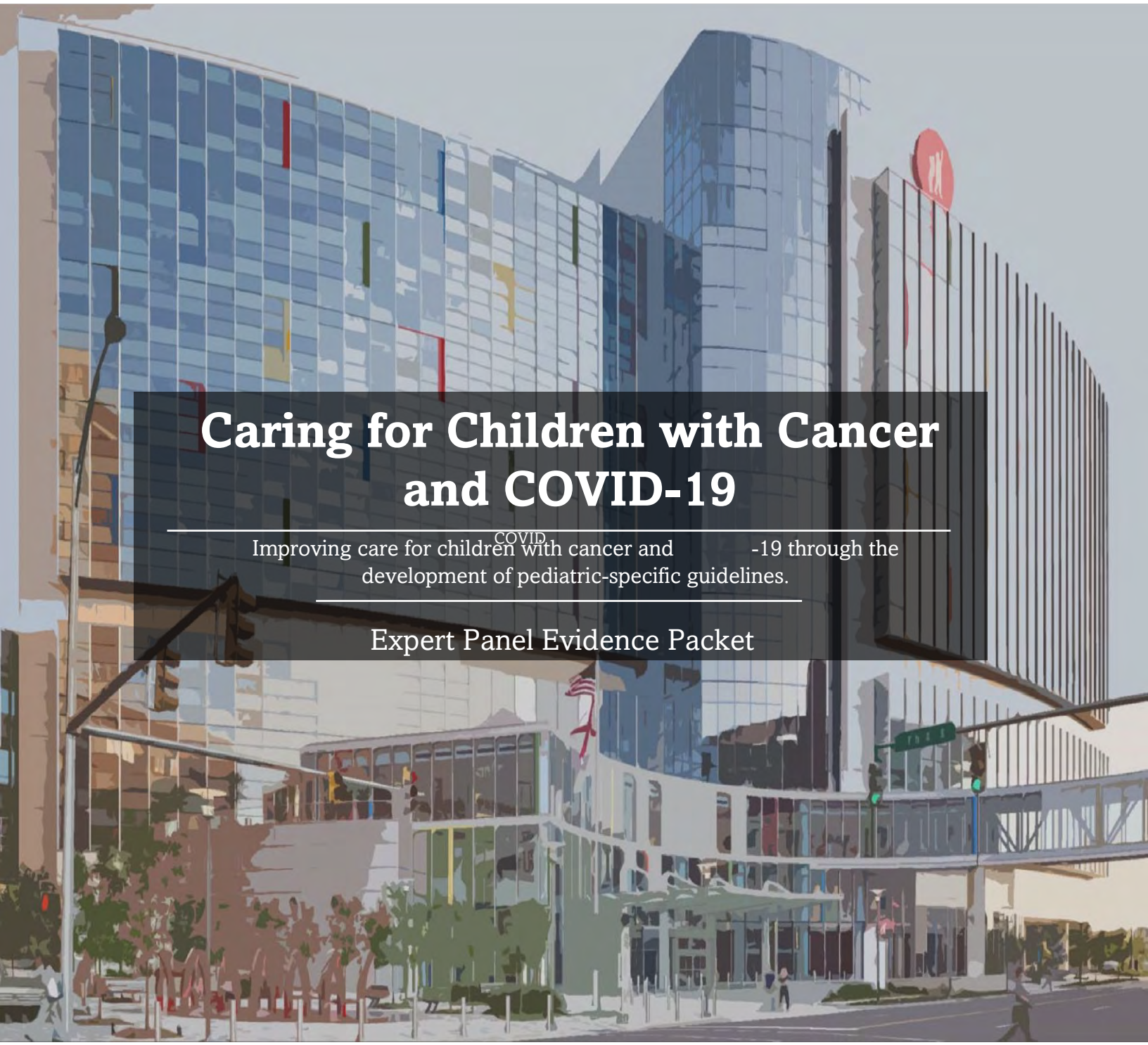
INSTITUTE FOR CANCER OUTCOMES & SURVIVORSHIP
The University of Alabama at Birmingham



Caring for Children with Cancer and COVID-19

Improving care for children with cancer and COVID-19 through the development of pediatric-specific guidelines.

Expert Panel Evidence Packet

Table of Contents

Background Information and Instructions

Project Background and Goals 5
COVID-19 Preface 6
CDC Preface 7
Guideline Identification....8
Modified Delphi Team Members 9
Research Team Biographies 10
Expert Panel Biographies....12
Summary of Tasks and Timeline 17
Rating Criteria and Process 18
Agenda for Modified Delphi Panel 20

Guidelines

Group 1. Prevention

1.1: Vaccinate children with cancer with 3 doses of the COVID-19 vaccine if they have not previously been vaccinated....22
1.2: Children with cancer should receive yearly COVID-19 Boosters....24
1.3: Include the COVID-19 vaccine in revaccination guidance after HSCT 25
1.4: Use pre-exposure prophylaxis for children with cancer who are exposed to COVID-19 who cannot get vaccinated prior to anticipated exposures (who are 12 years and older and weigh at least 40kg).... 26
References 28

Group 2. COVID-19 Treatment

2.1: For children with cancer and symptomatic COVID-19 who are ≥ 12 years old and within 5 days of symptom onset, give Paxlovid. 30
2.2: For children hospitalized with cancer who are ≥ 28 days and ≥ 3 kilos, who have symptomatic COVID-19 (even if COVID-19 was not the primary reason for their hospitalization), give remdesivir if can be given within 7 days of symptom onset.....32
2.3: For children with symptomatic COVID-19 who are outpatient, have co-morbid risk factor (e.g. respiratory disease, obesity), unvaccinated, and within 7 days of symptom onset, give remdesivir 32
2.4: For children within 100 days of allotransplant with COVID-19, give remdesivir.....32
2.5: Follow the IDSA or CDC recommendations for administration of COVID-19 treatments beyond remdesivir and Paxlovid (e.g., glucocorticoids for the critically ill). 35
2.6: Consider testing for MIS-C based on clinical scenario....36
2.7: Do not use post-exposure prophylaxis for children with cancer undergoing chemotherapy....38
2.8: Do not use post-exposure prophylaxis for children with cancer after allotransplant. 39
References....40

Group 3. Cancer Treatment

3.1: Continue to dose-adjust and hold chemotherapy per chemotherapy protocols when children with cancer have COVID-19 42
3.2: Do not hold chemotherapy in a child with cancer and COVID-19, if meets criteria to continue as scheduled in the protocol AND (1) has mild COVID-19, (2) are not hospitalized for COVID-19, (3) Does not have comorbidities, AND 4 (4) are < 11 years old 42
3.3: Consider holding chemotherapy for 48 hours in children with cancer and COVID-19 who are ≥ 11 years old or have comorbidities 42
3.4: Consider doing lumbar punctures awake for children with cancer and COVID-19 who would be due for lumbar punctures but can not receive them with sedation due to institutional protocols 46
3.5: If lumbar punctures are postponed due to COVID-19, ensure that patients receive the planned total number of lumbar punctures during their therapy 47
3.6: Treat children with cancer and COVID-19 per institutional guidelines for fever and neutropenia 49
References 51

Group 4. Precautions

4.1: Follow standard isolation procedures (comparable to non-immunosuppressed patients) for children with cancer and COVID-19 56
4.2: Healthcare workers caring for children with cancer should follow CDC guidelines for length of isolation after infection 58
4.3: Healthcare workers caring for children with cancer and COVID-19 should receive the COVID-19 vaccine 60
4.4: Programs should have protocols in place to not have children with COVID-19 in shared spaces, including waiting rooms and infusion rooms 61
References 63

Background Information and Instructions

Project Background

COVID-19 has affected children with cancer—leading to significant morbidity and mortality, as well as changes in cancer therapy for many children infected by COVID-19. Children with cancer who develop COVID-19 face a uniquely high-stakes clinical course because infection risk and severity intersect with immunosuppression, treatment intensity, and the consequences of delaying or modifying cancer therapy. Yet critical gaps remain in our understanding of COVID-19 in this population, and we still lack clear, pediatric oncology–specific guidelines for caring for children with cancer and COVID-19—particularly guidance on when to hold or modify chemotherapy in the setting of infection. Within the CDC's current paradigm, children with cancer and their families rely heavily on pediatric oncologists for individualized, risk-based guidance regarding COVID-19 prevention and management decisions.

Across centers, clinicians continue to confront practical, time-sensitive questions—how to mitigate risk, when to use COVID-19 therapeutics, how to time procedures, and when (or whether) to hold chemotherapy—often in the context of evolving evidence and variable institutional practices. This uncertainty contributes to meaningful variation in care, with decisions that directly affect both COVID-19 outcomes and cancer treatment continuity. The aim of this Modified Delphi Panel is to synthesize the best available evidence and multidisciplinary clinical expertise into expert panel–endorsed recommendations that support consistent, data-driven decision-making and take a crucial step toward standardizing care for children with cancer and COVID-19.

Project Goals

This project aims to develop an expert panel-endorsed set of pediatric oncology–specific guidelines for caring for children with cancer in the COVID-19 era. We will consider four themes: (1) Prevention (2) COVID-19 Treatment (3) Cancer Treatment (4) Precautions.

The specific goal of this expert panel is to provide structured feedback on the appropriateness and feasibility of the preliminary list of pediatric-specific proposed guidelines developed based on guidance for similar populations, and findings from interdisciplinary discussion. The result will be a list of expert panel-endorsed guidelines for children with cancer and COVID-19.

COVID-19 Preface

Developing guidelines for children with cancer and COVD-19 requires an understanding of the severity of COVID-19 in children with cancer. Therefore, we briefly summarize data regarding COVID-19 and children with cancer.
Several factors, including cancer, have been identified as comorbidities that put children at risk of severe COVID-19. There are higher rates of serious illness and mortality for COVID-19 among children with cancer compared to the general pediatric population.[1] For instance, a Turkish study compared COVID-19 cases in children with cancer and healthy children and found that children with cancer reported higher rates of both critical disease (20% vs 12%) and mortality (12% vs 1.9%).[1] However, another early report from the UK found a less severe disease course in children with cancer and COVID-19 that the findings from Turkey. [2] They described 54 children with cancer and COVID-19; 28% were asymptomatic, 63% had mild infections, and 10% moderate, severe, or critical infections. In that study, 3 children required intensive care, but no children died.

The most robust data from the US comes from the Pediatric Oncology COVID-19 Case Report (POCC), a registry of children with Cancer and COVID including data from over 100 centers in the US and over 2400 children with cancer and COVID-19. The initial report from POCC included 917 US children with cancer diagnosed with COVID-19 through the spring of 2021.[3] The majority (64%) were symptomatic, 31% were hospitalized, 11% required respiratory support, 10% were admitted to the ICU, and 1.6% died due to COVID-19.[3] Cancer therapy was modified in 45%.

Notably, it does not appear that children with cancer and COVID-19 who are re-infected have a milder course. In a 2025 POCC analysis looking at severity of COVID-19 infection in those with only a single COVID-19 infection (n=1950) and the second infections (n=125); odds of hospitalization ICU admission, and changes were not different for 1st vs 2nd infection.[4]

Recent analysis shows that children with cancer who are vaccinated and those who were infected after March 2022 (n= 802) have a milder course than those infected prior to March 2022 (n=1260) (*Unpublished data)*. Post March 2022, 23% of children with cancer and COVID-19 were admitted to the hospital, 2.5% admitted to the ICU, and 34% had changes in cancer directed therapy. In multivariable analysis, both vaccination and later era were associated with lower risk of hospitalization, ICU admission, and changes in cancer directed therapy.

There was a sub-analysis of children with Acute Lymphoid Leukemia (ALL) undergoing maintenance therapy.[5] Maintenance therapy is approximately 2 years and, although children are still receiving chemotherapy, it is less intense, they are usually not neutropenic, and frequently return to school and other activities. Compared with other children reported to POCC (n = 1,190), those in ALL-MTN (n = 481) were less often hospitalized (23% *v* 29%, $P = .01$) or admitted to the intensive care unit (ICU: 3% *v* 5%, $P = .01$); these findings persisted in multivariable analysis (hospitalization: odds ratio [OR], 0.7 [95% CI, 0.6 to 0.9]; ICU: OR, 0.5 [95% CI, 0.2 to 0.8]). However, cancer-directed therapy was changed more often for children in ALL-MTN (50% *v* 33%, $P \leq .01$; OR, 2.0 [95% CI, 1.6 to 2.5]). Therefore, although some of our least immunosuppressed children appear to have a milder course, they still have risk of hospitalization, ICU admission, and change in chemotherapy.
Notably, the POCC data are limited by who was getting COVID-19 testing and who was reporting their COVID-19 infection to their pediatric oncology team. Therefore, it may overestimate the disease severity.

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CDC Preface

The summaries of many of the proposed guidelines reference CDC websites and data. Related, some of our guidelines reference following CDC guidelines. Much of this work was done prior to 2025, when there were less concerns about the scientific rigor of what was coming out of the CDC. Therefore, many of the CDC references are older and are archived references (which have been cited as such). Additionally, some of the proposed guidelines recommend following CDC guidelines (e.g., Follow the IDSA or CDC recommendations for administrative of COVID-19 treatments beyond remdesivir and Paxlovid [e.g., glucocorticoids for the critically ill). We intend this with the understanding that adherence to CDC guidelines is appropriate only when the guidelines are scientifically rigorous. The eventual manuscript will include a similar statement. However, the lack of credible guidelines coming from the CDC makes this work even more important.

Guideline Identification

Step 1: Proposed List of Potential Guidelines

The proposed list of draft guidelines was created by starting with the real-world clinical problems. We used the content of these questions and multidisciplinary discussion to define the key decision points where clinicians most need consistent, evidence-informed guidance, with particular attention to situations where practice variation may influence both infectious outcomes and continuity of cancer treatment. In particular, as developers of a pediatric oncology COVID-19 registry with ≥2000 children we regularly get clinicians asking questions about the management of children with cancer and COVID-19, guidelines cover many of the questions we received.

Step 2: Literature Review

The research team then conducted a literature review on each proposed guideline focusing on evidence for and against each one.

Step 3: Expert Panel Review

Experts were selected based on demonstrated experience caring for children with cancer and/or managing COVID-19–related clinical decisions in high-risk pediatric populations, as well as leadership and scholarship in areas directly relevant to this project (e.g., oncology, infectious diseases, pharmacy, nursing, and clinical epidemiology). Our goal was to ensure broad representation across disciplines involved in real-world decision-making and to include perspectives that reflect diverse practice settings.

Individually, experts will review the evidence compiled for each proposed guideline and rate the importance and feasibility of each guideline. After the initial ratings, we will have our Modified Delphi panel discuss first rounds scores as well as the evidence for and against each measure. After the discussion, the experts will then rerate the list of proposed guidelines.

Step 4: Next Steps

We will finalize the expert panel–endorsed, prioritized list of guidelines and disseminate it (e.g., manuscript/summary materials) to support standardized, evidence-based care across centers.

Modified Delphi Team

Principal Investigator

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Swetha Pinninti MD

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Kevin Buckley MD

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Christopher Dvorak MD

Danielle Friedman MD, FACS

Wendy Landier PhD, CRNP, FAAN

Olga Militano PharmD

Maki Okada MS, CPNP-PC, FNP-BC

Andrew Ostrenga PharmD

Pratik Patel MD

Agnes Reschke MD

Sue Zupanec MN, NP

Jennifer Blumenthal MD

Research Team Biographies

Emily Johnston MD, MS

Dr. Emily Johnston is an Associate Professor with tenure of Pediatric Oncology at the University of Alabama at Birmingham. Her research focuses on establishing quality measures for end-of-life care for children with complex chronic conditions that can be used as a tool to identify disparities in care. In addition to her research, she cares for children with solid tumors and so routinely cares for children with cancer and COVID-19. Dr. Johnston received her BA from Carleton College, then completed her medical training (medical school through pediatric hematology-oncology fellowship and a master's in health service research) at Stanford University. She joined the faculty at the University of Alabama at Birmingham in 2018.

Ritikraj Arya BA

Ritikraj Arya is a Clinical Research Coordinator at the Institute for Cancer Outcomes and Survivorship at the University of Alabama at Birmingham. He received his BA in Biology at Brown University. Ritik's passions lie in reducing the barriers to high-quality end-of-life care for children and their families as well as reducing disparities in care.

Jamie Holdsambeck MPA

Jamie Holdsambeck is a Clinical Research Coordinator at the Institute for Cancer Outcomes and Survivorship at the University of Alabama at Birmingham. She received her BS in Political Science and Journalism at the University of Montevallo and her MPA at the University of Alabama at Birmingham. Jamie is passionate about reducing barriers to high-quality care and reducing disparities in care for children and their families. She is currently completing her MPH at the University of Alabama at Birmingham.

Anka Raicevic BA

Anka Raicevic is a Clinical Research Coordinator at the Institute for Cancer Outcomes and Survivorship at the University of Alabama at Birmingham. She received her BA in Chemistry from Carleton College. Anka is deeply committed to improving access to high-quality end-of-life care for children and their families while addressing inequities in care.

Natalie Berman-Schneider

Natalie Berman-Schneider is a junior at Carleton College studying Biology and Spanish. She plans to pursue medical school with the goal of specializing in pediatrics, with interests in oncology or surgery. She is an extern with Dr. Emily Johnston, and her interests include psychosocial research, pediatric health equity, and culturally responsive medical communication.

Katherine Hess

Katherine Hess is a senior at Carleton College studying Mathematics. She intends to attend medical school pursuing a career in pediatrics and is exploring potential subspecialties. She is an extern with Dr. Emily Johnston engaging in clinical observation, and her interests include pain management and symptom relief, childhood development, and family-centered care models.

Expert Panel Biographies

Kevin Buckley MD

Kevin Buckley is an Assistant Professor of Pediatric Infectious Diseases and Immunology at Wake Forest School of Medicine and the Director of Pediatric Transplant Infectious Diseases and the PrOTeCT compromised host program at Advocate Health Levine Children's Hospital in Charlotte, NC. He is board certified in Pediatric Hematology/Oncology and Pediatric Infectious diseases and manages children with primary and secondary immune deficiencies. His research background is in basic immunology studying B- and T-cell development. He completed his pediatric residency and fellowship training at UAB.

Brooke Cherven PhD, MPH, RN, CPON

Dr. Cherven is an Associate Professor of Pediatrics at Emory University School of Medicine and Nurse Scientist in the Aflac Cancer & Blood Disorders Center at Children's Healthcare of Atlanta. Her research program, which is supported by NIH funding, focuses on reproductive health among adolescents and young adults with cancer, including fertility assessment after cancer treatment, sexual health, and HPV vaccination. In my role as Nurse Scientist, I work closely with clinical nurses in Aflac and across the Children's system to advance nursing research and innovation.

Kathleen Chiotos MD, MSCE

Dr. Katie Chiotos is an Associate Professor of Anesthesiology and Critical Care Medicine at the Perelman School of Medicine at the University of Pennsylvania and an Attending Physician in Critical Care Medicine and Infectious Diseases at the Children's Hospital of Philadelphia (CHOP). She is also the Medical Director of the CHOP Antimicrobial Stewardship Program, as well as Associate Fellowship Program Director for Research and Scholarship in the Pediatric Critical Care Medicine fellowship program. Dr.Chiotos's research program spans implementation science, diagnostic stewardship, and clinical epidemiology, with a particular focus on improving the diagnosis and management of pediatric pneumonia and sepsis; reducing broad-spectrum antibiotic overuse in the pediatric inpatient setting; and understanding the impact of antibiotic exposure on antimicrobial resistance. She has led or collaborated on numerous federally funded studies, including Centers for Disease Control and Prevention (CDC)-supported projects aimed at reducing empiric vancomycin use in pediatric sepsis, improving n antibiotic prescribing for community-acquired pneumonia, and characterizing the respiratory and gastrointestinal microbiome in post-acute critically ill children. In addition, Dr. Chiotos serves as site principal investigator for national studies on viral epidemiology, vaccine effectiveness, and the immunobiology of severe influenza, RSV, and COVID-19 in hospitalized children. She has also contributed to major national guideline and taskforce efforts, including service on the National Institutes of Health (NIH) and Infectious Diseases Society of America (IDSA) COVID-19 Treatment Guidelines Panels, the Society for Critical Care Medicine (SCCM) Pediatric Sepsis Definitions Taskforce, and the IDSA Sepsis Advisory Panel. Her work has resulted in numerous high-impact publications in *Clinical Infectious Diseases*, *Pediatrics*, and *JAMA Pediatrics*.

Christopher Dvorak MD

Dr. Christopher Dvorak is Professor of Pediatrics, Chief of the Division of Pediatric Allergy, Immunology, & Bone Marrow Transplantation at the University of California San Francisco (UCSF), and Director of the FACT-Accredited Pediatric Cellular Therapy Laboratory for UCSF Benioff Children's Hospitals. He is a member of the UCSF Helen Diller Family Cancer Center and the UCSF Broad Center of Regeneration Medicine and Stem Cell Research. He is a Fellow of the American Society of Transplantation and Cellular Therapy (ASTCT). He is the national Co-PI of the Primary Immunodeficiency Treatment Consortium (PIDTC). He is immediate past Chair of the Cancer Control and Supportive Care Committee of the Children's Oncology Group (COG), a past Chair of the Supportive Care Strategy Group of the Pediatric Transplant and Cellular Therapy Consortium (PTCTC), and past Co-Chair of the Non-Malignant Diseases Working Committee in the Center for International Blood and Marrow Transplant (CIBMTR). He has served as the national Principal Investigator for multiple multi-center clinical trials in the COG, PTCTC, and PIDTC. His expertise is in designing clinical trials aimed at decreasing transplant-related morbidity/mortality, as well as optimizing approaches to transplant for very young children, especially those with immunodeficiencies.

Danielle Friedman MD, MS

Dr. Danielle Novetsky Friedman is an Associate Member in the Department of Pediatrics at Memorial Sloan Kettering Cancer Center and Director of the Pediatric Long-Term Follow-Up Program. She is a clinician-scientist focused on the care of survivors of childhood, adolescent, and young adult cancers, with a research focus on cardiometabolic late effects and lifestyle interventions. She serves as Co-Chair of the Children's Oncology Group Long-Term Follow-Up Guidelines and a member of the ASCO Evidence-Based Medicine Committee and contributes to international guideline harmonization efforts.

Wendy Landier PhD, CRNP, FAAN

Dr. Wendy Landier is a Professor in the Division of Pediatric Hematology/ Oncology and Deputy Director of the Institute for Cancer Outcomes and Survivorship in the School of Medicine, University of Alabama at Birmingham, and holds a secondary appointment in the UAB School of Nursing's PhD Program. She earned her Master's Degree at UCLA and PhD from the University of Hawaii. She is a pediatric nurse practitioner with a clinical focus in cancer survivorship. Her research focuses on understanding and improving health outcomes in childhood cancer survivors, with an emphasis on secondary cancer prevention; implementation and refinement of guidelines for survivorship care; and acquisition of health knowledge by childhood cancer survivors and their parents and caregivers. She currently co-leads an NCI-funded multisite trial that is evaluating the effectiveness and implementation of an evidence-based intervention aimed at increasing HPV vaccination rates in childhood cancer survivors.

Olga Militano PharmD

Olga Militano obtained her Bachelors of Science in Pharmacy degree from Long Island University College of Pharmacy in 1996, followed by a traditional post-baccalaureate PharmD degree from the same institution in 1999. Subsequently, she completed a Pediatric Pharmacotherapy residency at the Shands at the University of Florida in 2000. She has been a clinical pharmacy specialist in the field of Pediatric Oncology/BMT for over two decades, first at Children's Hospital of New York Presbyterian/Columbia University and now as a lead clinical research pharmacist with Children's Oncology Group for the past 10+ years. Throughout her career she has held a variety of positions including pharmaceutical industry, medical writing, general pediatrics and clinical pharmacy/electronic medical records consulting. The field of Pediatric Oncology and Stem Cell Transplant has always fascinated her with its multifaceted aspects of patient care, rapid practice changes and collaborative work environment. she tremendously enjoys being able to contribute to the management of children with cancer through clinical interventions, research endeavors, guidelines development and education.

Maki Okada MS, CPNP, FNP

Maki Okada has been a pediatric oncology nurse since 2003. She started her career as a bedside nurse in pediatric hematology/oncology/BMT. As a nurse practitioner, she has cared for survivors of childhood cancer, and has been caring for leukemia and lymphoma patients. Maki is involved in Children's Oncology Group as a study nurse. It is important to her that patients and families receive compassionate and cutting edge care as they journey through the hardest chapter of their lives. She is honored to work alongside world class nurses, physicians, and therapists as she cares for her patients. When she is not caring for patients, she can be found enjoying time with her husband and her two boys who are growing up way too fast!

Andrew Ostrenga PharmD

Andrew Ostrenga, Pharm.D., is the Assistant Director of Pharmacy for Pediatrics and a Clinical Pharmacist in Pediatric Hematology/Oncology at the University of Mississippi Medical Center. He also serves as a Clinical Assistant Professor at the University of Mississippi School of Pharmacy. He received his Doctor of Pharmacy from the University of Mississippi in 2005 and went on to complete a Pharmacy Practice Residency at the University of Mississippi Medical Center. Dr. Ostrenga has extensive experience in pediatric oncology pharmacotherapy, clinical research, and interdisciplinary education, and he has provided longstanding leadership within the Children's Oncology Group Pharmacy Committee. His professional interests include medication safety, pharmacokinetics, pharmacogenomics, supportive care, and the optimization of therapeutic outcomes in pediatric patients with cancer.

Pratik Patel MD

Dr. Pratik Patel is a dually trained pediatric infectious diseases and hematology/oncology physician who cares for children at Children's Healthcare of Atlanta and serves as an Assistant Professor of Pediatrics at Emory University School of Medicine. He is the founding medical director of the Transplant and Oncology Infectious Disease team within the Division of Pediatric Infectious Diseases. He also practices as a pediatric oncologist on the leukemia and lymphoma team in the Aflac Cancer and Blood Disorders Center and is the founding director of its Infection Defense Program, dedicated to preventing, diagnosing, and treating infections in children with cancer and blood disorders.

Agnes Reschke MD

Dr. Agnes Reschke is a dual-trained pediatric critical care physician and pediatric oncologist at Cincinnati Children's Hospital Medical Center, with specialized expertise in onco-critical care. Her clinical and research work focuses on the care of critically ill children with cancer, including those undergoing hematopoietic stem cell transplantation and advanced cellular therapies. These highly vulnerable patients require integrated, multidisciplinary care that addresses both their oncologic and critical care needs. Dr. Reschke is dedicated to improving survival and quality of life for this population through collaborative clinical care, translational research, and multi-institutional studies focused on treatment-related toxicities, oncologic emergencies, organ failure, and extracorporeal life support. She is an active member of the PALISI network and is deeply committed to education and mentorship, having received multiple teaching awards throughout her training.

Sue Zupanec MN, NP

Sue Zupanec is a Nurse Practitioner in the Section of Leukemia and Lymphoma within the Division of Hematology/Oncology at The Hospital for Sick Children in Toronto. She currently serves as Chair of the Nursing Discipline and the Patient-Reported Outcomes Committee with the Children's Oncology Group, where she champions patient and family-centered research. Sue is also a member of the Executive Committee for the Garron Family Cancer Centre. With a career dedicated to advancing pediatric oncology nursing, she brings expertise in clinical care, research leadership, and advocacy to improve outcomes for children, teens, and young adults with cancer.

Jennifer Blumenthal MD

Dr.Jennifer Blumenthal is an Associate in Critical Care Medicine in the Department of Anesthesiology, Critical Care and Pain Medicine and an Assistant in Pediatrics in the Division of Infectious Diseases at *Boston Children's Hospital*. She also serves as an Instructor of Anesthesia at Harvard Medical School. Dr. Blumenthal earned her medical degree from the University of Alabama and completed her residency and fellowship training at the Boston Combined Residency Program and Boston Children's Hospital. She is board-certified in Pediatrics, Pediatric Critical Care Medicine, and Pediatric Infectious Diseases, and her clinical and research interests include pediatric critical care and infectious disease management.

Summary of Expert Panel Tasks and Timeline

Introductory Meeting	
Goal:	Familiarize panel members with the Modified Delphi Panel process, tasks of the panel, and answer any questions.
Instructions:	Participate in an introductory Zoom meeting to learn about the project and clarify any questions.
Review Evidence and Complete Survey	
Goal:	Review proposed guidelines including the available evidence and rate each measure in preparation for the Modified Delphi Panel.
Type:	Independent Work
Instructions:	1. Review the attached booklet 2. Rate each measure using REDCap survey (see email) 3. Complete the survey

Modified Delphi Panel Meeting	
Goal:	Discuss panel members' preliminary ratings, any areas of disagreement, and any areas where panel members request further discussion.
Type:	Virtual meeting (Zoom)
Instructions:	Participate in group discussion and provide a second set of ratings.

Complete Guideline Ranking	
Goal:	Re-rank the proposed guidelines based on additional insight obtained from the group discussion
Type:	Independent Work
Instructions:	Re-rank guidelines using REDCap survey (see email)

Rating Criteria and Process

Rating Criteria for the Proposed Guidelines

The expert panel is tasked with rating each guideline using two criteria: 1) Importance and 2) Feasibility of implementation.

In some cases, a guideline reflects an area with limited evidence regarding outcomes of interest. In these cases, we ask that you draw on your expert opinion and judgment, as well as your personal and professional experiences.

There will be text boxes to expand upon your ratings as necessary and provide any additional comments, such as health or cost implications, preferences for specific practice examples, additional relevant references or resources, or how you would suggest we modify the guideline. There will also be an opportunity to suggest additional guidelines at the end.

Ratings will be completed using the following 9-point scale for each outcome of interest.

Rating Scale Definitions

Rating	Definition
1	This guideline is **highly unlikely** to meaningfully impact [outcome of interest]
2,3	This practice is **somewhat unlikely** to meaningfully impact [outcome of interest]
4,5,6	This practice is **uncertain or unreliable** in its impact [outcome of interest]
7,8	This practice is **somewhat likely** to meaningfully impact [outcome of interest]
9	This practice is **highly likely** to meaningfully impact [outcome of interest]

Rating Criteria for Guidelines

Rating Criteria	Action	When should a quality measure receive a high rating?
1. Importance	Rank the guideline in terms of its potential impact on the care experience for children with cancer and COVID-19 (i.e., perception that a guideline would be meaningful, productive, and contribute to the general well-being of patients, families, and/or providers	A guideline is rated highly if it measures something that is likely to improve the care experience for children with cancer and COVID-19 (i.e., perception that a guideline would be meaningful, productive, and contribute to the general well-being of patients, families, and/or providers) This judgment should be made based on a combination of: • Scientific evidence • Expert opinion drawn from clinical and/or professional experience • Insight drawn from non-medical field
2. Feasibility of Implementation	Rank the guideline in terms of implementation feasibility (i.e., ease of integrating into diverse outpatient and inpatient settings, considering complexity, time demands, and training requirements).	A guideline is rated highly if the practice is easy to integrate into a busy clinical practice, can be implemented with minimal training requirements/ resource investment and is appealing and acceptable to clinicians and health system leadership across diverse outpatient clinical settings (practice types, length of visit, clinical resources, patient demographics) with minimal modification. This judgment should be made based on a combination of: • Implementation of feasibility considerations raised in scientific evidence • Expert opinion drawn from clinical and/or professional experience

Agenda for Modified Delphi Panel

1. Welcome
    - Introductions
        - Name
        - Institution
        - Area of expertise related to this panel

2. Discuss Goal
    - To develop an expert panel-endorsed list of guidelines related to caring for children with cancer during the COVID-19 era.

3. Discuss Proposed Guidelines

Guidelines

Group 1. Prevention

1.1: Background

This section discusses how to manage COVID-19 prevention in children with cancer, including primary vaccination and boosters, revaccination after HSCT, and the use of pre-exposure prophylaxis for those who cannot be vaccinated.

1.1: **Vaccinate children with cancer with 3 doses of the COVID-19 vaccine if they have not previously been vaccinated.**

Children with cancer face significant immunosuppression due to their underlying disease and its treatment, making them especially vulnerable to infectious diseases such as COVID-19.[1] While chemotherapy-induced immunosuppression stifles immediate vaccine efficacy, children with cancer can still mount a meaningful immune response over time. [2] Given the increased morbidity and mortality rates among pediatric cancer patients with COVID-19, COVID-19 vaccination is a viable strategy to help boost immunity and protect from serious COVID-19.[3] The CDC and IDSA recommends all severely immunocompromised persons- including children with cancer- receive the COVID-19 vaccination, as they are at risk for severe illness and adverse outcomes.[4]

COVID-19 vaccinations are particularly important, as immunity from COVID-19 infection wanes overtime; therefore, vaccines are in important tool in preventing serious COVID-19 infection. This remains true for children who are actively receiving chemotherapy, children who previously received chemotherapy, and also healthy children. Although immunosuppression may impact the efficacy of COVID-19 vaccines, a recent study published in *Cancer* showed that a third vaccine dose, compared to the traditional two-dose regimen, mounts a positive immune response in pediatric cancer patients.[5] This study found that after two doses of the COVID-19 vaccine, detectable antibodies were documented in 76.2% of pediatric cancer patients, and after a third-dose of the COVID-19 vaccine, seroconversion rate had increased significantly to 90%. However, vaccination response may be dependent upon the type of malignancy a child has.[6] A recent study found that vaccine efficacy was higher in patients with solid tumors compared to patients with hematologic malignancies. Thus, while vaccination is a tool to boost immune response, vaccination and timing of doses may need to be personalized based on the individual's medical needs.

Children with cancer receiving the COVID-19 vaccine is limited by low COVID-19 vaccine uptake. As of 2023, COVID-19 vaccine uptake among children remained low; only 48% of cancer patients had been vaccinated against COVID-19. [7] Vaccine hesitancy is a major barrier to disease prevention. A recent study found that providers can play an integral role in influencing caregiver decision-making regarding vaccination.[8] Caregivers who spoke directly to cancer care professionals about vaccines were more likely to vaccinate both their child and themselves.

Key Points

- CDC recommends COVID-19 vaccination for immunocompromised individuals
- Children with cancer can mount an immune response to the COVID-19 vaccine, particularly a 3-dose series (as opposed to a 2-dose series)
- The immune response to COVID-19 vaccine varies with underlying malignancy
- Vaccine hesitancy is a barrier to COVID-19 vaccination in children with cancer

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1.2: Children with Cancer Should Receive Yearly COVID-19 Boosters

Currently, there are no official COVID-19 booster guidelines that apply specifically to children with cancer. However, both the CDC and the IDSA recommend that children who are at increased risk for severe illness from COVID-19, such as those who are immunocompromised, receive updated COVID-19 vaccinations as part of ongoing protection against the virus.[9]

According to the CDC and IDSA, children who are moderately or severely immunocompromised, which includes children with cancer, should receive a COVID-19 booster following the immunocompromised vaccination schedule.[9] For immunocompromised persons aged 6 months and older, the CDC and IDSA recommends receiving the most recent updated COVID-19 vaccine. The appropriate number of doses and the interval between them may vary depending on the child's age, medical condition, treatment plan, and previous vaccination history. These decisions are best made in consultation with the child's oncology or hematology care team to ensure optimal immune response and safety.

The administration of an updated COVID-19 vaccine may be delayed if the child recently had a COVID-19 infection. In this situation, the CDC advises waiting approximately three months after symptom onset, or three months after a positive test in asymptomatic cases, before receiving the next COVID-19 vaccine dose.[4]
As discussed above, vaccine hesitancy may impact the ability of clinicians to vaccinate their patients.

Key Points

- CDC and IDSA recommends annual COVID-19 vaccine boosters for immunocompromised individuals
- The specific dosing needs may vary with underlying malignancy and other clinical factors

1.3: Include the COVID-19 vaccine in revaccination guidance after HSCT

Patients who have recently undergone Hematopoietic Stem Cell Transplantation (HSCT) are severely immunocompromised, making them more susceptible to adverse outcomes and mortality from COVID-19 infection.[10] Additionally, HSCT wipes out existing immune memory.[11] Therefore, HSCT recipients lose immunity to infections they were previously exposed to and lose immunity to diseases they were previously vaccinated against. Therefore, HSCT recipients are vulnerable to vaccine-preventable disease post-transplant, including COVID-19, regardless of their prior vaccination status. HSCT recipients who contract COVID-19 are at risk of severe disease and mortality; 29% were admitted to the ICU and 19% in one study of 2031 adult HSCT receipients.[12]

HSCT recipients can mount a response to COVID-19 vaccination. A multicenter prospective study compared responses to the Pfizer-BioNTech BNT162b2 mRNA vaccine between HSCT recipients and healthy children.[13] Thirty-nine children (5 and 11 years who recently underwent a HSCT and thirty-five healthy children were administered 2 doses of Pfizer-BioNTech's mRNA vaccine, at 3-week intervals. Patients who contracted COVID-19 between the first and second doses were withdrawn from the study. This study found that most HSCT recipients who participated in the study demonstrated immune responses comparable to responses in the control group. The HSCT group had a median concentration of 3596 BAU/mL (a unit for measuring antibodies) compared to 3868 BAU/mL in the control group after vaccination. For some HSCT recipients, additional doses of the vaccine were needed to mount a sustainable vaccine response, demonstrating the need for individualized vaccination schedules in pediatric HSCT recipients. Of the thirty-nine children who underwent an HSCT, 15 of them received a third dose of the COVID-19 vaccine, 4-6 weeks after the second dose.

A retrospective observational study examined 93 oncology patients between the ages of 5 and 25 years [14]. Of the 93 patients, 25 were HSCT recipients and were at least 100 days post-transplant at the time of their first vaccination. Of the HSCT recipients, over 75% showed a strong ACE2 receptor blocking activity. The primary difference in viable vaccine response was found in children who were receiving chemotherapy compared to children who were not, with children who were receiving chemotherapy mounting poorer responses to the COVID-19 vaccine.

The CDC and a recent post-HSCT proposed vaccination protocol by Silva-Pinto, recommend COVID-19 vaccination for HSCT recipients, even those who were vaccinated prior to transplantation, starting approximately 12 weeks, after the transplant.[11] Of note, Silva Pinto's guidelines call for a 3 dose schedule.

Key Points

- HSCT recipients need to be revaccinated for disease preventable diseases after HSCT
- HSCT recipients can mount a response to COVID-19 vaccination
- CDC and IDSA recommend revaccinating for COVID-19

1.4: Use pre-exposure prophylaxis for children with cancer who are exposed to COVID-19 who cannot get vaccinated prior to anticipated exposures (who are 12 years and older and weigh at least 40 kg)

While COVID-19 vaccines are recommended for patients with cancer, some families may not follow that recommendation, given growing vaccine hesitancy.[15] For these children, immunization with monoclonal antibodies is a potential strategy to prevent COVID-19.

In March 2024, the U.S. Food and Drug Administration (FDA) granted Emergency Use Authorization (EUA) to Pemgarda (pemivibart), a long-acting monoclonal antibody, for use as pre-exposure prophylaxis in individuals aged 12 years and older who weigh at least 40 kg and are moderately to severely immunocompromised.[16] It is currently the only pre-exposure prophylaxis authorized for use by the FDA. The FDA specifies that individuals actively undergoing treatment for solid tumors or hematologic malignancies are eligible for Pemivibart due to moderate-to-severe immunocompromise. It also recognizes that individuals with hematologic malignancies like chronic lymphocytic leukemia (CLL), non-Hodgkin lymphoma (NHL), multiple myeloma, or acute leukemia have poor vaccine response—even while not on active treatment—and are thus eligible. According to IDSA guidelines, patients with solid tumors who completed treatment more than a year ago are considered lower-risk immunocompromised patients and may not be eligible for pemivibart use.[17]

Pemivibart's EUA was based on interim results from the Phase 3 CANOPY trial.[16] This trial consisted of two cohorts: one immunocompromised and one non-immunocompromised [18]. Non-immunocompromised participants received either pemivibart or placebo, while immunocompromised participants received only pemivibart. Doses were administered 90 days apart. Among non-immunocompromised participants, only 1.9% of pemivibart recipients developed symptomatic COVID-19 over six months, compared to 11.9% in the placebo group, representing an 84.1% relative risk reduction. Protection persisted through 12 months without redosing, with symptomatic COVID-19 rates of 4.7% in the treatment group versus 18.1% in placebo.[18] Among immunocompromised participants, the 6-month incidence of symptomatic COVID-19 was 3.7%.[18] The trial found that neutralizing antibody levels in immunocompromised participants who received pemivibart reached predefined thresholds associated with protection, based on levels observed in non-immunocompromised individuals and prior monoclonal antibody trials.[19] This allowed researchers to 'bridge' the evidence and infer likely efficacy in immunocompromised patients—a strategy known as immunobridging.

Pemivibart is administered as a 4,500 mg intravenous infusion approximately every three months.[16] It is important to note that immunocompromised patients were found to be at higher risk of serious treatment-emergent adverse events (TEAEs), with 11.4% of immunocompromised participants reporting serious TEAEs compared to only 1.9% of non-immunocompromised pemivibart recipients reporting TEAEs, including but not limited to infusion related reactions (IRRs), hypersensitivity reactions (HSRs), and flu-like symptoms.[18] Furthermore, anaphylaxis occurred in 0.6% of recipients (4 out of 623), requiring administration in a monitored healthcare setting with resuscitation equipment readily available.[16] Therefore, it will usually require children with cancer to receive the infusion at their treatment center, which may strain family and clinic resources.

Importantly, Pemivibart has retained neutralizing activity against many currently circulating COVID-19 variants, including JN.1, KP.3.1.1, XEC, and LP.8.1, according to in vitro testing conducted by Invivyd, Inc.[20] This differentiates it from an earlier pre-exposure prophylaxis, Evusheld (tixagevimab/cilgavimab), a monoclonal antibody granted EUA in December 2021 for immunocompromised adults and adolescents.[21] Evusheld initially

reduced symptomatic COVID-19 risk by approximately 77% in the PROVENT trial [22], but its EUA was revoked by the FDA in January 2023 after losing efficacy against new Omicron subvariants, including XBB.1.5 [21]. Thus, ongoing monitoring of pemivibart's effectiveness against emerging variants is critical.

While pemivibart is authorized only for individuals aged 12 and older and weighing at least 40 kg, many pediatric oncology patients meet these criteria. However, no safety or efficacy data are currently available for children under 12.[2] For eligible older children with cancer who cannot receive vaccination or mount an adequate vaccine response prior to high-risk exposures such as school attendance during community surges, pemivibart may provide benefit.

Key Points

- Pemibivibart is available for pre-exposure prophylaxis
- IDSA recommends Pemivibart for pre-exposure prophylaxis for moderately to severely immunocompromised individuals
- Pemivibart reduces rates of symptomatic COVID-19 in immunocompromised individuals
- Pemivibart is associated with treatment related adverse events, including infusion related reactions and anaphylaxis; these are more common in immunocompromised individuals
- Pemivibart is an IV infusion that needs to be given in a healthcare setting
- Pemivibart has maintained efficacy against currently circulating COVID-19 variants

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Group 2. COVID-19 Treatment

Background

This section discusses how to manage COVID-19 infection in children with cancer, focusing on treatment strategies, risk-based decision-making, and key clinical considerations across care settings

2.1: For children with cancer and symptomatic COVID-19 who are ≥ 12 years old and within 5 days of symptom onset, give Paxlovid.

Paxlovid is authorized by the U.S. Food and Drug Administration (FDA) for the treatment of mild to moderate COVID-19 in adults and pediatric patients aged 12 years and older who weigh at least 40 kg and are at high risk for progression to severe disease, including hospitalization or death.[1] The Centers for Disease Control and Prevention (CDC) similarly recommends Paxlovid for outpatient treatment in this population, provided it is initiated within 5 days of symptom onset.[2] However, this therapy is not authorized for children under 12 years of age or weighing less than 40 kg. Guidance from the Pediatric Infectious Diseases Society supports considering antiviral therapy for high-risk pediatric patients with mild to moderate COVID-19 if treatment can be initiated within 5 days of symptom onset. [3] However, this guidance does not specifically address use in children under 12 years of age

These initial recommendations were based on studies showing that Paxlovid reduces hospitalization rates and mortality in high risk adults. In a meta-analysis of 3 randomized control trials, one prospective cohort study, and 25 retrospective cohort studies, the groups receiving Paxlovid had significantly lower rates of hospitalization (RR = 0.53; 95% CI: 0.24-0.69, $p < 0.001$), all-cause mortality (RR = 0.36; 95% CI: 0.27-0.50, $p < 0.001$), intensive care unit admission (RR = 0.45; 95% CI: 0.27-0.73, $p = 0.001$), and emergency department visits (RR = 0.67; 95% CI: 0.54-0.83, $p < 0.001$) compared to control groups. Additionally, the Paxlovid group had shorter duration of hospitalization. [4] However, not all data supports the impact of Paxlovid on COVID-19 outcomes. In an open-label randomized control trial of 264 adults in China with severe co-morbidities and COVID-19, there were no significant differences in mortality or time to COVID-19 viral clearance in the treatment and the control arm.

However, most of the initial studies were conducted in adults with limited data in children, however, initial approvals included approval for children 12 years and older and were largely based on suppositions that adolescent and adult physiology and pharmacokinetics would be similar. There is scant data in children, particularly in children less than 12 years of age. A 2022 study examined the feasibility, safety, and efficacy of Paxlovid in children 6-14.[5] This study included 5 children with COVID-19 who were treated with Paxlovid and 30 matched controls who were not treated with Paxlovid. Paxlovid was initiated within 5 days of symptom onset in all 5 children with minimal adverse events after initiation. One child had diarrhea and another had elevation in liver enzymes after Paxlovid initiation. Clearance of viral shedding was not different between treatment and control groups. In clinical practice, if a child with cancer develops symptomatic COVID-19, presents within the early

treatment window, Paxlovid may be considered under a case-by-case framework—particularly if other therapeutic options are limited or harder to come by. A 2025 cohort study involving 30 children with severe or critical COVID-19 with a mean age of 7.5 years (SD: 4.6 years), showed that children treated with Paxlovid experienced significantly shorter times to viral clearance (4.9 vs. 11.0 days), fever resolution (11.2 vs. 16.4 days), and overall symptom recovery (4.6 vs. 17.6 days) compared to matched controls. Importantly, the incidence of adverse events was equal in both groups at 16.7%, with no serious adverse events reported [7]. Most children in the study had underlying medical conditions, including immunocompromised states, indicating that early antiviral therapy with Paxlovid may be a safe and effective option for treating severe COVID-19 in children, including those less than 12 years old. However, there is no FDA approved treatment option for this group.

Concerns for the use of Paxlovid in younger children include the lack of comprehensive pharmacokinetic and safety data, the high potential for drug-drug interactions due to the ritonavir component, and the possibility of altered liver or kidney function in children undergoing chemotherapy. Paxlovid is known to interact with several common medications, including immunosuppressants and antifungals frequently used in oncology, which may complicate treatment decisions and necessitate careful pharmacologic review [8].

Key Points

- Paxlovid is FDA- and CDC-approved for high-risk patients ≥12 years and ≥40 kg
- Most studies show Paxlovid reduces rates of hospitalization, ICU admission, and death in high risk adults with COVID-19
- There is limited data about Paxlovid in children, particularly young children
- Observational data suggest that early Paxlovid use in high-risk children under 12, including those with cancer, may shorten time to viral clearance and symptom duration with few adverse events.

2.2: For children hospitalized with cancer who are ≥ 28 days and ≥ 3 kilos, who have symptomatic COVID-19 (even if COVID-19 was not the primary reason for their hospitalization), give remdesivir if can be given within 7 days of symptom onset.

2.3: For children with symptomatic COVID-19 who are outpatient, have co-morbid risk factors (e.g., respiratory disease, obesity), unvaccinated, and within 7 days of symptom onset, give remdesivir

2.4: For children within 100 days of allotransplant with COVID-19, give remdesivir

Remdesivir is a nucleotide analog that inhibits the SARS-CoV-2 RNA-dependent RNA polymerase and is currently the only FDA-approved antiviral authorized for pediatric patients aged ≥28 days and ≥3 kg.[9] It can be used in both the inpatient and outpatient setting (unlike Paxlovid), which is only approved in the outpatient setting. Further, it has been approved down to 28 days and 3 kilograms, which means some patients not eligible for Paxlovid can have Remdesivir. In a 2020 randomized controlled trial of 1,062 hospitalized adults, remdesivir was associated with a shorter time to recovery compared with placebo.[10,11] Therefore, Remdesivir is recommended by the IDSA for adults with mild moderate COVID-19 at increased risk for progression to severe disease, including adults with hematologic malignancies and those with solid tumors on immunosuppressive therapy. [12] Additionally, Remdesivir is recommended for adults with severe COVID-19.

However, data for remdesivir use in children is limited, as no randomized controlled trials have evaluated its use in children hospitalized with COVID-19. A single arm open-label study of 77 children who received remdesivir showed tolerability and low incidence of serious side effects. [9] Similarly, the 2024 Gilead Sciences (CARAVAN) trial evaluating remdesivir in children <18 years showed that pediatric dosing produced pharmacokinetic data similar to adults and demonstrated 85% clinical improvement at the last assessment, with no serious safety concerns.[9] In the compassionate-use cohort, 16% of children experienced serious adverse events, though most were related to complications of COVID-19 infection or underlying comorbidities.[13] Reported adverse effects of remdesivir include nausea, vomiting, and elevations in liver enzymes. Rare events such as sinus bradycardia have also been noted in children.[14]

Children with risk factors for progression to severe infection can receive nirmatrelvir/ritonavir (Paxlovid) for 5 days orally or remdesivir for 3 days intravenously. Remdesivir requires early administration—generally within 5–7 days of symptom onset—to be effective.[15] For children who are hospitalized, remdesivir is recommended when there is confirmed severe COVID-19 infection and/or a new need for supplemental oxygen. [10] In these cases, remdesivir is recommended for 5 days or until inpatient discharge. If oxygen needs are greater, including high-flow nasal cannula or non-invasive ventilation, a combination of remdesivir and dexamethasone is recommended. However, less stringent criteria for use in children with cancer (e.g., use even if they do not require supplement oxygen) may be prudent given the risk for progression to severe COVID-19 infection.

Remdesivir's role in outpatient management was demonstrated in the adult PINETREE trial. A three-day course of Remdesivir initiated early in the course of infection provided an 87% reduction in hospitalization.[6] These results formed the basis for extending outpatient treatment to high-risk children, including those with cancer. The pediatric safety data was cited above.

Additional data supports Remdesivir's utility in the outpatient setting: A 2023 retrospective cohort at Texas Children's Hospital evaluated 187 high-risk pediatric outpatients treated with the three-day remdesivir regimen and found it to be safe, feasible, and well tolerated. All patients were treated within seven days of symptom onset, and no serious adverse events and post-treatment hospitalizations occurred; only mild infusion-related symptoms and transient laboratory abnormalities were reported.[16] Although limited by its single-center, retrospective design and lack of vaccination data, the study provides real-world support for outpatient remdesivir use in medically complex children.

Based on these findings, the NIH, CDC, and IDSA recommend a three-day outpatient remdesivir regimen for non-hospitalized children at high risk for progression to severe disease.[17,10] Oral antiviral options, such as nirmatrelvir/ritonavir, are limited to children ≥12 years and ≥40 kg and carry significant drug–drug interaction concerns, making them unsuitable for many younger, unvaccinated, or medically complex children. Remdesivir is therefore the primary antiviral option for outpatient pediatric patients who are not eligible for oral therapy. [2] Despite these findings, clinical and logistical challenges remain. There are no large randomized controlled trials evaluating the outpatient effectiveness of remdesivir in pediatric cancer patients, and much of its use in this population is derived from retrospective adult outpatient data, and open-label pediatric pharmacokinetic studies. In addition, remdesivir requires three consecutive intravenous infusions, which may be impractical for families with limited transportation, insurance barriers, or lack of access to pediatric infusion centers.[18] Nonetheless, remdesivir remains the most evidence-supported intravenous antiviral option for high-risk pediatric outpatients who are ineligible for oral agents and remain vulnerable to severe COVID-19 outcomes.

For patients after HSCT, a study on remdesivir-associated outcomes among immunocompromised patients in the omicron-dominant era, remdesivir was associated with lower mortality rates in subgroups of patients with cancer, hematological malignancies, and solid organ or hematopoietic stem cell transplants.[19] In another study, remdesivir was associated with lower odds of hospital readmission in immunocompromised patients.[20] A narrative review of remdesivir use in patients with hematologic malignancies also found that remdesivir is the preferred treatment for high-risk patients.[21] Specifically, the review identified that remdesivir is the most appropriate treatment for recipients of allogenic HSCT or CAR T cell therapy with COVID-19. These studies, however, only included immunocompromised adult patients. There is limited research on the safety and efficacy of remdesivir in pediatric patients within 100 days of allotransplant.

Key Points

- Remdesivir is generally safe and effective for use in children with COVID-19
- Data from CARAVAN trial and other studies show similar pharmacokinetics in adults and children with few serious drug-related events, and improved clinical outcomes.
- Remdesivir is approved for hospitalized children with severe COVID-19 with or without a new oxygen requirement
- It may be prudent to use less stringent criteria for Remdesivir administration in hospitalized children with cancer and COVID-19 given their risk for progression to severe disease
- Remdesivir may reduce rates of hospitalization among high risk children with COVD-19 in the outpatient setting
- Remdesivir is considered the preferred treatment regime for high risk patients with COVID-19, including patients after HSCT
- There may be logistical challenges in administering Remdesivir in the outpatient setting, given the requirement for IV administration for 3 days
- Remdesivir is the main FDA-approved outpatient antiviral for children ≥28 days and ≥3 kg, with safety and effectiveness supported by pediatric data.
- Early initiation within seven days of symptom onset is recommended
- Given that Remdesivir is IV and requires 3 days of administration, there may be challenges with access

2.5: Follow the IDSA or CDC recommendations for administration of COVID-19 treatments beyond remdesivir and Paxlovid (e.g., glucocorticoids for the critically ill).

The Infectious Diseases Society of America (IDSA) and the Centers for Disease Control and Prevention (CDC) provide current guidance for managing COVID-19. For cases requiring treatment beyond standard antivirals like remdesivir and nirmatrelvir/ritonavir (Paxlovid), clinicians should follow the latest recommendations from either organization for the treatment of children with severe COVID-19. These include the use of additional agents—such as glucocorticoids and select immunomodulators—for patients with severe or critical illnesses, where excessive inflammation contributes to tissue damage and anti-inflammatory therapies have shown benefit in adults.[10] Given the rapidly evolving data on COVID-19 and the changes of COVID-19 strains, specific guidelines beyond Paxlovid and Remdesivir are hard to develop.

Many therapeutic options exist beyond remdesivir and Paxlovid such as tocilizumab, baricitinib, and tofacitinib. [22] However, it is a rapidly evolving field with limited pediatric data, it is not possible to develop specific guidelines for treating children at this time. Most data supporting these treatments come from adult studies, and pediatric research remains ongoing. Clinical decisions should weigh disease severity, immune status, age specific approvals, and the latest IDSA and CDC guidance to ensure safe and evidence-based management of COVID-19 across all populations. [23]

Key Points

- CDC and IDSA guidance supports antivirals and, in severe pediatric cases, selected anti-inflammatory or immunomodulatory therapies.
- Evidence for treatments beyond remdesivir and Paxlovid in children is limited and largely based on adult data.
- Management should be individualized using disease severity, immune status, and current national recommendations.

2.6: Consider testing for MIS-C based on clinical scenario

Multisystem Inflammatory Syndrome in Children (MIS-C) is a rare but serious post-COVID-19 complication observed in the children with COVID-19. Children with cancer appear to be at a higher risk of developing MIS-C compared to the general pediatric population (1.2% of infected children with cancer vs. 0.6% in the general pediatric population).[24] The syndrome typically presents several weeks after an acute COVID-19 infection, underscoring the importance of maintaining a high index of suspicion in recently infected patients, particularly those who are immunocompromised or have underlying malignancies.

The diagnosis of MIS-C requires meeting specific clinical and laboratory criteria. Clinically, the following must be present: a subjective or documented fever (temperature >38°C), illness severe enough to require hospitalization or resulting in death, evidence of systemic inflammation with a C-reactive protein (CRP) level >3.0 mg/dL, and new onset organ involvement in at least two systems. These organ manifestations may include cardiac involvement (left ventricular ejection fraction <55%; coronary artery dilation, aneurysm, or ectasia; or elevated troponin), mucocutaneous findings (rash, oral mucosal inflammation, conjunctivitis, or extremity changes), shock, gastrointestinal symptoms (abdominal pain, vomiting, or diarrhea), or hematologic abnormalities (platelet count <150,000 cells/μL or absolute lymphocyte count <1000 cells/μL). The patient must be under 21 years of age, and other plausible diagnoses must be excluded. Laboratory confirmation of COVID-19 infection through RNA PCR, antigen, or antibody detection is also required.[25]

Of note, the incidence of MIS-C has decreased from early in the COVID-19 pandemic, but occasional cases are still occurring. The CDC reported an increase in cases in the fall of 2023, corresponding to increased rates of COVID-19 at that time. Among 117 patients (https://www.cdc.gov/mis/about/index.html) identified, approximately half required ICU level care; many of the children with MIS-C were unvaccinated or had been vaccinated but likely had waning immunity based on timing of their previous COVID-19 vaccine.[26]

Since an MIS-C diagnosis must be made with the exclusion of alternative diagnoses, it is difficult to diagnose in children with cancer. The varied clinical presentations of MIS-C often overlap with other infections common in immunosuppressed children.[27] Furthermore, gastrointestinal symptoms and cardiac dysfunction associated with MIS-C are also associated with some chemotherapies. Therefore, a diagnosis of MIS-C in children with cancer requires a high index of suspicion.

A diagnosis of MIS-C in pediatric cancer patients may be important due to the poor outcomes associated with MIS-C. In a study conducted of children with cancer and COVID-19, patients with MIS-C had higher odds of hospitalization (OR, 42.9) and intensive care unit admission (OR, 11.4). Furthermore, COVID-19 contributed to the death of children with MIS-C more often than children without MIS-C (20.1% vs. 1.0%) [24]. Further, knowing if a child with cancer has MIS-C is important for directing and making decisions for their ongoing medical treatment.

Key Points

- MIS-C is a rare but potentially serious complication of COVID in children
- Although MIS-C rates have decreased later during the pandemic, it still occurs
- Children with cancer have a higher risk of developing MIS-C after COVID-19 compared to the general pediatric population.
- Diagnosis is challenging due to overlapping symptoms with infections and chemotherapy effects, requiring careful clinical and laboratory evaluation.
- MIS-C in pediatric cancer patients is associated with higher hospitalization, ICU admission, and mortality, making early recognition critical for management.

2.7: Do not use post-exposure prophylaxis for children with cancer undergoing chemotherapy.

Current guidance from the Centers for Disease Control and Prevention (CDC) and the Infectious Diseases Society of America (IDSA) does not support the use of post-exposure prophylaxis (PEP) for COVID-19 in children who have undergone, or are receiving, cancer treatment, or have undergone allogeneic hematopoietic cell transplantation (allo-HCT). These patients are immunocompromised, therefore, preventive and early therapeutic strategies are essential.[28] Earlier in the pandemic, monoclonal antibodies such as casirivimab and imdevimab (REGEN-COV) were available under an Emergency Use Authorization (EUA) from the U.S. Food and Drug Administration (FDA) for both adults and adolescents at increased risk for severe COVID-19. However, the EUA was revoked in 2024 after accumulating evidence demonstrated that circulating COVID-19 variants, particularly Omicron lineages, were no longer susceptible to the therapy. The FDA stated that "REGEN-COV is not authorized for use in any U.S. region at this time because of the high frequency of the Omicron variant, which is not susceptible to the antibody".[29]

The original authorization was based on an early clinical trial data that showed REGEN-COV could reduce symptomatic COVID-19 cases by up to 81% among household contacts of infected individuals.[30] These studies supported its short-term benefit during the pre-Omicron era, when variants remained sensitive to neutralization by the antibody. However, subsequent laboratory and epidemiologic data confirmed that these antibodies lost activity against newer variants, leading both the FDA and IDSA to conclude that monoclonal antibody therapy was no longer an effective preventive tool.

Current IDSA guidelines recommend against the use of casirivimab/imdevimab for post-exposure prophylaxis, stating that monoclonal antibody therapy "should not be used" in areas where circulating variants are resistant.[10] The CDC echoes this position, emphasizing the importance of maintaining up-to-date vaccination, implementing serial testing after exposure, and initiating antiviral treatment such as remdesivir promptly if infection develops.[2]

Key Points

- Early antibody therapies worked as post-exposure prophylaxis in the pre-Omicron era
- In the post-omicron era, monoclonal antibody PEP has been less effective
- FDA revoked PEP emergency use authorization in 2024 due to data about its lack of efficacy against the later strains

2.8: Do not use post-exposure prophylaxis for children with cancer after allotransplant.

Current guidance from the Centers for Disease Control and Prevention (CDC) and the Infectious Diseases Society of America (IDSA) does not support the use of post-exposure prophylaxis (PEP) for COVID-19 in children who have undergone allogeneic hematopoietic cell transplantation (allo-HCT). These children are considered immunocompromised, making prevention and early treatment important. The CDC outlines that "pre-exposure prophylaxis (prevention) medication is available for some people who are moderately or severely immunocompromised" but explicitly notes that this medication—pemivibart (Pemgarda™)—"is not authorized for treatment of COVID-19, or for post-exposure prophylaxis of COVID-19 in individuals who have been exposed to someone infected with SARS-CoV-2".[31]

The IDSA's 2025 COVID-19 management update mirrors this stance, recommending pre-exposure prophylaxis (PrEP) for immunocompromised individuals when circulating variants remain susceptible, but it provides no recommendation for PEP. Their guideline specifies that PrEP with pemivibart may be considered "when predominant regional variants are remain susceptible (conditional recommendation, low certainty of evidence)".[17] The rationale for this limited recommendation reflects ongoing uncertainty about monoclonal antibody effectiveness as variants evolve, as well as a lack of evidence supporting post-exposure prophylaxis. Research supports these cautious positions. Immunocompromised children demonstrate markedly lower immune responses to vaccination. In one meta-analysis, seropositivity rates after vaccination were only 30.7% in solid-organ transplant recipients and 50% in those with hematologic malignancies, compared with 92.4% among immunocompetent individuals.[32] This reduced response underscores why a layered prevention approach—vaccination, careful exposure monitoring, infection-control practices, and early treatment when infection occurs—is more reliable than unapproved post-exposure interventions.

Current data and national guidelines show that post-exposure prophylaxis should not be used for children after allogeneic transplant. Scientific evidence shows that monoclonal antibody-based prophylaxis has not demonstrated consistent effectiveness against circulating variants, and no product has received FDA approval for post-exposure use. The focus should instead remain on up-to-date vaccination, eligibility-based pre-exposure prophylaxis, serial testing after exposure, and timely antiviral treatment if infection develops.

Key Point

- CDC and IDSA do not recommend COVID-19 post-exposure prophylaxis for children after allogeneic transplant; pemivibart is authorized only for pre-exposure use.

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Group 3. Cancer Treatment

Background

This section discusses how to manage chemotherapy treatment in the setting of COVID-19 infection among children undergoing treatment for cancer.

3.1: Continue to dose-adjust and hold chemotherapy per chemotherapy protocols when children with cancer have COVID-19

3.2: Do not hold chemotherapy in a child with cancer and COVID-19, if meets criteria to continue as scheduled in the protocol AND

(1) has mild COVID-19
(2) are not hospitalized for COVID-19
(3) Does not have comorbidities,
AND
(4) are < 11 years old.

3.3: Consider holding chemotherapy for 48 hours in children with cancer and COVID-19 who are ≥ 11 years old or have comorbidities

Evidence for the three statements above is intertwined, thus summarized jointly below.

Dose intensity: Thanks to innovations in therapy and risk stratification, overall survival in children with cancer has increased consistently over the last five decades, now hovering around 80%.[1] Dose inensity is how much chemotherapy is given over a given time frame. Increasing dose intensity has played in integral role in this incrase in survival. Although increased dose intensity is associated with increases in survival, it is also associated with

increased toxicities. However the change in survival and toxicities varies between children and adults as well as with cancer diagnosis.[2] Dose intensity decreases when chemotherapy is held or reduced.

Impact of Dose Adjustment and Treatment Interruptions: Receiving less than the prescribed dose iin a chemotherapy regime is associated with an increased risk of relapse, with nuances across diseases. Two-year disease-free survival in a late-1980s cohort of children and young adults with osteosarcoma was superior in patients who received ≥80% of the scheduled dose-intensity than those who received less (87% vs. 65%, p<0.01),[3] and 10-year disease-free survival (adjusting for clinical and surgical factors along with disease response) was superior among those who received ≥90% of scheduled dose-intensity (76.5% v.s. 57.3%; p<0.02).[4] In a meta-analysis of 17 studies with 23 arms (2257 patients, 1976 to 2006), 5 year event free survival was superior with higher delivered dose intensity of methotrexate and ifosfamide.[5] In Ewing Sarcoma, 5-year event free survival was associated with the percentage of the protocol dose of Vincristine (low dose reductions: 95% [CI 75-100] vs. high dose reductios: 39% [CI 18-63]) and Dactinomycin (higher intensity/less reductions: 94% [CI 73-100], lower intensity/more reductions: 48% [CI 25-75].[6] Wilms Tumor investigators worked to optimize dose intensity without increasing hematologic toxicities.[7] In low-grade Hodgkin Lymphoma, actuarial survival was not associated with dose intensity,[8] although the methods of measuring dose intensity are unclear._Among 209 children with with acute lymphoblastic leukemia unfavorable features in the early 1980s, the percentage of prescribed therapy (vincristine, asparaginase, anthracycline) they received was associataed with having a subsequent disease relapse; children receiving less therapy (in the middle and lower tertiles of the percentage of therapy received) were 3 and 5 times more likely to relapse had a than were those in the upper tertile (P = 0.025, test for trend).[9] In a multisite Children's Oncology Group study (94 sites; 2004-2009), Bhatia et al monitored 6MP adherence in ALL (median age: 6y, range 1-21y [R01 CA096670]) using electronic 6MP monitoring (MEMS);[10–12] patients who took <95% of prescribed doses of 6MP had a higher risk of relapse than patients whose adherence rates were ≥95% (HR range from 3.6 to 5.5, with p-values ranging from 0.002 to 0.05)[10] and adherence rates <90% associated with increased relapse risk (HR=3.9; P = .01).[10–12] While prescribed dose intensity itself (above the protocol-identified dose) had varying associations with outcomes,[13] taking less than the protocol-prescribed dose was associated with relapse as above. Among children who did take ≥95% of prescribed 6MP doses, high intra-individual variability in metabolite (TGN) levels contributed to increased relapse risk (HR= 4.4; 95% CI, 1.2-15.7; P = .02). These adherers with varying TGN levels also had varying 6MP dose intensity (OR=4.5; 95% CI, 1.5-13.4; P = .01) and 6MP drug interruptions (OR, 10.2; 95% CI, 2.2-48.3; P = .003).[11]

Chemotherapy interruptions for viral infections: There are no specific studies that have examined the impct of interruptions in cancer-directed therapy in the setting of COVID-19 or other viral infections on disease survival.

COVID-19 and Disease Severity Among Children with Cancer: On page 6, we described the general clincal course of childrne with cancer and COVID-19 infection; here we focus on which groups are at risk for more severe clincal courses.Most of the data on the clinical course of COVId-19 among children with cancer comes from the POCC cohort (as described early). Early in the pandemic, among 917 children (≤21y) from 94 institutions, children with hematologic malignancies were at increased risk for hospitalization (RR=1.6, 95%CI 1.3-2.1 as were children with ANC <500 (RR=1.4, 95%CI 1.2-1.7) and those with public insurance (OR=1.3, 95%CI=1.04-1.7).Children with at least one comorbidity were at increased risk of hospitalization (RR=1.3, 95%CI 1.1-1.6) and ICU admission (RR=2.3, 95%CI 1.5-3.6). Children ≥11yo had an increased risk of ICU admission (RR=1.8, 95%CI 1.1-2.9) with a trend towards an increased risk of hospitalization (RR=1.2, 95%CI 1.0-1.5).[14] Over the course of the pandemic, these analyses were extended to sub-groups. Children with hematologic malignancies and Down Syndrome had higher odds of hospitalization (OR=2.8, 95%CI 1.53-5.14), ICU admission (OR=4.2, 95%CI 1.9-9.1), and need for respiratory support (OR=4.2, 95%CI 2.0-8.8) than children with cancer and COVID-19 infections without Down Syndrome.[15] Among adolescents and young adults (n=831), those 15-21yo had lower odds of ICU admission than those 22-39yo in multivariable analyses.[16] Comparing children with acute lymphoblastic leukemia in maintenance therapy (n=1,190) to other children, those with the higher odds of hospitalization was associated with Hispanic ehtnicity (OR=1.54, 95%CI1.2-2.0), public or no insurance and public or no insurance (OR=1.49, 95%CI 1.2-1.9). Having an ANC <500

was associated with hospitalization (OR=35 , 95%CI 2.6-4.6) but not ICU admission. Comorbid conditions were associated with both increased hospitalization (OR=1.7, 95%CI 1.4-2.2and ICU admission (OR=3.5, CI 2.2- 5.6)

Other Viruses and Disease Severity Among Children with Cancer: In adults with cancer, RSV infection leads to lower respiratory tract infections in up to 60% of subjects. [17–20] Among those that develop a lower respiratory tract infection, , mortality rates range between 50% and 100%.[17–20] St. Jude reviewed 58 RSV infections among chidlren receiving cancer treatment or BMT over 8 consecutive RSV seasons including (19% solid tumors, 40% acute lymphoblastic leukemia 41% acute myeloid leukemia, BMT, or SCID).[21] All the deaths were in children with lower respiratory tract infections, all of which were children before or after BMT or children <2yo who were receiving therapy for acute myeloid leukemia (AML). Lower respiratory tract infections (28% of total) were more common in children wtih AML/BMT/SCID. Independent predictors of lower respiratory tract infections were profound lymphopenia (<100 cells/mm3) and age <2yo; neutropenia was not a predictor. Co-infection was rare (7%) and limited to BMT/AML/SCID patients with parainfluenza or aspergillus. In a cohort of young (<4yo) otherwise healthy children, co-infection increased the odds of lower tract disease and acute illness.

Non-neutropenic fever and/or infection in chidlren with cancer: While evidence-based guidelines regarding management of neutropenic fever (including approach to risk stratifying) in children receiving cancer-directed therapy or BMT have been endorsed by Children's Oncology Group and are updated iteratively over time,[22] there are no defined evidence-based guidelines regarding non-neutropenic fever (or afebrile illnesses). However, the Esbenshade Vanderbilt (EsVan) models accurately predicts bloodstream infection risk in febrile non-neutropenic (ANC ≥500) children with cancer.[23–25] The final prospective evaluation of the model evaluated 2,565 episodes of non-neutropenic fevers, with 4.7% bloodstream infections, rare complications, and only one potential infection-related death.[25] Each model includes a different array of varaibles, with all except the initial EsVan model including "exposure to chemotherapy within 24 hours of fever presentation that causes fever,"[25] thus the chemotherapy administration preceeded the fever. With this in mind, the EsVan models are helpful to consider chemotherapy administration in the setting of an afebrile or uncomplicated viral infection such as SARSCoV2. The variables included in the most predictve model (EsVan2b) include: type of central venous catheter, hypotension, shaking chills, BMT, upper respiratory infection sytmptoms, age, maximum fever, ANC. However, they do not include diagnosis of any specifric viruses (COVID-19, influenza, etc).

Treatment and Supportive Care in Pediatric Oncology is Highly Protocolized: It is key to consider the way in which two general characteristics of the field of pediatric oncology are relevant to devloping or changing strategies for care management, specifically (i) it is *highly protocolized*, and (ii) *there is a strong research culture*. Essentially research and clinical care are *highly integrated*.[26] The 'strong research culture'[29] likely stems from how rare childhood cancer is compared with adult cancer, coupled with the inability for adult research to be generalized to children.[27] This culture is reflected in the availability of collaborative cooperative group Phase III studies for many diagnoses[26] (and earlier phase trials). It is considered standard of care to offer a trial if one is available. When a child does not enroll on a trial, pediatric oncologists treat with *best available treatment protocols*,[26,28] which are usually the standard arm of the most recent trial.[26,28] These protocols also include recommendations and/or requirements for supportive care. When evidence-based clinical practice guidelines are not available, clinicians most often refer to these protocol recommendations for guidance re chemotherapy administration in the face of hematologic and non-hematologic toxicities. Because hematologic toxicities are a common side effect of cancer-directed therapy, chemotherapy is often temporarily held or doses reduced in the face of neutropenia and/or thromobocytopenia to avoid short-term (infectious and/or bleeding) and long-term (marrow injury) complications.[29] Pediatric cancer protocols provide clear guidelines as to what laboratory evidence of bone marrow suppression (ANC, PLT usually) would warrant pausing chemotherapy until the marrow had recovered. The protocols also provide clear guidance as to management of chemotherapy in the face of non-hematologic toxicities (infectious toxicities, transaminitis, hyperbilirubinemia, seizures, neuropathy, etc.). While these may include recommendations according to how far above/below the upper

limits of normal a laboratory value is, it may also include guidance according to CTCAE grading (NCI Common Toxicity Grading Criteria for Adverse Events).[30]

One example of recommendations regarding infectious complications is provided here from the currently active high-risk acute lymphoblastic leukemia trial (AALL1732): "Infectious toxicities: Do not interrupt inotuzumab ozogamicin dosing for uncomplicated fever or febrile neutropenia. Dosing may be held for severe infection at the discretion of the treating physician. If doses are held for infection, they should be resumed/made up when severe symptoms have improved prior to Day 22. Doses delayed beyond Day 22 should be omitted. There are no modifications to inotuzumab ozogamicin dosing in InO Block 2 if dosing was delayed or omitted due to infection in InO Block 1."

Key Points

- Dose intensity is a cornerstone of the incrase in survival among children with cancer
- Redductions or interruptions in chemotherapy increase relapse risk across many pediatric cancers.
- Subsets of children, including those >11 and those with comorobidites are at risk of severe COVID-19 .
- Evidence strongly supports adherence to protocol-prescribed dosing, with lower delivered doses consistently linked to worse survival outcomes
- Pediatric oncology care is highly protocol-driven, and chemotherapy decisions during infections should follow established trial or protocol guidance.

3.4: Consider doing lumbar punctures (LPs) awake for children with cancer and COVID-19 who would be due for LPs but can not receive them with sedation due to institutional protocols.

Lumbar punctures (LPs) are procedures used diagnostically and therapeutically in children with cancer. In diseases where malignant cells can be identified in the central spinal fluid (CSF), e.g. brain tumors, leukemias, lymphoma, LPs are often part of the initial diagnostic staging work-up. LPs can also be used to introduce chemotherapy into the intrathecal space for therapeutic or prophylactic purposes. Patients with acute lymphoblastic leukemia (ALL) may receive more than 20 LPs to deliver intrathecal chemotherapy.
Among children with cancer, LPs are usually performed under general anesthesia, most commonly propofol. In a retrospective study of 48 hospitals in the Pediatric Health Information Systems (PHIS) between October 2015 and December 2019, Wright et al identified that intravenous and inhaled anesthetics were used in 98.2% of lumbar puncture procedures among patients with Acute Lymphoblastic Leukemia (ALL[31]). Propofol was the most common anesthetic, representing 80% of cases.

Institutions may have protocols that limit the administration of anesthesia in the setting of respiratory viral illnesses, such as COVID-19 due to both concerns about poor outcomes with anesthesia in these settings, risk the medical team contracting COVID-19, and other infection control concerns Consequently, these protocols may interfere with the planned administration of intrathecal chemotherapy in a patient with COVID-19.
Recently, there has been increased interest in minimizing the use of general anesthesia for LPs as anesthesia itself can lead to longer term cognitive dysfunction in pediatric cancer survivors.[32] Because of this, studies have now demonstrated that focused interventions can safely improve the rates of LPs without using general anesthesia. [33] Waters et al. offered patients who could remain still during a simulated LP the option of doing a LP with a topical anesthetic, and the option for an oral or IV anxiolytic (lorazepam, 0.05 mg/kg PO/IV, max dose 2mg, or midazolam, 0.2mg/kg po, max dose 20 mg) which most patients received.[34] At baseline, 100% of patients had their LPs performed "with sedation" (not defined). After the quality improvement intervention, that number dropped to 48%. Berko et al. reduced the rate of GA (defined as IV propofol or an inhaled flurane) from 73.1% (baseline) to 55.6% (post quality improvement intervention) among patients ages 1-25 at any stage of treatment.[35] Alternatives to GA were moderate sedation (defined as IV fentanyl (maximum 2 mcg/kg dosing for analgesia) and midazolam (maximum 0.1 mg/kg for anxiolysis)) or mild sedation (defined as IV or oral midazolam only). The breakdown of mild vs. moderate sedation and the use of local anesthesia was not reported in the published abstract.

Key Points

- LPs are often delayed during COVID-19 due to anesthesia restrictions, which can disrupt planned intrathecal chemotherapy.
- Evidence supports that it is possible to perform LPs without general anesthesia using local anesthetic and mild/moderate sedation when needed.

3.5: If lumbar punctures are postponed due to COVID-19, ensure that patients receive the planned total number of lumbar punctures during their therapy.

Early treatment for pediatric Acute Lymphoblastic Leukemia (ALL) did not include central nervous system (CNS) directed therapy, resulting in frequent relapses in the CNS. Consequently, prophylactic treatment of the CNS became a backbone of therapy. [36] Over time, the use of long-term intrathecal chemotherapy (ITC) has been shown to have similar outcomes to radiation therapy (+/- short term intrathecal chemotherapy) with less toxicity for both B cell and T cell ALL.[37] Currently, the overall survival of children diagnosed with ALL is now greater than 90%. However, involvement of the CNS in the setting of relapse continues to occur in 30-40% of relapses.[38]

Adherence to protocol therapy is essential to maintaining predicted outcomes. However, Hashmi et al reported on 110 patients who had both ALL and COVID-19.[39] Among this group, 96 (87%) had disruptions in their treatment, regardless of the severity of their COVID-19 disease.[39] Data specific to interruption of ITC was not provided. Among patients followed in the "POCC Report", patients with hematologic malignancies were more likely to have changes to their cancer directed treatment (Johnston et al) and over 50% of children with ALL had their treatment modified during maintenance (Kahn et al).[14,40] An analysis of a subset of patients with ALL in maintenance for whom there was information about length of treatment delay and reason for treatment delay, it was identified that ITC was the only component of treatment that was delayed.[40]

Although data on outcomes related to protocol changes in the setting of COVID-19 are not available the following data provides support for maintaining the higher intensity ITC treatment plan specifically.

- In 1998, Pui et al demonstrated that early intensification of intrathecal chemotherapy demonstrated a significant decrease in central nervous system relapses in children with acute lymphoblastic leukemia (cumulative risk of an isolated CNS relapse at 5 years post-remission was 1.2% (95% confidence interval, 0% to 2.9%) and of any CNS relapse was 3.2% (0.4% to 6.0%).[41]
- Among 1251 children with ALL in an Australian cohort, 95 experienced methotrexate neurotoxicity. The 5-year CNS relapse-free survival was 89% when ITC was permanently discontinued and/or replaced with a different agent after a symptomatic neurotoxicity episode, compared with 95% if patients continued to receive protocol-prescribed doses of intrathecal methotrexate (P=.047).[42]
- Paul et al evaluated 150 patients, aged 18 years and older, diagnosed with Ph+ ALL. Outcomes were compared between patients who had received ≤ 8 ITC vs. those who received >8 (median 12). After adjusting for the follow-up time, the multi-variable analysis showed that >8 prophylactic ITC was significantly associated with decreased rate of CNS relapse (p = 0.03; HR = 0.104, 95% CI:0.001–0.801).[43]

Key Points

- CNS-directed intrathecal chemotherapy is essential in ALL, as inadequate CNS therapy is associated with high rates of CNS relapse.
- COVID-19 commonly disrupted ALL therapy, with intrathecal chemotherapy being the most frequently delayed component, especially during maintenance.
- Evidence supports completing the full planned number of LPs/intrathecal chemotherapy administrations, as higher intensity and continuation of protocol-prescribed intrathecal chemotherapy are associated with lower CNS relapse rates.

3.6: Treat children with cancer and COVID-19 per institutional guidelines for fever and neutropenia

Febrile neutropenia is a common complication of cancer treatment and can lead to hypotension, renal injury, respiratory failure, and death.[44,45] Therefore, guidelines for the management of febrile neutropenia have been published multiple times.[46–48] Traditionally, all children receiving cancer directed therapy with febrile neutropenia were admitted for parental antibiotics until they were afebrile, had improved neutrophil counts, and had negative cultures for at least 48 hours given the high risk of bacterial infection, sepsis, and death.[46] However, guidelines have evolved over time as we better understand who is most at risk of serious bacterial infection poor outcomes with febrile neutropenia.[45,47,49] Many programs now have protocols for managing low risk febrile neutropenia (patients at low risk of severe bacterial infection) outpatient and other programs for admitting and then stepping down to outpatient management when additionally low risk criteria are met.[46,49] Respiratory viral infections, including COVID-19, can also cause fever andbone marrow suppression.. Studies have found 30- 60% of children admitted with febrile neutropenia have a respiratory virus.[50,51]However, the presence of a documented respiratory viral infection does not mean a child cannot also have a bacterial infection. For instance, one Australian and Swedish study of 90 patients with febrile neutropenia found that 10 patients (or 11%) had a documented respiratory virus (by PCR or NPA) as well as a positive blood culture for bacteria.[51] This was similar to what was found in children with leukemia with culture-positive bacterial infections; half also had a respiratory viral infection.[52]

There is less data about co-infection with bacteria and COVID-19. One meta-analysis early in the pandemic, showed that bacterial co-infection (diagnosed at time of COVID-19 presentation) was present in 3.5% of patients;[53] more recent data continues to show co-infection rates among 2-10% of patients admitted with COVID-19.[54] However, those meta-analysis are largely driven by adult patients and the early data is largely from China. On review of the Pediatric Oncology COVID-19 Case (POCC) Report data, of the 2328 children ($\leq$21) undergoing active cancer treatment who were diagnosed with COVID-19, 97 (4.2%) had a bacterial co-infection (*unpublished data)*. Bacterial co-infections included pseudamonal infections as well as infections with *Klebsiella, MRSA, Staphylococcus Aureus, E coli,* and *Enterobacter,* amongst other pathogens.

Traditionally, documented respiratory viral infection has not impacted treatment for febrile neutropenia given the concern for co-infection with a serious bacterial infection.[46] Prior to COVID-19, there was a randomized controlled trial from Chile about de-escalation of IV antibiotics in the setting of a documented respiratory virus with negative blood cultures.[55] After 48-72 hours of hospitalization with IV antibiotics, patients were randomized to continue or stop IV antimicrobials. Of 301 children with febrile neutropenia, a documented respiratory virus, and negative cultures, 176 were randomized with 92 to maintain IV antimicrobials and 84 to stop. They found: "Median duration of antimicrobial use was 7 days (range 7–9 days) versus 3 days (range 3–4 days), with similar frequency of uneventful resolution (89/92 (97%) and 80/84 (95%), respectively, not significant; OR 1.48; 95% CI 0.32–6.83, p 0.61), and similar number of days of fever (2 versus 1), days of hospitalization (6 versus 6) and bacterial infections throughout the episode (2%–1%), with one case of sepsis requiring admission to PICU in the group that maintained antimicrobials, without any deaths."[55] A similar study was repeated in Child in 2021-2023 had similar findings.[56] In that study though, 25 children (18%) had COVID-19.

There are a number of algorithms that sites can or do use to determine who is low vs high risk for febrile neutropenia. Many include clinical presentation as well as diagnosis.[23,57–60] Most do not include respiratory virus positivity or respiratory symptoms,[57] although some of Adam Esbenshade MD, MSCI (a pediatric oncologist

with expertise in risk stratification in febrile neutropenia) included upper respiratory viral symptoms, his most recent models do not.[23] There are no algorithms that specifically incorporate COVID-19 infection.

Key Points

- Febrile neutropenia is a common complication of chemotherapy treatment among children and can lead to significant morbidity and mortality due to serious bacterial infections
- Respiratory viral infections, including COVID-19, do not exclude bacterial co-infection, which occurs in a minority but clinically significant proportion of cases.
- COVID-19 status is not incorporated into febrile neutropenia risk-stratification algorithms, so care decisions should not deviate solely based on SARS-CoV-2 positivity

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Group 4. Precautions

Background

As testing for COVID-19 is central to the next two measures, here is a quick overview of COVID-19 tests. There are two primary types of COVID-19 tests: antigen tests and nucleic acid amplification tests (NAAT). Positive antigen tests indicate the presence of segments of COVID-19 virus involved in viral replication and indicate active infection.[1] Conversely, positive NAAT tests only indicate the presence of COVID-19 genetic material. Rapid antigen tests have lower sensitivity (47%) when compared with NAAT (up to 59% in symptomatic individuals when testing is performed three days after symptom onset).[2] In most cases, a single negative NAAT is sufficient to rule out COVID-19; however, in situations of high clinical suspicion, a second NAAT and interim isolation are recommended. While NAAT testing is useful in detecting initial COVID-19 infection, tests can remain positive up to 90 days after infection. To be confident of clearance of COVID-19 infection, 2 antigen tests are recommended for individuals with symptoms and 3 antigen tests are recommended for patients without symptoms; each test must be conducted 48 hours apart.[3]

4.1: Follow standard isolation procedures (comparable to non-immunosuppressed patients) for children with cancer and COVID-19

Under current CDC guidelines, it is recommended that all patients follow standard infection control protocols for viral respiratory infections.[4] If a patient tests positive for COVID-19 (via either antigen testing or NAAT), regardless of whether they are immune compromised, isolation is recommended until they have been fever free for 24 hours AND are exhibiting improving symptoms with additional precautions to be followed for at least 5 days after discontinuation of isolation. In immunocompromised patients, severity of the infection is increased and length of infection is often prolonged; hence, isolation periods may be longer in children with cancer patients.[5]

Once isolation is discontinued, patients are recommended to follow additional precautions for 5 days to help mitigate the risk of spreading COVID-19 to others. These precautions include trying to have more air flow (e.g. open windows, use a portable HEPA filter), practicing good hand hygiene, wearing a well-fitting mask, social distancing, and using antigen tests if they will be around other people. Of note, NAAT's can remain positive long after active infection and should not be used to inform a patient's decision to attend a gathering.[4] However, antigen test results can be used to inform whether or not a patient attends a gathering, especially if it is a gathering that involves individuals who have risk factors for severe illness.

Notably, severely immunocompromised patients can exhibit prolonged viral shedding. For example, in a 2025 prospective cohort study of 9 severely and 32 moderately immunocompromised patients, 6 severely immunocompromised individuals tested culture-positive for COVID-19 beyond 10 days, and 2 remained culture-positive after 20 days.[6] No moderately immunocompromised patients remained culture-positive after 10 days.[6] Therefore, it is possible that immunocompromised individuals need longer isolation periods, should test before leaving isolation, and at least increase the length of time during which they should avoid gatherings, especially with other immunocompromised individuals.[6] For children, this could impact usage of shared waiting rooms/infusion rooms when receiving cancer-related treatments. However, it is important to note that in our fast-paced world that has seemingly moved on from the COVID-19 era, it may be difficult to follow these recommendations in practice due to a combination of factors, including anti-mask sentiments and pandemic fatigue.

Key Points

- CDC does not have separate isolation guidelines for immunocompromised individuals
- CDC isolation guidelines are based on resolution of fever and symptoms
- Immunocompromised individuals may have prolonged viral shedding and COVID-19 test positivity.

4.2: Healthcare workers caring for children with cancer should follow CDC guidelines for length of isolation after infection.

Adherence to CDC isolation and work restriction guidelines for healthcare workers with COVID-19 infection can help prevent transmission to high-risk pediatric oncology patients. While the CDC does not recommend work restrictions for most asymptomatic healthcare workers with COVID-19 exposure, it does provide guidelines for symptomatic healthcare workers,[7] which are outlined below.

For symptomatic healthcare workers, the CDC advises diagnostic testing with either antigen or NAAT tests. When test results are negative, return-to-work decisions should be based on the healthcare workers suspected or confirmed diagnosis. For confirmed COVID-19 cases, CDC guidance specifies that return-to-work timing should be determined by the severity of illness and whether the healthcare worker is immunocompromised.

For asymptomatic HCWs who are not moderately to severely immunocompromised, return work can happen once:

- At least 7 days have passed since the positive test. if a negative viral test is obtained within 48 hours of returning to work
- 10 days have passed since the positive test, if a second test is not performed 5-7 days after positive test or if a positive test on days 5-7

For healthcare workers with symptomatic COVID-19 who are not moderately to severely immunocompromised, return work can happen once they are fever for 24 hours without fever reducing medications and symptoms have improved **AND:**

- At least 7 days have passed since symptom onset **IF** a negative viral test is obtained within 48 hours of returning to work

OR

- 10 days have passed since symptom onsen **IF** a second test was not performed or if a second test was positive test at day 5-7,

Moderately to severely immunocompromised HCWs may shed replication-competent COVID-19 beyond 20 days after symptom onset or the first positive viral test. For example, in a 2025 prospective cohort study of 9 severely and 32 moderately immunocompromised patients, 6 severely immunocompromised individuals tested culture-positive for COVID-19 beyond 10 days, and 2 remained culture-positive after 20 days.[6] No moderately immunocompromised patients remained culture-positive after 10 days.[6] Consequently, a test-based return-to-work strategy, guided by consultation with an infectious disease specialist, is recommended for immunocompromised healthcare workers.

While studies have examined the effectiveness of shortening COVID-19 isolation for infected healthcare workers to 5 days, findings have been mixed. The primary rationale for a shortened isolation period is to mitigate staffing shortages in an already overburdened healthcare system. A November 2022 observational cohort quality improvement study involving 1,023 HCWs demonstrated that a 5-day early return-to-work program, with negative antigen testing on day 5, saved 714 total workdays and reported no documented transmission events among participating staff.[8] In contrast, another 2022 study of 729 participants found that 54.3% remained antigen-positive between days 5 and 9 post-infection, including 64.0% of symptomatic individuals.[9] These findings suggest that

while shortened isolation can ease staffing shortages, the CDC's more conservative 7–10 day isolation recommendations for non-immunocompromised individuals may remain warranted in high-risk settings such as pediatric oncology.

Key Points

- CDC has recommendations for healthcare workers to return to work after COVID-19 infection
- Following such guidelines can lead to staffing shortages

4.3: Healthcare workers caring for children with cancer and COVID-19 should receive the COVID-19 vaccine

Pediatric oncology patients are highly vulnerable to infections due to immunosuppression from chemotherapy, radiation, or their underlying conditions.[10] Because these patients often cannot mount effective immune responses to vaccines, they rely on the immunity of those around them, especially healthcare workers. Vaccinating healthcare workers against preventable diseases like COVID-19 can help reduce transmission risk in healthcare settings.[11]

There is no federal mandate requiring healthcare worker vaccination; states determine their own policies.[12] Still, the CDC recommends healthcare workers be vaccinated to reduce the spread of diseases such as COVID-19.[13] Initial COVID-19 vaccine uptake among healthcare workers was high. A 2021 survey found that 94% of eligible healthcare personnel were vaccinated, primarily to protect themselves and their loved ones.[14]

Because vaccine protection wanes overtime, the CDC recommends an additional COVID-19 vaccination based on individual-based decision making. In particular, they specifically recommend boosters for those over the age of 65, at high risk for severe COVID-19, and those living in a long-term care facility.[15] However, they do not specifically recommend boosters for healthcare workers. Despite high annual influenza vaccination rates among healthcare workers, COVID-19 booster vaccine coverage remains low. In 2023–2024, only 15.3% of acute care hospital personnel received a COVID-19 booster, compared to 80.7% for influenza.

Key Points

- Healthcare worker's receiving COVID-19 vaccines can protect children with cancer
- There are no federal mandates about COVID-19 vaccination among healthcare workers
- Despite high initial COVID-19 vaccine update among healthcare workers, booster update is lower

4.4: Programs should have protocols in place to not have children with COVID-19 in shared spaces, including waiting room and infusion rooms

Children receiving cancer treatment are often immunocompromised, which makes them more vulnerable to serious illness if they are exposed to COVID-19.[16] To reduce this risk, programs that care for these children follow infection-control protocols, including in shared spaces like waiting rooms and infusion areas. These protocols are informed by guidance from the Centers for Disease Control and Prevention (CDC), which provides general standards for healthcare facilities to limit the spread of COVID-19.

CDC guidance includes screening and triage measures to identify patients who may have COVID-19 before they enter shared spaces and directing those at risk to private rooms or separate areas whenever possible. Waiting rooms are recognized as high-risk environments, so facilities are advised to minimize their use, create separate waiting areas, or move patients directly into exam or treatment rooms. In infusion and treatment settings, the CDC recommends transmission-based precautions to ensure that patients with suspected or confirmed COVID-19 are not placed in shared spaces with others.[17] Facilities may adjust scheduling or designate specific rooms to prevent overlap, helping protect vulnerable groups such as children undergoing chemotherapy.

The CDC notes infants and those with underlying conditions, including cancer, experience higher hospitalization rates compared with other children, underscoring the importance of strict infection-control measures in these environments.[18] Because waiting rooms involve multiple people in close proximity, often for extended periods, they are considered especially risky for airborne transmission of COVID-19. The CDC notes that these environments can increase exposure due to limited ventilation and prolonged contact among patients.[17] To reduce this risk, facilities are encouraged to manage patient flow carefully, shorten time spent in waiting areas, and implement controls such as improved air filtration and masking. The Infectious Diseases Society of America (IDSA) supports this layered approach, emphasizing that interventions like ventilation, source control, and patient separation are most effective when combined.[7] These measures are particularly important in protecting children who are immunocompromised.

Research also shows that physical distancing can help reduce the spread of COVID-19. One study found that after statewide distancing measures were introduced, the daily growth rate of new cases slowed by about 0.9% within four days.[19] These findings suggest that measures which reduce close contact—such as limiting time in waiting rooms—can contribute to lowering transmission risk in healthcare settings. Given that consistent physical distancing is not always feasible in the post-COVID era, reducing close contact in settings like waiting rooms remains a practical way to protect vulnerable patients, such as those with cancer.

While CDC/IDSA protocols recommend separate waiting areas, strict patient-flow control, and dedicated isolation spaces, hospitals often face space constraints that make this difficult. A qualitative study of U.S. hospitals found that many clinicians “reported difficulties finding or creating space for separate patient flows or dedicated areas for patients with suspected COVID-19,” especially during surges, which sometimes forced compromises in protocol implementation.[20]

Key Points

- Shared spaces put patients at risk of COVID-19 transmission
- Considerations of how to keep COVID-19 positive patients out of shared spaces, such as triaging for individuals who my have COVID-19 are needed
- In shared spaces, practices such as social distancing can help reduce transmission rates
- Some of these recommendations can be difficult to implement due to time and space constraints

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