502
 Hepatoportoenterostomy, 288
 Hepatosplenomegaly, 287
 Hereditary renal cystic disease, 406, 407
 Hexadentate chelator, 316
 HIE, *see* Hypoxic ischemic encephalopathy (HIE)
 High frequency oscillatory ventilation (HFOV), 123
 High value care, 344–347
 Hirschsprung's disease, 285
 Histamine, receptor antagonist (H2RA), 268
 History of Presenting Illness (HPI), 87
 HIV post-exposure prophylaxis (PEP), 109
 HIV/AIDS, 15
 HMB, *see* Heavy menstrual bleeding (HMB)
 Horner's syndrome, 486
 HSCT, *see* Hematopoietic stem cell transplantation
 (HSCT)
 HTS, *see* Hypertonic saline (HTS)
 Human leukocyte antigen (HLA), 271
 Human papillomavirus (HPV), 349–351
 Hydrocortisone, 253
 Hydromorphone, 236
 Hydroxyurea, in sickle cell disease, 315
 Hyperbilirubinemia, 286
 Hyperdynamic shock, 227
 Hyperglycemia, 125
 Hyperlipidemia, 14
 Hypertension, 14
 diagnosis, 404
 epidemiology, 403
 evaluation of target organ damage, 404
 treatment, 404
 Hyperthyroidism, acquired, 261
 Hypertonic saline (HTS), 333
 Hypertrophic cardiomyopathy (HCM), 74–75
 Hypoglycemia
 insulin induced, 252
 neonatal, 427
 Hypoplastic left heart syndrome (HLHS), 63
 Hypotension, orthostatic, 455
 Hypothalamus, 251, 257, 259
 Hypothermia
 neuroprotective effects, 226
 post-cardiac arrest, 226
 therapeutic, 427
 Hypothyroidism
 acquired, 261
 congenital, 259
 Hypoxia, 233
 Hypoxic ischemic encephalopathy (HIE), 424
 diagnosis, 425–426
 management, 426–427
 pathophysiology, 425
 prognosis, 427
- I**
- IBD, *see* Inflammatory bowel disease (IBD)
 Ibuprofen, 236
 Idelvion®, 322
 Idiopathic short stature (ISS), 256
 IgA nephropathy, 397, 398

- Ileoanal pull-through with anal anastomosis (IPAA), 282
- Immune thrombocytopenia (ITP), 318
- Immunoglobulin A (IgA), 272
- Immunoglobulin E (IgE), 40, 51
- Immunology, 126
- Immunomodulator, 281
- Immunophenotype, acute lymphoblastic leukemia, 461
- Immunotherapy, acute lymphoblastic leukemia, 470–473
- Inborn errors of metabolism (IEM), 375
 - disease-modifying therapy for, 385
 - small-molecule, 376–378
- Indirect calorimetry, 125
- Inertial trauma, 99
- Infant
 - developmental phase, 136, 201
 - emotional development, 141, 144, 147, 150, 152, 160, 165, 170, 174, 179, 184, 188, 193, 198
 - fine motor development, 142, 146, 150, 154, 158, 168, 173, 177, 181, 186, 190, 195, 200
 - gross motor development, 142, 145, 149, 154, 158, 162, 167, 172, 176, 182, 187, 191, 196, 201
 - intellectual development, 141, 145, 149, 153, 157, 161, 167, 171, 176, 180, 185, 190, 195, 200
 - language development, 148, 152, 157, 161, 166, 171, 175, 180, 184, 189, 194, 199
 - research for clinicians and practitioners, 203–204
 - serve and return interaction shapes brain circuitry, 135
 - social development, 140, 143, 147, 151, 155, 159, 164, 169, 173, 178, 183, 188, 192, 198
 - social emotional development, 136–139
 - stress, 202–203
 - formula, 417
 - mental health, 133–135
 - prevention/management of procedural pain, 422–424
- Infantile spasm (IS), 444–445
- Infant-parent interaction, 415–416
- Infectious disease, 126
 - Clostridium difficile* infection, 353
 - human papillomavirus, 349–351
 - measles, 352–353
 - meningococcal disease, 360–361
 - MRSA infection, 357
 - Zika virus infection, 361
- Inflammatory bowel disease (IBD)
 - clinical presentation, 277
 - diagnosis, 278
 - epidemiology, 276–277
 - evaluation, 277–279
 - extra-intestinal manifestation, 277
 - histology, 279–280
 - management, 280
 - aminosalicylate, 280–281
 - biologic therapies, 281
 - corticosteroid, 280
 - immunomodulator, 281
 - outcome, 282
 - surgical management, 281–282
 - pathophysiology, 277
- Infliximab block, 281
- INFORM trial, 317
- Inhaled steroids, 256
- Inheritance, 442
- Inherited arrhythmias, 75–76
- Inotuzumab ozogamicin, 471
- Insulin, induced hypoglycemia, 252
- Insulin like growth factor (IGF), 256
- Intellectual development, 139, 141, 145, 149, 153, 157, 161, 167, 171, 176, 180, 185, 190, 195, 200
- Intellectual disability (ID), 217, 515
- International Cardiac Collaborative on Neurodevelopment (ICCON), 64
- International Liaison Committee on Resuscitation (ILCOR), 421, 422
- International Neuroblastoma Pathology Classification (INPC), 487
- International Neuroblastoma Risk Group Staging System (INRGSS), 488, 489
- International Neuroblastoma Staging System (INSS), 488
- Interpersonal therapy (IPT), 521
- Inter-pregnancy intervals (IPIs), 210
- Intestinal dysmotility, 285
- Intestinal failure
 - causes, 285
 - diagnosis, 284
 - management, 284
 - central access preservation, 286
 - enteral nutrition, 285
 - parenteral nutrition, 284
 - surgery, 286
 - transplantation, 286
- Intrachromosomal amplification of chromosome 21 (iAMP21), 465
- Intravenous antimicrobial therapy, 230
- Intravenous epinephrine, 54
- Iron chelation, in thalassemia, 316–317
- Iron-deficiency anemia
 - definition, 313
 - development, 314
 - diagnosis, 313–314
 - treatment, 314–315
- Iron refractory iron deficiency anemia (IRIDA), 315
- Irritability, ASD, 215
- Irritable bowel syndrome, 275
- ISS, *see* Idiopathic short stature (ISS)
- J**
- Jaundice, 296
- Juvenile fibromyalgia, 546
- Juvenile idiopathic arthritis (JIA), 542–546
- Juvenile myoclonic epilepsy (JME), 452

K

- Kawasaki disease (KD), 547
- Kelfer[®], 316
- Ketamine, 225, 229, 237
- Kidney tumors
 - histology and molecular profile, 491
 - staging, 491–492
 - symptoms, 490–491
 - treatment and outcomes, 492–493
- Kupffer cell, 295

L

- Landau-Kleffner syndrome (LKS), 446
- Language development, 139, 148, 152, 157, 161, 166, 171, 175, 180, 184, 189, 194, 199
- LARC, *see* Long-acting reversible contraception (LARC)
- Learning Early About Peanut (LEAP) study, 44
- Left ventricular mass index (LVMI), 404
- Left-sided obstructive lesions, 66
- Lennox Gastaut syndrome, 451–452
- Lesion, epileptogenic, 441
- Levonorgestrel (LNG) IUD, 17–18
- LGBTQ teens
 - caring for, 24
 - health considerations in, 27
 - sensitive care, 27
 - terminology, 24–25
- Li Fraumeni Syndrome, 490, 497
- Liletta[®], 17
- Liver-based small-molecule IEM, 385
- Liver progenitor cell (LPC), 296
- Liver tumors
 - histology and molecular profile, 502–503
 - staging, 503
 - symptoms, 502
 - treatment, outcomes, and surveillance, 503–504
- Long-acting reversible contraception (LARC), 15–17
- Loss of heterozygosity (LOH), 371
- L-thyroxine, 261
- Lutenizing hormone (LH), 18
- Lymphoblast, malignant B, 461
- Lymphoproliferative disease, 324

M

- Macrophage activation syndrome (MAS), 547–548
- Major depressive disorder (MDD), 520
- Malignant B lymphoblast, 461
- Malignant GCTs, 500
- Malignant migrating partial seizures of infancy (MMPSI), 444
- Malnutrition, 283
- Maple syrup urine disease (MSUD), 419
- Marijuana, 533
 - adverse effects
 - addiction, 9
 - cognitive development, 10
 - driving, 9–10
 - lung disease, 9
 - mental health, 10
 - testicular cancer, 9
 - dabbing, 9
 - edible marijuana, 9
 - epidemiology, 8
 - forms of use, 9
 - inhaled use, 9
 - medical marijuana, 9
 - pharmaceutical cannabinoids, 9
 - policy and legal considerations, 10
 - screening and history, 10–11
 - and sexual health, 10
 - synthetic marijuana, 9
- MAS, *see* Macrophage activation syndrome (MAS)
- Masculinizing hormones, 26
- Massively parallel DNA sequencing, 369
- Measles, 352
- Measles-mumps-rubella (MMR) vaccine, 209
- Media and adolescents
 - benefits, 29
 - guidance for parents and patients, 30
 - risks, 28–29
- Medical marijuana, 9
- Medical neglect, 110
- Medication, 33, 224
- Meningococcal B vaccine, 360
- Meningococcal disease due to serogroup B (MenB), 360
- Mental Development Index (MDI), 64
- Mental health, 513, 521, 532
- Mental retardation (MR), 515
- Mental status, assessment, 242
- Metabolic Red Flags, 387
- Metabolics, 369, 375–376
 - clinical paradigm, 376–383
 - disease-modifying therapy for IEM, 385
 - DNA-based test, 384–385
 - newborn screening, 383
- Metabolism
 - clinical paradigm, 376
 - high-value ‘routine’ laboratory findings in, 380–381
 - syndromic presentations in, 382–383
 - therapeutic approaches in, 381
- Metabolomics, 386
- Metaiodobenzylguanidine (MIBG) imaging, 487
- Methicillin-resistant *Staphylococcus aureus* (MRSA) infection, 357–359
- Microbiology, sepsis, 227
- Midazolam, 237
- Migraine headaches, 15
- Minimal residual disease (MRD), 463
- Mircoarray, chromosomal, 370
- Mirena[®], 17
- Mirror box therapy, 546
- Mixed lineage leukemia (MLL) gene, 465
- Molecular Absorbent Recirculating System (MARS), 299

- Movement disorder, 531
Moxetumomab pasudotox, 471
MR spectrometry (MRS), 100
Multidimensional Anxiety Scale for Children (MASC), 524
Multiple intraluminal impedance (MII), 268
Multisystemic therapy, 517
Musculoskeletal (MSK) assessment tool, 537–542, 546
Myocardial viability, 70
- N**
- NAFLD, *see* Nonalcoholic fatty liver disease (NAFLD)
NAS, *see* Neonatal abstinence syndrome (NAS)
Natural moisturizing factors (NMFs), 47
Nausea, 274–275
Near-infrared spectroscopy (NIRS) monitoring, 117
Neglect, 109–111
Nelarabine, 469–470
Neoadjuvant treatment, 485
Neonatal abstinence syndrome (NAS), 428
 clinical manifestation, 429
 drugs, 430
 in infants, 430
 management, 429–430
 pathophysiology, 429
Neonatal cholestasis
 diagnosis, 288
 etiology, 287
 management, 288–289
 pathogenesis, 286–287
 presentation, 287
Neonatal encephalopathy, 424
Neonatal hypoglycemia, 427–428
Neonatal intensive care unit (NICU), 432–437
Neonatal nutrition, 416
Neonatal oximetry screening, 68–69
Neonatal resuscitation, 421–422
Neonatal sepsis, 424
Neonatal-perinatal medicine, 415
Neonate functional gastrointestinal disorder, 273
Neonatology, 415
Nephroblastomatosis, 490
Nephrogenic rests, 490
Nephrolithiasis, 408–413
Nephrology, 391
Nephrotic syndrome, 391
Neuroblastoma
 histology and molecular profile, 487
 retroperitoneal, 488
 staging for, 487–488
 symptoms, 486–487
 treatment and outcomes, 488–490
Neurocritical Care Society, 122
Neurodevelopmental disorder, 515
Neurology
 delirium, 121
 status epilepticus, 122
 traumatic brain injury, 120
Neutropenia
 factors that affect neutrophil count, 326
 management, 326–327
 sign and symptom, 326
New York Heart Association (NYHA)/Ross classification, 62
Newborn
 blood spot screening, 419
 care, 416
 cleaning, 418
 diaper care, 418
 routine bathing, 418
 skin, 418
Newborn intensive care unit (NICU), 231
Newborn screening (NBS), 383–384, 418–420
Nexplanon®, 17
Next generation sequencing (NGS), 369, 371
N9-GP®, 322
Non-acidic reflux, 268
Nonalcoholic fatty liver disease (NAFLD)
 diagnosis, 290
 histologic evaluation, 291
 laboratory evaluation, 291
 management, 292
 radiologic evaluation, 291
 pathogenesis, 290
 presentation, 290
 screening, 291–292
Nonalcoholic steatohepatitis (NASH), 289
Nonepileptic paroxysmal events, 439
 benign neonatal sleep myoclonus, 457
 breathholding spells, 456
 non-epileptic seizure, 458–459
 orthostatic hypotension, 455
 postural orthostatic tachycardia syndrome, 455
 pseudosyncope, 456
 reflex anoxic seizure, 455
 self-induced syncope, 455
 stretch syncope, 455
 syncope, 453, 456–457
 tic disorder, 457–458
 vasovagal syncope, 453–455
Non-epileptic seizure, 458
Non-IgE mediated food allergy, 40
Non-inflammatory musculoskeletal pain, 546–547
Non-rhabdomyosarcoma (non-RMS), 497, 498
Nonsteroidal anti-inflammatory drug (NSAID)
 , 21, 23, 543
Non-suicidal self-injury (NSSI), 516, 522–523
Non-syndromic hearing loss, 373
Noonan’s syndrome, 255
Novel therapy approach, acute lymphoblastic leukemia, 468
Nucleic acid amplification test (NAAT), 108, 354
Nutrition, 282–283
 guidelines, 124
 neonatal, 416–417
- O**
- Obesity, 14

- Obsessive compulsive disorder (OCD), 525
 Obstructive shock, 240
 Ohtahara syndrome, 443–444
 Oligonucleotide array, 371
 One-way valve effect, 239
 Opioid agents, pain, 236, 237
 Oppositional defiant disorder (ODD), 515
 Oral allergy syndrome, 41
 Oral analgesics, pain, 236
 Oral anticoagulant, 323
 Oral food challenge, 43
 Orchiectomy, 500
 Organellar disease, 378–379, 382–383
 Orthostatic hypotension, 455
 Osteomyelitis, 341
 oral vs. intravenous antibiotic therapy, 342–343
 transition to oral antibiotics, 343
 Osteosarcoma, 493–496
 Otoacoustic emission (OAE), 419
 Ovarian GCTs, 501
 Ovulation, 18
 Oxyhemoglobin, 117
- P**
- Paediatric BASIC, 128
 Pain
 assessment, 235
 non-pharmacologic management, 236
 opioid agents for, 236, 237
 pharmacologic management, 236–237
 topical agents, 238
 PALF, *see* Pediatric acute liver failure (PALF)
 PALISI guidelines, 123
 Pancreatitis, 299
 anatomic/obstructive risk factor, 300
 environmental risk factor, 300
 etiology, 300
 genetic risk factor, 300
 management, 300–301
 metabolic risk factor, 300
 presentation, 299–300
 ParaGuard®, 17
 Paraneoplastic syndrome, 486
 Parenteral nutrition associated liver disease (PNALD), 285
 Paroxysmal events, 439
 Past medical history (PMHx)
 fracture, 95
 physical injuries, 87
 Patch testing, 43
 Patient monitoring, 117
 Pediatric acute liver failure (PALF), 292, 122
 diagnosis, 296–297
 management, 297–299
 pathogenesis, 295–296
 presentation, 296
 Pediatric Advanced Life Support (PALS)
 algorithms, 223
 Pediatric cardiology, genetic testing in, 74
 Pediatric chest pain, 76
 Pediatric Confusion Assessment Method (pCAM-ICU), 121
 Pediatric critical care
 ARDS, 122–123
 bioinformatics, 119
 capnography, 118–119
 cardiopulmonary resuscitation, 123–124
 cEEG monitoring, 119
 education
 courses, 128
 e-learning, 129
 simulation, 128–129
 glycemic control, 125
 hematology
 thromboprophylaxis, 126
 transfusion strategies, 126
 indirect calorimetry, 125
 neurology
 delirium, 121
 status epilepticus, 122
 traumatic brain injury, 120–121
 NIRS monitoring, 117–118
 nutritional guidelines, 124–125
 patient care bundles, 128
 patient monitoring, 117
 post-cardiac arrest management, 124
 sepsis, 126–127
 standardized handover tools, 127
 ultrasound technology, 119
 Pediatric cuffed endotracheal tubes, 224
 Pediatric early warning scores (PEWS), 127–128
 Pediatric emergency medicine, 227
 airway management, 223–224
 equipment for intubation, 224
 medication, 224–225
 post-cardiac arrest hypothermia, 226
 resuscitation, 223
 sepsis (*see* Sepsis)
 Pediatric Fundamental Critical Care Support (PFCCS), 128
 Pediatric gait arms legs and spine (pGALS), 537
 Pediatric intensive care unit (PICU), 232
 Pediatric nephrology, 391
 Pediatric Rheumatology—Care and Outcomes Initiative Network (PR-COIN), 544
 Pegylation, 321
 Periodic fever, 548, 549
 Periodic fever aphthous stomatitis, adenitis, and pharyngitis (PFAPA), 550–551
 Peripheral neurologic exam, 242
 Peripheral precocious puberty (PPP), 258
 Peripherally inserted central catheter (PICC), 341
 Pervasive developmental disorder, not otherwise specified (PDD-NOS), 208
 Phalates, 259
 Pharmaceutical cannabinoids, 9
 Phenylketonuria, 418
 Philadelphia chromosome (Ph), 465
 Physical abuse, 84, 89
 Physical injuries, 86–89

- Physical neglect, 110
 PICC, *see* Peripherally inserted central catheter (PICC)
 Pituitary gland, 251
 Pleomorphic RMS, 497
 Post-cardiac arrest hypothermia, 226
 Post-cardiac arrest management, 124
 Post-streptococcal glomerulonephritis, 397, 398
 Posttraumatic stress disorder (PTSD), 516
 Postural orthostatic tachycardia syndrome (POTS), 455
 PPI, *see* Proton pump inhibitor (PPI)
 PPP, *see* Peripheral precocious puberty (PPP)
 Precocious puberty, 258
 Prednisone poor response (PPR), 463
 Pregnancy, in CHD, 66–68
 Pre-hospital care trauma, 239
 Prematurity, 430–431
 Pre-oxygenation, 224
 Preschool Confusion Assessment Method (psCAM-ICU), 121
 Procedural pain, 236
 Progressive myoclonic epilepsy (PME), 452
 Prokinetic agent, 268
 Prolonged fever, 547
 Prophylactic antibiotics, 336–337
 Prophylaxis, 126
 Propofol, 225
 Propylthiouracil (PTU), 262
 Proton pump inhibitor (PPI), 268, 270
 Pruning, 133
 Pseudosyncope, 456
 Psychiatric illness, 513, 514, 534
 Psychogenic pseudosyncope (PPS), 456
 Psychomotor Development Index (PDI), 64
 Psychosis, 533–534
 Psychosocial support, 109
 Psychostimulant, 518, 519
 Psychotherapy, 26
 Psychotic spectrum disorder
 diagnosis, 528
 prevalence, 527–528
 treatment, 528–529
 PTSD, *see* Posttraumatic stress disorder (PTSD)
 Pubertal delay, 258–259
 Puberty
 blockers, 26
 control, 257–258
 definition, 257
 environmental exposures and, 259
 precocious, 258
 Pulmonary vascular disease, 66
 Pulse oximetry screening, 69
- Q**
 Quality of life (QOL), 65
- R**
 Radial orchiectomy, 500
 Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) trial, 336
 Rapid sequence intubation (RSI), 224, 225
 Rapidly progressive renal dysfunction (RPGN), 397
 Rare tumors, 500–504
 RCC, *see* Renal cell carcinoma (RCC)
 Recombinant growth hormone, 257
 RECSS trial, 317
 Recurrent respiratory papillomatosis (RRP), 349
 Red cell transfusion trigger, 317
 Reflex anoxic seizure, 455–456
 Reflex sympathetic dystrophy, 546
 Reflux, 267
 diagnostic considerations, 268
 management, 268–269
 Renal cell carcinoma (RCC), 490, 493
 Renal dysfunction, 298
 Renal Fanconi syndrome, 406
 Renal replacement therapy (RRT), 400
 Renal tubular disorder, 406–407
 Renal tumors, 490, 493
 Renin-angiotensin system, 491
 Respiratory syncytial virus (RSV), 332
 Resuscitation, 223
 Retinal hemorrhage, 99
 Retinoblastoma, 504
 Retroperitoneal neuroblastoma, 488
 Return of spontaneous circulation (ROSC), 124
 Rhabdoid tumors, 493
 Rhabdomyosarcoma (RMS), 497, 499
 Rheumatology, 537
 Risk-adapted therapy, acute lymphoblastic leukemia, 467
 RMS, *see* Rhabdomyosarcoma (RMS)
 Rocuronium, 225
 RSV, *see* Respiratory syncytial virus (RSV)
 Russel Silver syndrome, 255
- S**
 Sarcomas, 493–500
 SBI, *see* Serious bacterial infection (SBI)
 SCD, *see* Sickle cell disease (SCD)
 Schizophrenia, 528
 Screen for Child Anxiety and Related Emotional Disorder (SCARED), 524
 Screening, brief intervention and referral to treatment (SBIRT), 11
 Seizures, 216
 Selective serotonin reuptake inhibitors (SSRIs), 21, 521, 522, 525
 Self-induced syncope, 455
 Self-reported food allergy, 39
 Sensorial stimulation (SS), 423
 Sensorineural hearing loss (SNHL), 359
 Sentinel chromosome translocation, 465
 Sentinel node biopsy, 498
 Sepsis, 126, 425
 cold shock, 228
 definition, 226
 diagnosis, 228
 epidemiology and risk factors, 226–227
 etiology, 227
 management, 228–230

- microbiology, 227
 - pathophysiology, 227–228
 - warm shock, 228
 - Septic shock, 226
 - clinical presentation, 228
 - cold vs. warm, 228
 - diagnosis, 228
 - mortality, 227
 - treatment, 228, 229
 - Sequencing-based technology
 - gene panel, 373
 - principles, 371–372
 - whole-exome sequencing, 373
 - Serious bacterial infection (SBI), 338
 - Serum-specific IgE testing, 43
 - Severe myoclonic epilepsy of infancy (SMEI), 446
 - Severe sepsis, 226
 - Sexual abuse, 84
 - Sexual abuse and assault, 105–108
 - Sexual attraction, 25
 - Sexual health, marijuana use and, 10
 - Sexual maturity rating (SMR), 106
 - Sexual orientation, 25
 - Sexually transmitted infections (STI), 108
 - Second generation antipsychotics (SGA), 528
 - diabetes, 530
 - dyslipidemia, 531
 - movement disorder, 531–532
 - Shaken Baby Syndrome, 97
 - Shimada system, 487
 - Shock, *see Specific types of shock*
 - Short gut syndrome
 - central access preservation, 286
 - definition, 283
 - enteral nutrition, 285–286
 - parenteral nutrition, 284–285
 - surgery, 286
 - transplantation, 286
 - Short stature, 255
 - Sickle cell disease (SCD), 315–316
 - Single nucleotide polymorphism (SNP) array, 371
 - Skeletal injury, 93
 - Skin and soft tissue infection (SSTI), 358
 - Skin prick testing, 42
 - Skylaa®, 17
 - Sleep problems, 217
 - Small-molecule disorder, 376–382
 - Smoking, 14
 - SNHL, *see* Sensorineural hearing loss (SNHL)
 - Social development, 139, 140, 143, 147, 151, 155, 159, 164, 169, 173, 178, 183, 188, 192, 198
 - Social emotional development, 136–139
 - Social media, 28–30
 - Social Responsiveness Scale (SRS), 211
 - Soft tissue sarcomas
 - histology and molecular profile, 497–498
 - staging, 498
 - symptoms, 497–498
 - treatment and outcomes, 498–500
 - Solid tumors
 - imaging, biopsy, and surgical considerations, 485–486
 - survivorship/late effects, 505
 - Spinal cord injury without radiographic abnormality (SCIWORA), 242
 - Splenectomy, 318, 319
 - SSTI, *see* Skin and soft tissue infection (SSTI)
 - Standardized handover tools, 127
 - Status epilepticus, 122
 - Steroid, inhaled, 256
 - Stevens Johnson syndrome, 527
 - Stress, developmental phase, 202
 - Stressor-related disorder, 515
 - Stretch syncope, 455
 - Subacute sclerosing panencephalitis (SSPE), 209
 - Subcutaneous immunotherapy (SCIT), 49
 - Subdural hemorrhage, 98
 - Sublingual immunotherapy (SLIT), 49–51
 - Suboptimal communication, 127
 - Substance use, *see also* Marijuana
 - adolescents, 8
 - behavioral treatment, 12–13
 - detox/withdrawal, 12
 - disclosure of, 12
 - SBIRT, 11
 - support groups, 12–13
 - treatment, 12
 - Substance use disorder (SUD)
 - clinical point, 533–534
 - diagnosis, 532–533
 - prevalence, 532
 - treatment, 533
 - Substrate reduction therapy (SRT), 385
 - Succinylcholine, 225
 - Sucrose, 237–238
 - Sudden cardiac death, 75–76
 - Suicide, 521
 - Surface tumors, 494
 - Synapses, 133
 - Synaptogenesis, 133
 - Synthetic marijuana, 9
 - Systemic inflammatory response (SIRS), 226
 - Systemic JIA (sJIA), 547
 - Systemic lupus erythematosus (SLE), 547
 - Systemic vascular resistance (SVR), 227
- T**
- T-ALL, 461–463
 - CNS-directed therapy, 468
 - genetics of, 466
 - novel therapy for, 469
 - risk-adapted therapy, 467
 - T cell, engineered, 472
 - T-cell receptor gamma delta (TCR $\gamma\delta$), 272
 - T cell receptor (TCR) gene, 463
 - T lymphoblast, 462
 - TCIs, *see* Topical calcineurin inhibitors (TCIs)
 - TCs, *see* Topical corticosteroids (TCs)
 - Team composition, 231–232
 - Teratomas, 500

- Testicular GCTs, 500
 Tetralogy of Fallot (TOF), 62, 74
 TEWL, *see* Transepidermal water loss (TEWL)
 Thalassemia, iron chelation in, 316
 Therapeutic hypothermia, 427
 Thoracic trauma, 244
 Thrombocytopenia, immune, 318–319
 Thrombogenic mutation, 14
 Thrombopoietin (TPO) receptor agonist, 318
 Thromboprophylaxis, 126
 Thrombosis, 319, 323
 Thymic stromal lymphopoietin (TSLP), 466
 Thyroid disease, 259
 Thyroid stimulating hormone (TSH), 259
 Thyrotropin-releasing hormone (TRH), 259
 Tic disorder, 457
 Tics and Tourette syndrome (TS), 217–218
 Toddler functional gastrointestinal disorder, 273
 Toddler's fracture, 95
 Topical agents, pain, 238
 Topical calcineurin inhibitors (TCIs), 46, 48
 Topical corticosteroids (TCSs), 46, 48
 Total iron binding capacity (TIBC), 314
 Tourette Syndrome International Database Consortium Registry, 217
 Tracheal intubation, 223
 Tranexamic acid (TXA), 23, 240
 Transepidermal water loss (TEWL), 45
 Transferrin saturation (TS), 314
 Transfusion associated necrotizing enterocolitis (TA-NEC), 318
 Transfusion medicine, 317
 Transfusion strategies, 126
 Transient loss of consciousness (TLOC), 456
 Transitional cell tumors, 502
 Transitioning patients
 - to adult healthcare, 31
 - with chronic disease, 31–32
 - in clinical practice, 31
 - completion, 32
 - health values, 31
 - health-related skills and knowledge, 31–33
 - planning, 32
 - policy for, 31
 - readiness, 32
 - tracking and monitoring, 32
 - transfer of care, 32
 Transport modes, 232–233
 Transport team
 - airway and breathing considerations, 233
 - circulatory considerations, 233–234
 - composition, 231
 - disability and exposure considerations, 234
 - supplies and equipment, 234–235
 Transposition of the great arteries (TGA), 63
 Trans Student Educational Resources (TSER), 24
 Trauma, 515–516
 - ABCDE approach, 239, 240
 - abdominal, 244
 - airway, 239
 - AVPU scale, 241
 - brain injury, 243–244
 - breathing, 239–240
 - circulation and hemorrhage control, 240
 - exposure and temperature control, 241
 - fluid resuscitation and hemorrhage, 240–241
 - GCS, 241
 - pre-hospital care, 239
 - panel, 242
 - primary survey, 241–242
 - scope of, 238–239
 - secondary survey, 242–243
 - thoracic, 244
 Traumatic brain injury (TBI), 118, 120
 TRICC trial, 317
 TRIPICU trial, 317
 Trisomy 21, 255
 Tube thoracostomy, 233
 22q11 microdeletion syndrome, 64
 Tyrosine kinase inhibitor (TKI), 465
- U**
- Ulcerative colitis, 279
 Ulipristal acetate (UPA), 18
 Ultrasound technology, 119–120
 Umbilical cord core, 418
 Undifferentiated syndrome, 386
 Upper gastrointestinal series (UGI), 278
 Urinary tract infection (UTI)
 - bacteremic, 337–338
 - clinical presentation, 393
 - diagnosis, 335–336, 393
 - pathogenesis, 392
 - treatment, 393
 - urinary tract imaging, 393–394
 Ursodeoxycholic acid (UDCA), 289
 Uveitis, 544
- V**
- Vaccine
 - hepatitis B vaccine, 109
 - human papillomavirus, 349–351
 - meningococcal B, 360
 - MMR vaccine, 209
 Vasovagal syncope, 453
 Ventricular septal defects (VSDs), 62, 64
 Vernix caseosa, 418
 Very preterm infant (VPT), 430
 Vesicoureteral reflux (VUR)
 - antibiotic prophylaxis, 395
 - definition, 394
 - diagnosis, 394–395
 - prophylactic antibiotics in children with, 336
 - surgical intervention, 395
 Video capsule endoscopy (VCE), 279
 Viral hepatitis, 292–293
 Viral lower respiratory tract pathogens, 331
 Visceral hypersensitivity, 275

Voice and communication therapy, 26
Volumetric capnography, 119
Vomiting, 274, 275
von Willebrands disease, 491

W

WAGR syndrome, 490
Warfarin, 323
Warm shock, 227, 228
Wear and tear effect, 202
Weight loss surgery (WLS), 292
West syndrome, 444

Whole-exome sequencing (WES), 369, 373–374
Whole-genome sequencing (WGS), 211, 374
Wilms tumors, 490–491

Y

Yolk sac tumors, 500
Yupze method, 18

Z

Zika virus (ZIKV), 361–362