

Patient Safety and Quality in Pediatric Hematology/Oncology and Stem Cell Transplantation

Christopher E. Dandoy
Joanne M. Hilden
Amy L. Billett
Brigitta U. Mueller
Editors

 Springer

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*To our patients and their families,
who entrust us with the care of
their children.*

*To our families and friends, who
provide us with unwavering
support.*

*To our mentors, colleagues, and
mentees, who teach us every day.*

Foreword

Our systems are too complex to expect merely extraordinary people to perform perfectly 100% of the time. We as leaders must put in place systems to support safe practice.

As I began this book, I was flooded with memories. From the first days of my 50-year career in healthcare, a college student working as a part-time radiology clerk, pediatric hematology and oncology has had a huge impact on me. At Boston Children's Hospital, Division 28 was the inpatient oncology unit, Division 20 was the inpatient research unit for rare hematologic and other illnesses, and the TTC (tumor therapy clinic) was the outpatient center of our partner Children's Cancer Research Foundation (now Dana-Farber Cancer Institute). The children coming to radiology from these places were often desperately sick, yet they demonstrated great courage and resilience and showed us laughter as well as amazing support of those on the journey with them. Their parents appeared suffering and desperate yet somehow were, because they had to be, resolved and engaged. Siblings and grandparents were often dazed yet were there for the child and each other. All held a deep trust in their care team: the expertise and passion of the staff, clinicians, researchers, and so many more, focused on care, caring, hope, and discovery. The team, in turn, seemed to be always supporting the children, huddled in the reading room consulting while pouring through hundreds of films as well as in the clinic, in the lab, and at the bedside morning, noon, and night. They were committed to figuring it out together. They are extraordinary people, indeed, individually and collectively.

Today, 50 years later, after having served as a hospital administrator at Boston Children's Hospital, an executive at Dana-Farber Cancer Institute, a professor at Harvard T.H. Chan School of Public Health, an improvement advisor at IHI (Institute for Healthcare Improvement), and a trustee for the Lahey Health System and Winchester Hospital, my respect for these extraordinary people in the hematology and oncology journey—patients, families, staff, groups, networks, collaboratives, and communities—has deepened enormously. Along with many, I'm forever grateful for the scientific advancement, dramatically better clinical outcomes, and the continuous quality improvement in hematology, oncology, and hematopoietic stem cell transplantation (Hem/Onc/HSCT).

Over the same period, and notably the last 25 years, I confronted the growing and sobering reality of healthcare administrative and clinical practice: adverse outcomes didn't all have to happen. There was significant preventable suffering, harm, tragedy, death, as well as cost waste under all our watches. Circumstances of the tragic overdose that led to the death of Betsy Lehman allowed me, as well as many others, to learn deeply the personal and organizational impacts for all the victims of harm, the patient, family, staff, and community [1]. I discovered that many of our mental models were faulty; things we believed to be true were not. I learned about mindfulness and, as a leader, developed both a preoccupation with failure and a deep understanding of and passion for quality improvement and patient safety. We pursued the respectful management of serious clinical adverse events [2] after they occurred for patients, family members, and staff, with an overarching aim to eliminating their occurrence in the first place. Along the way at my organizations, across the country and around the world, I met many victims of medical error, children and adults, including patients from hematology and oncology, who were seriously harmed due to poor systems, structures, and processes. I've stood on many occasions before and cried with families and staff who were devastated after preventable harm contributed to death. Often, the same people courageously discussed how they could pursue together three questions: what happened, why did it happen, and what can be done to prevent it from happening again. I've learned that we can't expect people, even exceptional people, who suffer from being human and work in complex, often broken, systems to be perfect 100% of the time. To achieve together the outcomes we seek, leadership at every level must put in place the learning, systems, structures, and processes, to support the *right care in the right place at the right time, every time* [3]. This journey applies to everyone, individually and collectively, never worrying alone. I've seen at every level the power and experienced the pride of working in and with high-quality, continuously improving organizations.

This book is edited by a talented expert team—Christopher Dandoy MD, Joanne Hilden MD, Amy Billett MD, and Brigitta Mueller MD—that had a clear vision for systematic continuous improvement in pediatric hematology and oncology and for driving out unintended variation, suffering, harm, tragedy, death, and cost waste. Drawing on the best experience, evidence, and learning from not only pediatrics but the larger healthcare universe, they bring to the text their personal journeys and their clinical/administrative expertise as well as the quality of care journeys of their organizations, Cincinnati Children's Hospital, Boston Children's/Dana-Farber Cancer and Blood Disorders Center, Children's Hospital of Colorado, and Johns Hopkins All Children's Hospital. They are joined by chapter authors with a wide breadth of experience from these and other leading pediatric hematology and oncology services, as well as from healthcare improvement organizations. Many of these writers I've had the privilege of meeting, working with, and learning from through healthcare delivery, in the university classroom, and/or in the improvement setting.

As I read this book, structured in three sections (Introduction to Safety and Quality Improvement, Getting Started, and Quality and Safety Principles Unique to Pediatric Hematology/Oncology/Bone Marrow Transplantation), I noted the breadth and depth of coverage. Content on quality and safety was presented across the care

continuum—from detection to posttreatment survivorship and/or care at the end of life—and settings wisely ranging from the home and ambulatory environment to the inpatient service. The content is strong with theories, principles, models, tools, frameworks, examples, case studies, and extensive citation. While many of the citations are well known, I was excited by all the new content I was introduced to. Pediatrics historically has taught us much in the wider healthcare community and specifically about patient- and family-centered care. This teaching and role modeling continues in the text with an emphasis on the patient and family in quality and patient safety. The focus throughout on and learning from collaboration and teamwork at every level (macro, mezzo, micro) is powerful, with the patient and family as essential partners.

As the authors note, patient safety and quality improvement is all about change. For many years, in classrooms at the Harvard T.H. Chan School of Public Health, I've taught a course on leading change. The opening slide on opening day is "Most Change Fails" and the citation is "everyone," referencing the many studies across the industry showing the significant failure rates of change initiatives on execution along with the lack of spread and sustainability. Clinical leaders flooded every classroom with failures they were familiar with. Individuals and organizations are doing "lots of this and that" and are "cooking without a recipe, a framework." To counter that, the authors offer wonderful resources on systematic quality improvement science and methods, implementing evidence-based care, spread, and sustainability. Together they can build a culture of excellence and improvement by making change a foundational habit and not just an epidemic of "projectitis." Throughout the text, they take on the importance of standardized practices while at the same time recognizing unique needs. An important, supportive, and very helpful chapter is the focus on careers in quality improvement and patient safety.

As previously noted, improvement is all about confronting our mental models, the things we believe to be true because *they are!* Many may say "our patients are sicker" suggesting adverse events such as infections in the immunocompromised are inevitable, but the authors through this book, and many others, believed and have experienced that improvement and reduction of harm are possible. Rising to this challenge is essential.

Underscoring the editors' suggestions, readership for this book should be global and include a wide range of clinical and administrative professionals in hematology/oncology, as well as patient and family advisors and other interested parties—it is about them! As an extension of the IHI Getting Boards on Board work [4], I would strongly encourage the text be made available to governance and executive clinical and administrative leadership of organizations with a hematology/pediatric oncology focus for discussion; these leaders are ultimately responsible for the overall culture, quality of care, and leading change. There is much learning in the text that can be applied to pediatrics overall and to the broader quality and safety community.

As with most texts, this isn't just a onetime read but is an essential reference in the journey of individuals and teams to achieve the aims and outcomes we all seek for those we are privileged to partner with, respect, and serve: our patients, families, staff members, groups, and communities.

Again, we owe so much to so many for all they have contributed to improving healthcare quality and patient safety. It has been a privilege to be part of this improvement journey and specifically this text. At the same time, there are many references in the chapters ahead, paraphrasing that, for all that has been done, “We’re early in our journey...” and “There is so much more we must do to improve quality and reduce cost.”

To do things differently, we must see things differently. When we see things we didn’t see before, we can ask questions we didn’t know to ask before. (Nelson [5])

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References

1. Conway J, Nathan D, Benz E, Shulman LN, Sallan SE, Ponte PR, et al. Key learning from the Dana-Farber Cancer Institute’s 10-year patient safety journey. In: 42nd Annual meeting of American society of clinical oncology educational book, Atlanta, GA, June 2–6, 2006, p. 615–19.
2. Conway J, Federico F, Stewart K, Campbell MJ. Respectful management of serious clinical adverse events. Cambridge: Institute for Healthcare Improvement; 2011.
3. Kaplan G, Lopez MH, McGinnis JM. Transforming health care scheduling and access: getting to now. Washington: Institute of Medicine; 2015. p. 118.
4. Conway MS. Getting boards on board: engaging governing boards in quality and safety. *Jt Comm J Qual Patient Saf.* 2008;34(4):214–20.
5. Nelson EC, Batalden PB, Godfrey MM, editors. Quality by design: a clinical microsystems approach. Wiley; 2011. p. 260.

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Finally, thank you to the patients and their families. We appreciate your insights, confidence, trust, and teamwork. We could not do our work without your work.

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Chapter 1

Introduction to Patient Safety and Quality in the Pediatric/Hematology Oncology and Hematopoietic Stem Cell Transplant Practice

**Christopher E. Dandoy, Joanne M. Hilden, Amy L. Billett,
and Brigitta U. Mueller**

A family takes their 4-year-old girl into the hospital for concerns of new bruising and lower extremity pain. The child has been symptomatic for a few weeks, but the symptoms significantly worsened over the past few days. The parents anxiously wait for the lab results to return, not knowing what to expect. The emergency room physician enters the room with a solemn face and explains that their child likely has

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leukemia and would need to be admitted to the hospital. The words hang in the air, “your child has cancer.” The parents do not yet know the massive lifestyle change in store for them. They do not realize the amount of time they will spend in the clinic, in the inpatient unit, and in a waiting room while their child undergoes yet another procedure. They do not know, at this time, the number of medications their child will take on a daily basis for the next several years and how easy it will be to confuse these complicated-sounding medications. There are many long days and sleepless nights ahead for them, but they will do it. They will give their complete trust to the physicians, nurses, pharmacists, and hospital staff to care for their girl.

Years earlier, the leaders and caregivers in the pediatric hematology oncology practice initiated a chemotherapy safety program. They formed a team with physicians, nurses, advanced practice providers, pharmacists, administrative staff and leadership, and patients/families. The established safety guidelines included a standardized process of chemotherapy prescribing, dispensing, administering, documenting, and monitoring. The team initiated oversight of the chemotherapy management practices. They started tracking errors and near misses to understand how to target ongoing improvement. Recommendations for avoiding chemotherapy errors call for standardized approaches, development of policies and procedures for system improvement, and review of errors by interdisciplinary professional staff.

Importantly, the parents can rest assured that their child will be given the right medication, at the right time; they will be engaged in the treatment and the care of their child, and they will learn how to give the proper medications at home.

Standing on the Shoulders of Giants

Advances in Pediatric Oncology

Prior to World War II, children with cancer were treated by surgeons, general practitioners, and pediatricians [1]. Most cancer diagnoses were universally fatal, and treatment was associated with high morbidity and mortality. During World War II, chemotherapy came into being and was applied in lymphoma [2–4] and Wilms tumor [5]. In 1958, multi-agent chemotherapy was shown to improve outcomes [6]. Cures for leukemia were achieved by the addition of central nervous system-directed therapy [7] and then intensification of chemotherapy [8]. In 1986, cure rates for acute leukemia rose above 80% with the inclusion of four-drug induction regimens [9]. Stage IV neuroblastoma went from incurable to curable (>50% 2-year event-free survival) through intensification of chemotherapy and introduction of radiotherapy, autologous stem cell transplant, 13-cis-retinoic acid [10], and immunotherapy [11]. These are but a few examples of the dramatic improvements related to better chemotherapy, better supportive care such as infection prevention, and better risk stratification.

As pediatric cancer is a relatively rare disease, and substantial gains cannot be made without collaboration, clinical collaborative groups began to form. In the mid-1990s, four primary childhood cooperative groups received funding by the National Cancer Institute [12]: two groups, the Children's Cancer Study Group (CCSG) and the Pediatric Oncology Group (POG), studied a diverse array of childhood cancers, while two other groups, the Intergroup Rhabdomyosarcoma Study Group (IRSG) and the National Wilms Tumor Study (NWTS) Group were cancer-specific. In 2000, these four pediatric groups voluntarily merged to create the Children's Oncology Group (COG) [12], which is now the world's largest organization devoted exclusively to pediatric cancer research. Approximately 10,000 children ages 0–14 [13] and approximately 70,000 adolescent and young adults (ages 15–39) are diagnosed with cancer in the United States each year [14], many of whom are cared for in children's hospitals and enrolled in COG studies. The first 3–4 IRS studies lead to steady improvements in outcomes without ever showing that the experimental arm had a better outcome compared to the standard arm. This reflects multiple changes in care delivery including changes in staging, risk assignment, and supportive care in addition to the clinical research questions being asked [15]. In some ways, this clinical research group served as a quality improvement collaborative that standardized care, studied outcomes, shared results with all, and instituted additional changes in care.

Advances in Pediatric Hematology

Some of the most impactful advances in modern medicine have been made through transfusion medicine. In 1969, the feasibility of storing platelets at room temperature, revolutionizing platelet transfusion therapy [16], was a key advancement in successful treatment of leukemia and other malignancies. In 1986, the Prophylactic Penicillin Study (PROPS) found that children should be screened in the neonatal period for sickle cell hemoglobinopathy and that those with sickle cell anemia should receive prophylactic penicillin therapy, thus reducing pneumococcal septicemia rates [17]. Clinical trials over the past 30 years have demonstrated significant advances in improving outcomes in sickle cell disease through the administration of hydroxyurea, limiting episodes of acute chest syndrome and pain crises and decreasing transfusions and overall morbidity and mortality [18–26]. Chelation therapy has proven effective at reducing the toxic effects of chronic transfusion in children with β -thalassemia major [27, 28]. In the late 1950s and much of the 1960s, fresh frozen plasma (FFP) was the primary treatment for hemophilia A and hemophilia B. As only a small amount of factor VIII and factor IX are in each unit of FFP, children and young adults required large volume transfusions and required hospitalizations, oftentimes delaying treatment and gradually leading to chronic joint disease with crippling deformities [29, 30]. The successful cloning of the factor VIII gene in 1984 was a major

breakthrough [31], allowing production of recombinant human factor VIII [32, 33] and leading to clinical trials showing efficacy of recombinant factor VIII in hemophilia A patients [34].

Advances in Pediatric Hematopoietic Stem Cell Transplantation (HSCT)

Attempts to treat human patients with supralethal irradiation and marrow grafting were reported by Thomas et al. in 1957 [35]; however, successful transplants in leukemic patients only occurred in HSCT recipients of marrow from an identical twin donor [36, 37]. In the early 1960s, increased pessimism grew in the medical community surrounding HSCT [38], based on poor outcomes. However, by the end of the decade, antibiotic efficacy had improved, transfusion technology had advanced, and more effective cancer agents were developed. In 1968, three patients in the United States and the Netherlands suffering from severe combined immunodeficiency syndromes successfully underwent HSCT [39–41], and by the 1970s and 1980s, HSCT was utilized on a more frequent basis for difficult-to-treat leukemias [42–45]. Over the next 20 years, advances in antiviral therapies [38], extension of graft selection to umbilical cord blood [46–49], and further understanding of HLA matching [49–52] improved outcomes. Today, over 50,000 individuals undergo HSCT annually as the establishment of registries throughout the world has extended access to stem cell grafts [53–56].

In 1676, in a letter to Robert Hooke, Sir Isaac Newton declared, “if I have seen further, it is only by standing on the shoulders of giants.” For the last 50 years, and the centuries before it, thousands of lifetimes have been spent understanding the mechanisms and developing the interventions we utilize in our daily practice. As Newton eluded, we are carried aloft and elevated by the magnitude of the giants before us. Unfortunately, many of the breakthrough discoveries are not applied reliably today, and examples include transcranial Doppler ultrasonography screening for stroke prevention in sickle cell disease and timely antibiotic administration in febrile immunocompromised patients. It is our responsibility and stewardship to ensure our patients receive the right care at the right time, in as safe a manner as possible.

Complexity in Pediatric Hematology, Oncology, and HSCT Healthcare Delivery

In healthcare, complexity can be defined or calculated by the interrelatedness, or influence of system components on each other, inside the system [57].

- *Simple systems* have few components with little interrelatedness. An example of which would be a nurse entering vital signs into the electronic medical record (EMR).
- *Complicated systems* have many components, but low interrelatedness. An example of this would be many nurses and physicians entering data into the EMR, each individual interacting in a limited manner for their specific tasks.
- *Relatively complex systems* have few components with high interrelatedness. Due to the small number of components, they are amendable to change but more difficult to manage or predict. An example of this would be a hematology clinic with a rotation of physicians and nurses. Inside of the group, there may be considerable differences in performance and management of patients between similar teams. These divergences could include variations in protocol compliance and medical errors, showing variable performance between the teams.
- *Complex systems* have many components with high interrelatedness. These systems are challenging to describe, predict, and manage. An example of this would be a hematology oncology unit, with multiple physician providers, rotating residents, dozens of nurses, and multiple patients with a variety of illnesses who are treated on a variety of protocols. Each individual component (i.e., patients, nurses, physicians, residents) of the system is interrelated within and across team members.

The healthcare delivery system is complex. And in addition to providing care in a complex system, our patients are often critically ill, with multi-organ dysfunction, requiring continuous management from different healthcare professionals in multiple settings. Our therapies are not trivial, and the medications and interventions we provide have a narrow therapeutic window; incorrect dosing, timing, or administration can lead to significant morbidity and mortality [58, 59]. Finally, healthcare providers are under significant constraints, attempting to continue to provide safe and equitable healthcare in light of drug shortages, increased documentation requirements, and reduced reimbursement [60]. Healthcare is experiencing increased fragmentation with unintended consequence from care transitions and handoffs [61]. Resident handoffs are more frequent secondary to duty hour regulations, and hospitalists have commonly adopted shift-work-type systems [62]. Hospitalized patients are passed between doctors an average of 15 times during a single five-day hospitalization. If information is omitted or misunderstood, there may be serious clinical consequences [63, 64].

Adding to the complexity is the explosion of new data produced by the brightest minds around the world. Access to the information can be difficult as the volume is so high. Over the past 60 years, Blood has published 125 volumes containing a total of 43,042 original manuscripts, including 2729 clinical trials [65]. In addition, molecular information to diagnose and characterize disease as well as monitor progression or response is increasing, and staying current with the latest advances can be challenging.

Despite these challenges, pediatric hematology/oncology caregivers also have potential strengths that can be leveraged to improve patient safety and quality of

care. We are all familiar with standardization of care which is a key component of the many clinical research trials. Team-based approaches are inherent in how we function in both inpatient and outpatient settings. We focus on enhancing the communication skills of our trainees. Thus, we are already enabled with critical skills to maximize patient safety and performance improvement.

Patient Safety

In the past 15 years, there has been a dramatic expansion of efforts focused on improving systems of care and understanding the science of quality and patient safety. The 1999 Institute of Medicine's (IOM) seminal report *To Err is Human: Building a Safer Healthcare System* publicized that approximately 100,000 deaths annually are due to preventable medical errors, at a cost of between \$17 and 29 billion [66]. The authors noted that with nearly 33.6 million admissions to hospitals in the United States annually, and with an estimated adverse event rate of 2.9–3.7% of hospitalizations [67, 68], nearly 50,000–100,000 individuals die each year secondary to medical errors [66] (a more recent analysis estimates the number of deaths to be more than 400,000 per year [69]). The IOM report called for a comprehensive effort by healthcare providers, insurers, government officials, and patients and was a catalyst in engaging a broad group of stakeholders in identifying and addressing the reasons why medical errors occur and how they can be prevented. The report brought the issues of medical error and patient safety to the forefront of national concern. A critical component of this process was the acknowledgment that humans, in this case even medical personnel with appropriate training such as physicians, nurses, and other key healthcare personnel, can make errors that could lead to patient harm or death.

Adverse drug events (ADEs) comprise the largest single category of adverse events experienced by hospitalized patients, accounting for about 19 percent of all injuries [70]. The occurrence of ADEs is associated with increased morbidity and mortality [71], prolonged hospitalizations [72], and higher costs of care [73]. A 2007 report from the IOM estimated that between 380,000 and 450,000 preventable ADEs occurred annually in US hospitals [74]. Assuming 400,000 preventable ADEs each year at an incremental hospital cost of \$5857 each, the estimated cost of ADEs in 2006 was 3.5 billion US dollars [74].

Pediatric hematology/oncology/hematopoietic stem cell transplant (HSCT) patients are highly susceptible to preventable harm. They usually have central venous catheters exposing them to infectious or thrombotic complications, receive toxic medications, are highly susceptible to healthcare-acquired infection, and are at high risk of home medication errors and non-adherence with oral agents such as chemotherapy, hydroxyurea, and iron chelators. Poor adherence with home medication is of particular concern in patients with cancer, as relapse rates are significantly associated with lower adherence [75]. The IOM defines patient safety as the prevention of harm to patients. Board members, organizations leaders, and frontline staff

in healthcare delivery systems have an obligation to prevent harm through the design of systems that account for human fallibility, cultivation of a culture of safety that prevents errors, and learning from the errors that do occur. In *To Err is Human: Building a Safer Health System*, safety was defined as freedom from accidental injury, as this is the primary safety goal from the patient’s perspective. The authors note that not all errors result in harm and that errors that do result in harm are called preventable adverse events [66]. The administration of chemotherapy to children and adolescents with cancer is a high-risk process with the potential to cause harm to both patients and nurses if not performed accurately and safely. This process requires strict adherence to established safety guidelines [76].

Quality Improvement

Modern quality improvement (QI), based on the theory and methods developed by Dr. Walter Shewhart and W. Edwards Deming in the 1920s, was originally applied in manufacturing industries in the mid-1900s and occasionally in the healthcare industry [77, 78]. In 2001, the IOM published *Crossing the Quality Chasm: A New Health System for the 21st Century* [79]. After the IOM report, there was a resurgence of QI in healthcare to provide safe, effective care. The IOM defined the six aims for improvement in healthcare: safe, effective, patient-centered, timely, efficient, and equitable (Table 1.1).

While QI has become a widespread method for improving care, its acceptance as a rigorous scientific method has faced challenges. Traditional experimental research designs examine effects of one or two isolated interventions under controlled conditions, where in contrast, QI methods involve multiple sequential changes over time and utilize continuous measurement and analysis. In complex and dynamic systems, QI allows for rapid testing and evaluation of new processes and methods for delivering care and addresses the gaps between the level at which a healthcare system currently functions and the level at which it could function.

Table 1.1 Institute of Medicine’s six aims for improvement [79]

Safe	Avoiding injuries to patients from the care that is intended to help them
Effective	Providing services based on scientific knowledge to all who could benefit and refraining from providing services to those not likely to benefit
Patient-centered	Providing care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions
Timely	Reducing waits and sometimes harmful delays for both those who receive and those who give care
Efficient	Avoiding waste, including waste of equipment, supplies, ideas, and energy
Equitable	Providing care that does not vary in quality because of personal characteristics such as gender, ethnicity, geographic location, and socioeconomic status

Variations in Healthcare: The Good and the Bad

In the 1970s, epidemiologists demonstrated substantial geographic variation in the delivery of healthcare [80, 81]. Over the next few years, geographic variation in patient management was repeated through multiple studies crossing nearly all disciplines. In fact, variation in practice is one of the most consistently documented characteristics of modern medicine and is not explained by case mix, confounding factors, or technical errors [82].

It is not uncommon for healthcare professionals to feel threatened by the effort to reduce variation in practice; however, understanding and addressing this fear can help reduce it [83]. Variation in healthcare delivery adds to costs and may lead to misinterpretation of clinical data. QI efforts can successfully reduce practice variation, without insult to the professional autonomy, dignity, or purpose of the providers [83].

Medical science and technology have advanced at an unprecedented rate during the past 50 years; and for providers there is more to know and more to manage than ever before. In light of these rapid changes, the nation's healthcare delivery system has fallen short in its ability to translate knowledge into practice appropriately. The IOM believes that in the next few years, "90% of clinical decisions will be supported by accurate, timely, and up-to-date clinical information, and will reflect the best available evidence" [84]. Clinical decision support (CDS) provides timely information, usually at the point of care, to help inform decisions about a patient's care. CDS tools and systems help providers by assuming some routine tasks, warning of potential problems, or providing suggestions for the clinical team and patient to consider. Oftentimes, CDS directs the provider to provide evidence-based care to their patients, but allows for justifiable deviations to ensure provider autonomy. CDS can be used on a variety of platforms (such as the Internet, personal computers, electronic medical record networks, handheld devices, or written materials) [85–87].

Alone we can do so little; together we can do so much

—Helen Keller

Through collaboration, the COG has improved the outcomes of pediatric oncology patients at a rate that far exceed that which could be done through individual hospitals working alone. Through collaboration, the Working to Improve Sickle Cell Healthcare (WISCH) group is improving sickle cell disease (SCD) screening and follow-up for those who have tested positive and improving care across the life span for individuals with SCD. The goal of the collaborative was to address quality of care through development and implementation of evidence-based guidelines and measurement of healthcare quality by ongoing quality improvement initiatives. Through the consortium, they have improved pain management for SCD patients both at home [88] and in the emergency department [89]; and they are improving the transition of care from the pediatric to adult setting [90].

Through the Children’s Hospital Association (CHA), 32 pediatric hematology oncology and bone marrow transplant units implemented standardized central line care to prevent central line-associated bloodstream infections (CLABSIs). Through the collaboration and shared learnings, the multicenter team reduced CLABSI rates across all centers by 27%, accounting for nearly 100 infections per year and many patient lives [91].

When possible, we should collaborate in patient safety and quality. It is imperative that we share our learnings with others, so that we can learn from each other. Much like the scientific discoveries that broke down barriers in pediatric hematology, oncology, and bone marrow transplant care, we too have an obligation to work together to improve the care of all children.

Book Structure

This book is structured in three sections.

Section 1

“Introduction to Safety and Quality Improvement” provides an introduction to the concepts of quality improvement and patient safety (Chap. 1). Chapter 2 provides an overview of the Model for Improvement, Lean, and Six Sigma and provides an overview of high-reliability organizations. Chapter 3 reviews patient safety, an introduction to human factors and creating a culture of safety and quality.

Section 2

“Getting Started” will provide the healthcare provider and team with the tools required to improve the quality of care in their practice. Chapter 4 provides the basics of team composition and emphasizes patient and family inclusion in healthcare delivery. In Chap. 5, the basics of improvement science methods are covered, including the Plan-Do-Study-Act cycle, identification of key drivers, and how to overcome barriers to implementation. Chapters 6 and 7 provide a comprehensive overview of data collection and improvement measurement, as well as mechanisms to maintain sustainability of the project proposal and spread, respectively. In Chap. 8, we provide an in-depth review of patient safety, including safety reporting systems, communication after adverse events, and root cause analysis with a specific focus on pediatric hematology oncology and stem cell transplant. Finally, we review mechanisms to implement evidence-based practices (Chap. 9).

Section 3

“Quality and Safety Principles Unique to Pediatric Hematology/Oncology/Bone Marrow Transplantation” provides a more granular review of specific topics that are important to our patient population. We review chemotherapy administration safety in the inpatient setting (Chap. 10), healthcare-associated infections (Chap. 11), catheter-related thrombus (Chap. 12), and blood product administration safety (Chap. 13). Home medication compliance and safety is a looming issue that is gathering focus, and Chap. 14 reviews the latest research, as well as evidence and measurement supporting quality improvement efforts. We provide a specific focus on pediatric oncology practices such as antibiotic stewardship, safe handoffs, and timely antibiotic administration in febrile immunocompromised patients (Chap. 15). Chapter 16 reviews practices focused on the population with nonmalignant hematology diseases, such as those with sickle cell disease or hemophilia. We discuss the specific issues involving bone marrow transplant patients in Chap. 17 and focus on quality and safety in palliative care (Chap. 18). Finally, in Chap. 19, we review mechanisms for providers to incorporate quality improvement and safety into their practice.

How to Use This Book

This book is for pediatric hematology and oncology physicians, advanced practice providers, nurses and unit leaders caring for pediatric hematology oncology/stem cell transplant patients, fellows and residents in training, pharmacists, and healthcare administrators hoping to make improvements in their practice and/or their organization. The contributors of this text include physicians, pharmacists, nurses, and quality improvement leaders. All chapters are written by experts in their fields and include the most up-to-date scientific and clinical information. The book provides a concise, yet comprehensive, summary of quality improvements and the safety issues of pediatric hematology patients. This book can be used by those with basic or advanced quality improvement of safety knowledge and will provide a foundation for those who build their practices. It is our hope that the tools described in this book can be used to improve the quality and provide safer care to our patients.

References

1. Wolff JA. History of pediatric oncology. *Pediatr Hematol Oncol*. 1991;8(2):89–91.
2. Gilman A, Philips FS. The biological actions and therapeutic applications of the B-chloroethyl amines and sulfides. *Science*. 1946;103(2675):409–15.
3. Goodman LS, Wintrobe MM. Nitrogen mustard therapy; use of methyl-bis (beta-chloroethyl) amine hydrochloride and tris (beta-chloroethyl) amine hydrochloride for Hodgkin's disease,

- lymphosarcoma, leukemia and certain allied and miscellaneous disorders. *J Am Med Assoc.* 1946;132:126–32.
4. Farber S, Diamond LK. Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl-glutamic acid. *N Engl J Med.* 1948;238(23):787–93.
 5. Farber S, D'Angio G, Evans A, Mitus A. Clinical studies on actinomycin D with special reference to Wilms' tumor in children. *Ann NY Acad Sci.* 1960;89:421–5.
 6. Frei E, Holland JF, Schneiderman MA, et al. A comparative study of two regimens of combination chemotherapy in acute leukemia. *Blood.* 1958;13(12):1126–48.
 7. Aur RJ, Simone J, Hustu HO, et al. Central nervous system therapy and combination chemotherapy of childhood lymphocytic leukemia. *Blood.* 1971;37(3):272–81.
 8. Link MP, Goorin AM, Miser AW, et al. The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. *N Engl J Med.* 1986;314(25):1600–6.
 9. Clavell LA, Gelber RD, Cohen HJ, et al. Four-agent induction and intensive asparaginase therapy for treatment of childhood acute lymphoblastic leukemia. *N Engl J Med.* 1986;315(11):657–63.
 10. Matthay KK, Villablanca JG, Seeger RC, et al. Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. Children's cancer group. *N Engl J Med.* 1999;341(16):1165–73.
 11. Yu AL, Gilman AL, Ozkaynak MF, et al. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. *N Engl J Med.* 2010;363(14):1324–34.
 12. O'Leary M, Krailo M, Anderson JR, Reaman GH. Group Cso. Progress in childhood cancer: 50 years of research collaboration, a report from the Children's oncology group. *Semin Oncol.* 2008;35(5):484–93.
 13. American Cancer Society: Cancer Facts and Figures. 2015. <http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-044552.pdf>. Accessed 19 Sept 2016.
 14. Keegan TH, Ries LA, Barr RD, et al. Comparison of cancer survival trends in the United States of adolescents and young adults with those in children and older adults. *Cancer.* 2016;122(7):1009–16.
 15. Maurer HM, Beltangady M, Gehan EA, et al. The intergroup Rhabdomyosarcoma study-I. A final report. *Cancer.* 1988;61(2):209–20.
 16. Murphy S, Gardner FH. Effect of storage temperature on maintenance of platelet viability—deleterious effect of refrigerated storage. *N Engl J Med.* 1969;280(20):1094–8.
 17. Gaston MH, Verter JI, Woods G, et al. Prophylaxis with oral penicillin in children with sickle cell anemia. A randomized trial. *N Engl J Med.* 1986;314(25):1593–9.
 18. Charache S, Terrin ML, Moore RD, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the multicenter study of hydroxyurea in sickle cell anemia. *N Engl J Med.* 1995;332(20):1317–22.
 19. Charache S, Barton FB, Moore RD, et al. Hydroxyurea and sickle cell anemia. Clinical utility of a myelosuppressive “switching” agent. The multicenter study of hydroxyurea in sickle cell anemia. *Medicine.* 1996;75(6):300–26.
 20. Kinney TR, Helms RW, O'Branski EE, et al. Safety of hydroxyurea in children with sickle cell anemia: results of the HUG-KIDS study, a phase I/II trial. *Pediatric Hydroxyurea Group Blood.* 1999;94(5):1550–4.
 21. Wang WC, Wynn LW, Rogers ZR, Scott JP, Lane PA, Ware RE. A two-year pilot trial of hydroxyurea in very young children with sickle-cell anemia. *J Pediatr.* 2001;139(6):790–6.
 22. Zimmerman SA, Schultz WH, Davis JS, et al. Sustained long-term hematologic efficacy of hydroxyurea at maximum tolerated dose in children with sickle cell disease. *Blood.* 2004;103(6):2039–45.
 23. Hankins JS, Ware RE, Rogers ZR, et al. Long-term hydroxyurea therapy for infants with sickle cell anemia: the HUSOFT extension study. *Blood.* 2005;106(7):2269–75.
 24. Voskaridou E, Tsetsos G, Tsoutsias A, Spyropoulou E, Christoulas D, Terpos E. Pulmonary hypertension in patients with sickle cell/ β thalassemia: incidence and correlation with serum N-terminal pro-brain natriuretic peptide concentrations. *Haematologica.* 2007;92(6):738–43.

25. Pashankar FD, Carbonella J, Bazy-Asaad A, Friedman A. Prevalence and risk factors of elevated pulmonary artery pressures in children with sickle cell disease. *Pediatrics*. 2008;121(4):777–82.
26. Wang WC, Ware RE, Miller ST, et al. Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG). *Lancet*. 2011;377(9778):1663–72.
27. Ehlers KH, Giardina PJ, Lesser ML, Engle MA, Hilgartner MW. Prolonged survival in patients with beta-thalassemia major treated with deferoxamine. *J Pediatr*. 1991;118(4 Pt 1):540–5.
28. Proper RD, Cooper B, Rufo RR, et al. Continuous subcutaneous administration of deferoxamine in patients with iron overload. *N Engl J Med*. 1977;297(8):418–23.
29. Kulkarni R, Soucie JM. Pediatric hemophilia: a review. *Semin Thromb Hemost*. 2011;37(7):737–44.
30. Bolton-Maggs PH, Pasi KJ. Haemophilias A and B. *Lancet*. 2003;361(9371):1801–9.
31. Gitschier J, Wood WI, Goralka TM, et al. Characterization of the human factor VIII gene. *Nature*. 1984;312(5992):326–30.
32. Wood WI, Capon DJ, Simonsen CC, et al. Expression of active human factor VIII from recombinant DNA clones. *Nature*. 1984;312(5992):330–7.
33. Eaton DL, Hass PE, Riddle L, et al. Characterization of recombinant human factor VIII. *J Biol Chem*. 1987;262(7):3285–90.
34. Lusher JM, Arkin S, Abildgaard CF, Schwartz RS. Recombinant factor VIII for the treatment of previously untreated patients with hemophilia A. Safety, efficacy, and development of inhibitors. Kogenate previously untreated patient study group. *N Engl J Med*. 1993;328(7):453–9.
35. Thomas ED, Lochte HL, Lu WC, Ferrebee JW. Intravenous infusion of bone marrow in patients receiving radiation and chemotherapy. *N Engl J Med*. 1957;257(11):491–6.
36. Thomas ED, Lochte HL, Cannon JH, Sahler OD. Supralethal whole body irradiation and isologous marrow transplantation in man. *J Clin Invest*. 1959;38:1709–16.
37. Thomas ED, Lochte HL, Ferrebee JW. Irradiation of the entire body and marrow transplantation: some observations and comments. *Blood*. 1959;14(1):1–23.
38. Thomas ED. Landmarks in the development of hematopoietic cell transplantation. *World J Surg*. 2000;24(7):815–8.
39. Bach FH, Albertini RJ, Joo P, Anderson JL, Bortin MM. Bone-marrow transplantation in a patient with the Wiskott-Aldrich syndrome. *Lancet*. 1968;2(7583):1364–6.
40. De Koning J, Van Bekkum DW, Dicke KA, Dooren LJ, Rádl J, Van Rood JJ. Transplantation of bone-marrow cells and fetal thymus in an infant with lymphopenic immunological deficiency. *Lancet*. 1969;1(7608):1223–7.
41. Gatti RA, Meuwissen HJ, Allen HD, Hong R, Good RA. Immunological reconstitution of sex-linked lymphopenic immunological deficiency. *Lancet*. 1968;2(7583):1366–9.
42. Thomas ED, Buckner CD, Clift RA, et al. Marrow transplantation for acute nonlymphoblastic leukemia in first remission. *N Engl J Med*. 1979;301(11):597–9.
43. Thomas ED, Sanders JE, Flournoy N, et al. Marrow transplantation for patients with acute lymphoblastic leukemia in remission. *Blood*. 1979;54(2):468–76.
44. Fefer A, Cheever MA, Thomas ED, et al. Bone marrow transplantation for refractory acute leukemia in 34 patients with identical twins. *Blood*. 1981;57(3):421–30.
45. Thomas ED, Sanders JE, Flournoy N, et al. Marrow transplantation for patients with acute lymphoblastic leukemia: a long-term follow-up. *Blood*. 1983;62(5):1139–41.
46. Broxmeyer HE, Douglas GW, Hangoc G, et al. Human umbilical cord blood as a potential source of transplantable hematopoietic stem/progenitor cells. *Proc Natl Acad Sci U S A*. 1989;86(10):3828–32.
47. Gluckman E, Broxmeyer HA, Auerbach AD, et al. Hematopoietic reconstitution in a patient with Fanconi's anemia by means of umbilical-cord blood from an HLA-identical sibling. *N Engl J Med*. 1989;321(17):1174–8.
48. Broxmeyer HE, Gluckman E, Auerbach A, et al. Human umbilical cord blood: a clinically useful source of transplantable hematopoietic stem/progenitor cells. *Int J Cell Cloning*. 1990;8(Suppl 1):76–89. discussion 89-91

49. Kohli-Kumar M, Shahidi NT, Broxmeyer HE, et al. Haemopoietic stem/progenitor cell transplant in Fanconi anaemia using HLA-matched sibling umbilical cord blood cells. *Br J Haematol.* 1993;85(2):419–22.
50. Malkki M, Single R, Carrington M, Thomson G, Petersdorf E. MHC microsatellite diversity and linkage disequilibrium among common HLA-A, HLA-B, DRB1 haplotypes: implications for unrelated donor hematopoietic transplantation and disease association studies. *Tissue Antigens.* 2005;66(2):114–24.
51. Petersdorf EW, Gooley TA, Malkki M, et al. HLA-C expression levels define permissible mismatches in hematopoietic cell transplantation. *Blood.* 2014;124(26):3996–4003.
52. Petersdorf EW, Malkki M, O'hUigin C, et al. High HLA-DP expression and graft-versus-host disease. *N Engl J Med.* 2015;373(7):599–609.
53. Ruutu T, Barosi G, Benjamin RJ, et al. Diagnostic criteria for hematopoietic stem cell transplant-associated microangiopathy: results of a consensus process by an international working group. *Haematologica.* 2007;92(1):95–100.
54. Gratwohl A, Baldomero H, Aljurf M, et al. Hematopoietic stem cell transplantation: a global perspective. *JAMA.* 2010;303(16):1617–24.
55. Niederwieser D, Baldomero H, Szer J, et al. Hematopoietic stem cell transplantation activity worldwide in 2012 and a SWOT analysis of the worldwide network for blood and marrow transplantation group including the global survey. *Bone Marrow Transplant.* 2016;51(6):778–85.
56. Yoshimi A, Baldomero H, Horowitz M, et al. Global use of peripheral blood vs bone marrow as source of stem cells for allogeneic transplantation in patients with bone marrow failure. *JAMA.* 2016;315(2):198–200.
57. Kannampallil TG, Schauer GF, Cohen T, Patel VL. Considering complexity in healthcare systems. *J Biomed Inform.* 2011;44(6):943–7.
58. Fernandez CV, Esau R, Hamilton D, Fitzsimmons B, Pritchard S. Intrathecal vincristine: an analysis of reasons for recurrent fatal chemotherapeutic error with recommendations for prevention. *J Pediatr Hematol Oncol.* 1998;20(6):587–90.
59. Hennipman B, de Vries E, Bökkerink JP, Ball LM, Veerman AJ. Intrathecal vincristine: 3 fatal cases and a review of the literature. *J Pediatr Hematol Oncol.* 2009;31(11):816–9.
60. Smith RB, Dynan L, Fairbrother G, Chabi G, Simpson L. Medicaid, hospital financial stress, and the incidence of adverse medical events for children. *Health Serv Res.* 2012;47(4):1621–41.
61. Himmelstein DU, Jun M, Busse R, et al. A comparison of hospital administrative costs in eight nations: US costs exceed all others by far. *Health Aff.* 2014;33(9):1586–94.
62. Nasca TJ, Day SH, Amis ES, Force ADHT. The new recommendations on duty hours from the ACGME task force. *N Engl J Med.* 2010;363(2):e3.
63. Jagsi R, Kitch BT, Weinstein DF, Campbell EG, Hutter M, Weissman JS. Residents report on adverse events and their causes. *Arch Intern Med.* 2005;165(22):2607–13.
64. Sutcliffe KM, Lewton E, Rosenthal MM. Communication failures: an insidious contributor to medical mishaps. *Acad Med.* 2004;79(2):186–94.
65. Collier BS. Blood at 70: its roots in the history of hematology and its birth. *Blood.* 2015;126(24):2548–60.
66. Kohn L, Corrigan J, Donaldson M. To err is human: building a safer health care system. Washington DC: National Academy of Sciences; 2000.
67. Thomas EJ, Studdert DM, Burstin HR, et al. Incidence and types of adverse events and negligent care in Utah and Colorado. *Med Care.* 2000;38(3):261–71.
68. Studdert DM, Thomas EJ, Burstin HR, Zbar BI, Orav EJ, Brennan TA. Negligent care and malpractice claiming behavior in Utah and Colorado. *Med Care.* 2000;38(3):250–60.
69. James JT. A new, evidence-based estimate of patient harms associated with hospital care. *J Patient Saf.* 2013;9(3):122–8.
70. Leape LL, Brennan TA, Laird N, et al. The nature of adverse events in hospitalized patients. Results of the Harvard medical practice study II. *N Engl J Med.* 1991;324(6):377–84.
71. Phillips DP, Christenfeld N, Glynn LM. Increase in US medication-error deaths between 1983 and 1993. *Lancet.* 1998;351(9103):643–4.