

SPECIAL REPORT

The COVID-19 pandemic: A rapid global response for children with cancer from SIOP, COG, SIOP-E, SIOP-PODC, IPSO, PROS, CCI, and St Jude Global

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Abstract

The COVID-19 pandemic is one of the most serious global challenges to delivering affordable and equitable treatment to children with cancer we have witnessed in the last few decades.

Abbreviations: CCI, Childhood Cancer International; COG, Children's Oncology Group; IPSO, International Society of Paediatric Surgical Oncology; PROS, Paediatric Radiation Oncology Society; R4HC, Research for Health in Conflict partnership; SIOP, International Society of Pediatric Oncology; SIOP-E, SIOP Europe; SIOP-PODC, SIOP Pediatric Oncology in Developing Countries; St Jude Global, Global Pediatric Medicine, St Jude Children's Research Hospital.

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This Special Report aims to summarize general principles for continuing multidisciplinary care during the SARS-CoV-2 (COVID-19) pandemic. With contributions from the leadership of the International Society for Pediatric Oncology (SIOP), Children's Oncology Group (COG), St Jude Global program, and Childhood Cancer International, we have sought to provide a framework for healthcare teams caring for children with cancer during the pandemic. We anticipate the burden will fall particularly heavily on children, their families, and cancer services in low- and middle-income countries. Therefore, we have brought together the relevant clinical leads from SIOP Europe, COG, and SIOP-PODC (Pediatric Oncology in Developing Countries) to focus on the six most curable cancers that are part of the WHO Global Initiative in Childhood Cancer. We provide some practical advice for adapting diagnostic and treatment protocols for children with cancer during the pandemic, the measures taken to contain it (e.g., extreme social distancing), and how to prepare for the anticipated recovery period.

KEYWORDS

acute lymphoblastic leukemia, Burkitt lymphoma, childhood cancer, COVID-19, Hodgkin lymphoma, low-grade glioma, nephroblastoma, pediatrics, retinoblastoma, SARS-CoV-2, WHO Global Initiative on Childhood Cancer, Wilms tumor

1 | INTRODUCTION

The COVID-19 pandemic presents an unprecedented global threat to the safe and effective care for children with cancer. In this rapidly changing and uncertain healthcare landscape, there is an urgent need among health professionals and families for informed guidance on the range of reasonable and safe adaptations to their services and cancer treatment, while protecting the health and safety of staff, patients, and families. This rapid global response from the international childhood cancer community aims to provide pragmatic solutions for the problems being faced by our medical and nursing colleagues for the care of children with cancer, regardless of where a child may live.

It is the international consensus that, wherever possible, children presenting with a likely diagnosis of cancer during this pandemic should undergo a clinical assessment and appropriate investigations to establish a confirmed diagnosis and be offered effective therapy within the resources available while mitigating against the risk of exposure to COVID-19.

The WHO Global Initiative for Childhood Cancer (GICC), launched in 2018, has set an ambitious goal of improving survival rates for the 90% of the world's children who live in low- and middle-income countries (LMIC) to 60% by 2030.^{1,2} The GICC has identified six common index cancers—acute lymphoblastic leukemia (ALL), Burkitt lymphoma (BL), Hodgkin lymphoma (HL), retinoblastoma, Wilms tumor, and low-grade gliomas (LGGs)—all have a very good prognosis in high-income countries (HICs) and can be treated with curative intent in low- and middle-income countries (LMICs), using established standards of care or resource-adapted treatment regimens such as those previously published by the SIOP-PODC (Pediatric Oncology in Developing Countries) group.^{3,4-8} Here our specific focus is on these index cancers as they account for the majority of cancers seen in HIC and LMICs, and the core principles for care and treatment of these cancers are generalizable across most other cancers seen in childhood.

It is already clear that maintaining services as usual during the COVID-19 pandemic is, in many settings, no longer possible.⁹ There is an urgent need for all healthcare providers to evaluate their pathways of care to ensure the continuity of curative treatments and palliative care as effectively as possible. Consideration must be given to how families access care in the presence of serious lockdowns and curfews and service delivery may need to be adapted to availability of qualified staff and suitable facilities. Moreover, in this time of uncertainty and fear, support for patients and their families at diagnosis and during treatment is crucial to ensure they can complete treatment safely. Just as importantly, as a professional child cancer community, we must advocate on behalf of the healthcare workforce to protect the health and safety of nursing, medical staff, and support staff. It is their availability that will ensure that children with cancer will survive this pandemic.

Here we provide a rapidly formed international clinical consensus, based on current experience and previous evidence (where available), to suggest “reasonable” modifications to adapt child cancer services and treatments, should services and healthcare teams become overwhelmed by pandemic demand. We also provide advice on preparing for the recovery period, where, sadly, many late diagnoses of childhood cancers can be anticipated from limited pandemic-related access to health care and public fear of infection inhibiting parents seeking early medical assessment of symptoms in their child.

2 | METHODOLOGY

Over the three weeks from March 27 to April 17, 2020, the senior authors consulted and coordinated with the leadership of the principal child cancer organizations—SIOP, SIOP-E, COG, SIOP-PODC, IPSO, PROS, ICPCN, St Jude Global, and the WHO—and formed 10 disease and specialty working groups (represented in authorship below)

TABLE 1 Summary of contents of supplements: A global response to pandemic COVID-19

Supplement contents summary	
Supplement I and Supporting Information Tables S1-S6	Disease-specific guidance for (1) acute lymphoblastic leukemia, (2) Burkitt lymphoma, (3) Hodgkin lymphoma, (4) retinoblastoma, (5) Wilms tumor, and (6) low-grade glioma.
Supplement II and Supporting Information Tables S7-S9	Specialty and service-specific guidance; (7) radiotherapy; (8) surgical recommendations; (9) palliative care, infectious disease supportive care; nursing, the Lombardy protocol for pandemic care.

from both HIC and LMIC settings, who met virtually and communicated by email, coordinated and supported by the SIOP administration team. The services and disease-specific recommendations are based on collective expert opinion to guide the safe and effective modification of treatment. The unpublished experience of colleagues located in regions who have already experienced significant COVID-19 infections, particularly from the Lombardy region in northern Italy, was also sought.

Our guidance is set out in this paper and two accompanying supplements whose detailed contents are described in Table 1.

3 | GENERAL GUIDANCE FOR ADAPTING CANCER SERVICES AND CANCER TREATMENT DURING THE COVID-19 PANDEMIC

The true impact of COVID-19 infection on children undergoing cancer treatment is at present unknown. Here, we recommend the principle that the standards of care for the diagnosis, treatment, and supportive care for children with cancer should not be compromised or electively modified during the pandemic, if at all possible. Globally, the majority of child cancer services are located within combined adult and pediatric hospitals. In these centers, the risk of cross infection of healthcare staff and patients may be very high, and access to diagnostic services such as radiology, pathology, and treatment services, specifically surgery and radiotherapy, may become radically reduced in addition to a redistribution of resources needed for COVID-19 adult patients. If resource constraints mandate treatment modification, these should be done by a whole service approach rather than by individual clinical decision-making and should ideally be endorsed by institutional governance or a regional/national professional organization.

We advise all cancer centers to adopt an anticipatory and planned process to adapt their service to potential resource limitations (Lombardy experience, see below and Supplement II). It is necessary to limit patient visits to clinics and hospital admissions such as the temporary cessation of routine surveillance and survivorship clinics to release medical and nursing staff for frontline clinical care. Where possible, all elements of cancer treatment should continue without modification unless resources become overwhelmed. We recommend maintaining lists of cases where care has been adapted and to develop a prioritized approach to review care when normal service capacity resumes.

4 | THE LOMBARDY EXPERIENCE, ITALY

Colleagues in charge of services in the main childhood cancer center serving the Lombardy region, Northern Italy, have provided highly practical information on how they have managed to deliver usual anticancer care while minimizing transmission of COVID-19 (Supplement II).¹⁰ The crucial factors for managing the overwhelming service demand included: (1) clear clinical leadership; (2) a dynamic standard operating procedure for the service; (3) SARS-CoV-2 viral testing of all staff and all patients prior to any elective procedures or admission; (4) professional monitoring of handwashing and the use of appropriate personal protective equipment (PPE) by staff and families on entering and leaving clinical areas; (5) restricting accompanying persons to one per patient; (6) “cohorting” of staff for work and rest periods; (7) physical separation of oncology staff from staff working in COVID-19 areas; and (8) elective reduction of high-risk procedures (CAR-T and stem cell therapies) to reduce the demand for intensive care services. Many services have already implemented some similar measures, but the key message from the Lombardy experience is the need to take an anticipatory approach to rapid service reconfiguration, implement strict and supervised PPE to protect all patients and all staff, and maintain safe but flexible clinical care. In case a healthcare professional had been infected, readmission to work requires two PCR-negative swabs.

5 | CLINICAL SPECTRUM OF COVID-19 IN CHILDREN AND IN CHILDREN WITH CANCER

The emerging experience from regions with high community transmission SARS-CoV-2 suggests that an age-related pattern of upper and lower respiratory tract syndromes of mild to moderate severity is the most common presentation of COVID-19 in children, but with some reports of a very severe clinical disease with life-threatening respiratory failure.¹¹⁻¹⁵ COVID-19 may also rarely manifest as a true systemic disease, including myocarditis, meningo-encephalitis, macrophage activation syndrome, and thromboembolic phenomena. At the time of manuscript preparation, data on the clinical spectrum and outcome of children with cancer and concurrent COVID-19 are limited, and further data are awaited.¹⁶ However, other coronaviruses can produce more severe disease in immunocompromised children with increased risk with coexisting pulmonary disease or concurrent lower respiratory tract infection.^{17,18} Although this is not yet proven for SARS-CoV-2/COVID-19, prolonged viral shedding (≥ 21 days) has

been documented in hematopoietic stem cell transplant (HSCT) recipients for other human coronaviruses, particularly in the setting of steroid use, and myeloablative conditioning.¹⁹ Failure to clear the infection has implications not only for infection prevention due to risks of nosocomial transmission but also for ongoing therapy. Clinical experience with other respiratory viruses in HSCT patients indicates that progression from a mild infection, such as an uncomplicated upper airway infection, to a more severe infection, such as a lower respiratory tract infection, is a potentially life-threatening complication and the clinical worsening may occur later in the course of the infection.²⁰

6 | RECOMMENDATIONS FOR ADAPTING THE DIAGNOSIS AND TREATMENT FOR THE WHO INDEX CANCERS

Here we set out reasonable and safe modifications to the diagnosis and treatment of children with cancer in centers with significant pandemic-related resource constraints. As there is no evidence base to inform or guide cancer care during a pandemic, these recommendations are formed by collective expert opinion and based on the principles of pediatric oncology. Moreover, there is no current evidence to support the elective reduction in cancer treatment to prevent or mitigate COVID-19, but deferring elective high-risk treatments may improve patient safety and preserve service capacity to meet pandemic demand.

6.1 | New diagnosis of childhood cancer

All children suspected of having cancer should be investigated without delay. Because many elements of later treatment depend upon the thoroughness of disease diagnosis, we recommend following existing institutional protocols and standards of care (SOC) to confirm a diagnosis, staging, and risk stratification, which will inform treatment beyond the pandemic. We can envisage circumstances where access to SOC diagnostic investigations may be limited by service constraints. Where a patient presents with advanced cancer and concurrent COVID-19 (either symptomatic or detected on screening), the essential investigations should be done to establish an accurate cancer diagnosis, and interim therapy to control disease may be a safe approach and permit recovery from COVID-19 before commencing disease-directed treatment. In nonemergency presentations with concurrent COVID-19, such as an abdominal mass, intraocular retinoblastoma, or low-stage Hodgkin lymphoma, it is reasonable and safe to defer diagnostic investigations until the child has recovered and proceed with resource-adapted investigations as best can be achieved. Multidisciplinary tumor board meetings should continue for decision-making, if necessary, through phone/teleconferencing to ensure social distancing.

We are concerned that children with the early clinical signs of cancer may remain in the community and not be referred or present for investigation due to travel restrictions, fear of presenting to hospital or family financial issues. Sadly, there is already evidence of delayed presentation of acute illness in children in high-prevalence areas.²¹

7 | ACUTE LYMPHOBLASTIC LEUKEMIA

ALL is the most common single childhood cancer, with the longest duration of treatment; hence, many cancer services will experience some COVID-19-related disruption to the care of children with ALL during the pandemic. Few COVID-19-positive ALL cases have been reported so far, and the clinical course of those that have been described is of a mild to moderately severe respiratory syndrome, although anecdotal reports of severe infections and fatal outcomes are emerging.^{15,16} Thus, the major threat to children with ALL may be COVID-19-related interruption of treatment, or in some settings, treatment noncompletion.

We recommend children presenting with ALL undergo full investigation to establish the diagnosis and risk stratification and commence treatment according to institutional SOC, protocols, or clinical trials. Children with concurrent COVID-19 and hyperleukocytosis should commence immediate treatment with supportive care and a steroid prophylaxis, and commence disease-directed therapy on recovery from COVID-19.²² If diagnostic flow cytometry and/or molecular diagnostics are temporarily unavailable, patients should initiate treatment based on bone marrow/blood cytomorphology, age, and complete blood counts.²³ Multiple extra unstained aspirate smears should be stored for later more detailed diagnostics. Where risk-adapted therapy is not possible, the majority of children with ALL can be treated and cured by standard chemotherapy, stratified by morphological response rather than molecular classification and MRD stratification. We do not recommend any elective modification of maintenance chemotherapy, but in high COVID-19 prevalence regions, clinic visits should be minimized by extended dispensing of maintenance chemotherapy supported by virtual contact for clinical review. Supporting the family in this way may ensure ongoing treatment compliance and avoid abandonment.

In Supplement I, Table 1, we provide guidance for adapting patient care if the COVID-19 pandemic disrupts access to diagnostic investigations and the supply of essential cancer chemotherapy.

8 | BURKITT LYMPHOMA

Burkitt lymphoma (BL) is the most aggressive malignancy seen in childhood; endemic and sporadic BL often present with advanced disease where there is a high risk of immediate treatment-related complications. In resource-poor settings, children may present with advanced disease and significant comorbidity, especially poor nutrition and concurrent chronic infection.^{4,24}

BL is exquisitely sensitive to chemotherapy, and even advanced disease can be cured if treated to completion with careful supportive care. At diagnosis in fully resourced and HIC settings with an emergency presentation, no pandemic modifications are recommended for the initial assessment and diagnosis, even if a child presents with concurrent COVID-19. In resource-limited settings especially in endemic LIC regions, a simplified assessment based on the constellation of clinical features, a minimally invasive biopsy and diagnostic imaging

with chest X-ray and ultrasound (US) is sufficient to establish a safe diagnosis and commence supportive care and therapy (Supplement I; Supporting Information Table S2).²⁵ The effective chemotherapy regimens in HIC and resource-limited settings are summarized in Supplement I and Supporting Information Table S2. Where disease is advanced with concurrent comorbidity, a treatment prophase with stepped dosing corticosteroids alone with supportive care, before commencing disease-directed chemotherapy, is a safe approach for achieving immediate disease control and may mitigate the severity of life-threatening tumor lysis syndrome.

9 | HODGKIN LYMPHOMA

We recommend all children and adolescents presenting with progressive lymphadenopathy undergo immediate clinical evaluation and the best available diagnostic imaging and biopsy. When treated with chemotherapy alone, or chemotherapy and radiotherapy, classical HL has an excellent chance of cure, even in resource-limited settings.^{26,27} However, like other childhood cancers with an excellent prognosis, the treatment of HL is risk stratified, based on disease stage, diagnostic risk factors, and the early disease response.²⁸ The COVID-19 pandemic may compromise the availability and access to the SOC investigations for a complete diagnosis, staging, and response evaluation for risk-based therapy. Although multiple treatment approaches are available, we recommend electing for outpatient-based therapy, according to setting-appropriate SOC or clinical trial, without protocol modification. Many LMIC settings during the pandemic will not have access to functional imaging for response-based treatment stratification, and access to radiotherapy may be very limited. In these settings, a chemotherapy-only approach to treatment without radiotherapy is safe and reasonable, especially for low- and intermediate-risk disease.^{26,29-32} Patients in many resource-limited settings with advanced disease, complicated by weight loss and poor nutrition, require careful attention to supportive care and nutritional support during the initiation of treatment. Various options for adapting the diagnosis treatment of HL and relapsed HL are considered in Supplement I and Supporting Information Table S3.

10 | RETINOBLASTOMA

When diagnosed early and treated in a well-resourced setting, retinoblastoma is nearly always cured, so the paramount considerations are the preservation of vision, the preservation of the globe, and the determination of a genetic predisposition.^{6,33-36} However, in many LMIC settings, retinoblastoma presents with advanced disease, with extraocular extension and local or distant metastasis, which carry a poor prognosis.^{37,38} A pandemic-adapted approach to the diagnosis and management of intra- and extraocular retinoblastoma in various resource settings is discussed in Supplement I and listed in Supporting Information Table S4. Intraocular retinoblastoma requires access to an experienced ophthalmologist for an immediate examina-

tion under anesthesia (EUA) to determine the intraocular extent of disease (cT1-CT3) and laterality, as this will determine treatment with either local therapy or local and systemic chemotherapy. Routine neuroimaging (MRI) for unilateral intraocular retinoblastoma could be deferred unless there is involvement of the optic nerve or a suspicion of extraocular involvement.³⁹ Given the likely resource constraints for interventional radiology and prolonged anesthesia, services should consider deferring intraarterial chemotherapy programs. In resource-limited settings, most patients with advanced intraocular disease and no salvageable vision will require immediate enucleation to control disease followed by systemic chemotherapy.^{33,36} We recommend standard post-enucleation chemotherapy without dose modification as an outpatient.³⁷ Guidance is provided in Supplement I and Supporting Information Table S4a and b, for posttreatment surveillance with a modified frequency of examination and follow-up.

11 | WILMS TUMOR

Pandemic-related service constraints will require a simplified but safe approach to the treatment of Wilms tumor. Sequential clinical trials from SIOP and the COG have adopted a risk-stratified approach to the treatment of Wilms tumor using clinical (SIOP and COG) and molecular (COG) risk factors to minimize treatment-related toxicity while achieving cure rates of over 90%.⁴⁰ The SIOP approach has formed the basis for a clinical guideline adapted for use in low-income countries.⁷ During this COVID-19 pandemic, elements of these approaches may not be practical or possible, and there will likely be disruption to the timing of planned surgery and radiotherapy. Specific guidance for the care of children with primary malignant renal tumors is set out in Supplement I. We recommend all children presenting with an abdominal mass undergo an immediate clinical assessment and diagnostic imaging, the minimum being an abdominal US scan and chest X-ray, and if available a CT scan of the chest and abdomen. For primary renal tumors in children (age > 6 months) during the pandemic, where the immediate nephrectomy (COG) approach is not possible, we recommend proceeding to SIOP-based preoperative chemotherapy, based on the best available disease staging, but without biopsy in children aged < 7 years.⁴¹ Surgery and radiotherapy (if indicated) should be timed according to the protocol, but if there are service delays, and the patient has responded to chemotherapy, we recommend continuing with a further course of preoperative chemotherapy until surgery can be performed. Postoperative treatment should be continued according to the initial (COG or SIOP-based) management approach adopted. Detailed guidance for the adapted management of infants < 6 months, bilateral and metastatic disease is given in Supplement I and Supporting Information Table S5.

12 | LOW-GRADE GLIOMA

For children with LGG receiving chemotherapy, the recommendation is to continue the planned treatment without modification.

However, some temporary changes could be considered in order to reduce hospital visits (Supplement I; Supporting Information Table S6). Among the different LGG protocols, monthly carboplatin and TPCV are the most suitable in this context.^{8,42,43} For newly diagnosed patients, situations are closely related to the resources available. As the diagnosis of LGG is generally only suspected on imaging studies, this raises more broadly the issue of the management of a child with newly diagnosed brain tumor. In HICs, most children with a suspected diagnosis of intracranial brain tumor will be managed urgently and undergo immediate surgery. This may not be the case in countries with limited resources or in areas where access to operating theater and ICU is affected by the COVID-19 situation. For these reasons, a number of places have adopted a shunt or third ventriculostomy-only approach when signs and symptoms of increased intracranial pressure can be controlled by CSF diversion. This allows a prompt discharge within 24 hours and delayed resection when the epidemic situation is improving. For children without neurofibromatosis type 1 (NF1) with a suspected diagnosis of LGG involving the optic pathway, the situation should be assessed carefully with various options, including wait-and-watch if the clinical symptoms allow, or immediate treatment with chemotherapy (or radiotherapy in older children) in the context of visual threat or symptoms requiring urgent intervention. Although there is a trend to recommend systematic biopsies of all suspected optic pathway gliomas outside the context of NF1, the current situation may influence surgical practice and decision-making.

13 | RADIOTHERAPY

Radiotherapy plays an essential role in the cure of many tumors in children. The COVID-19 crisis is likely to have a grave impact on the accessibility of radiotherapy centers. Because most pediatric cancers have a high probability of cure, curative cancer treatment in children should be a high priority. Radiation oncologists treating children have a heightened responsibility to triage and coordinate cases with their pediatric colleagues and to advocate for the treatment of pediatric patients within radiotherapy departments. Where pediatric patients are treated in predominantly adult centers, additional screening measures may be necessary, as asymptomatic COVID-19-positive children may pose an additional risk to adult cancer patients.

The COVID-19 pandemic will have a direct impact on radiotherapy resources, and all radiotherapy centers should have a contingency plan in place to deal with revised staffing and workflows at short notice⁴⁴⁻⁵⁰ and Supplement II. Consideration to centralizing radiotherapy treatment of children where possible is suggested. Prioritization and triaging of cases based on acuity, curability, etc., is essential. Delaying or deferring treatment, use of alternative modalities and condensed regimens, may be possible. Disease-specific radiotherapy adaptation has started to emerge from various societies and organizations.⁴⁶ Similar efforts are underway for pediatric tumors. Supplement II (Supporting Information Table S7) outlines levels of evidence for modified and condensed treatment regimens in each pediatric disease.

Palliative cases may present with urgent symptoms. When these can be managed medically, this should be considered but where radiotherapy is required, hypofractionation should be strongly considered.

14 | SURGERY

Recommendations for childhood cancer surgery need to be tailored according to the COVID-19 prevalence and health system capacity. The goals of care during the pandemic are to provide childhood cancer surgical care in a timely manner while optimizing available resources and limiting exposure in patients and health workers. Children often have curable cancers, with surgery being integral to this; however, some modifications in the timing and practice of surgery may be required to provide safe treatment without compromising oncological prognosis.

The risk of SARS-CoV-2 transmission is highest when intervening in the airway or respiratory system due to dense viral load aerosolization.⁵¹ This may occur during endotracheal intubation, bronchoscopy, or thoracic surgery procedures. Staffing should be minimized to essential personnel. Exposed team members are required to adhere to consensus guidelines, use airborne precaution PPE (e.g., N95 mask with face shield), and care for patients with suspected or confirmed COVID-19 cases in designated operative and perioperative area.^{52,53} The risk of transmission of infection during tumor surgery outside of the airway or chest would be considered low with adequate droplet precautions. There is little evidence to suggest that a minimally invasive approach is associated with increased intraoperative exposure or poses a higher risk of SARS-CoV-2 transmission,⁵⁴ but extra care should be taken in regard to smoke and gas evacuation if the surgeon chooses minimal invasive access.

During this evolving pandemic, surgery scheduling and prioritization is a shared decision involving the cancer care team and hospital leadership. Delays in the optimal timing of local control may be considered with extensions of chemotherapy where significant intraoperative blood loss is anticipated, postoperative critical care is needed, patient infection with SARS-CoV-2 or hospital resources would not enable an optimal surgical outcome. Elective procedures and surgery for benign or low-grade tumors with low metastatic risk should be delayed and reviewed within a planned timeframe. Supplement II (Supporting Information Table S8) provides more detailed considerations from the International Society of Paediatric Surgical Oncology (IPSO).

15 | PALLIATIVE CARE AND SUPPORT

Children with high-risk cancers represent a particularly vulnerable population during this COVID-19 pandemic, especially when it comes to palliative care needs. These children are at increased risk for symptom-related distress as well as psychological and emotional trauma as a result of the COVID-19 crisis in addition to their already incredibly distress-inducing cancer diagnosis. Attending to

multifactorial suffering, supporting complex decision-making, and managing clinical uncertainty are core attributes of pediatric palliative care that are critically important when contemplating how best to respond to these patients' and families' needs in the midst of this pandemic.⁵⁵ COVID-19 is leading to a surge in demand for health-care services, including shifting resources and requiring uncomfortable conversations about resource allocation. Integration of palliative care into the ongoing care of children with cancer may be best achieved during these difficult times by facilitating access to hospice and palliative care services early in the illness trajectory, promoting education, and developing policies and procedures that place greater emphasis on comfort and quality of life. The potential role and response of palliative care and hospice services in this COVID-19 pandemic are demonstrated in Supplement II and Supporting Information Table S9.

16 | NURSING

Nurses are on the frontlines of treating and preventing the spread of COVID-19. The burden of illness during the pandemic simultaneously adds stress to the health system and places healthcare workers at risk,⁵⁶ magnifying challenges to the delivery of pediatric oncology nursing care.

Nurses play a critical role in reducing patient and staff exposure and are well positioned to oversee and educate caregivers and support staff. Hospital leaders should provide written, evidence-based recommendations for infection prevention and control practices during the COVID-19 crisis, including guidelines for hand hygiene, use of PPE, staff and visitor screening, isolation of symptomatic patients, and environmental disinfection protocols. Nursing shortages due to COVID-19 or other illnesses challenge appropriate care even in HIC,⁵⁷ but threaten basic oncology care in LMICs. During Ebola⁵⁸ and H1N1⁵⁹ outbreaks, nurses had legitimate concerns about their occupational welfare, particularly in LMICs, where vigilance for nurse occupational safety overall is not always prioritized.⁶⁰ Lessons learned from SARS show that cultures of healthcare organizational resilience and justice improve psychosocial consequences of pandemic-related stress on workers.⁶¹ Thus, ongoing monitoring and appropriate interventions as needed for nurses' mental and physical well-being must be in place.

17 | SUPPORTIVE CARE AND PPE-CONSIDERATIONS

17.1 | Infection control and PPE

Hospitals need rigorous policies and procedures for the screening, isolation, and care of patients and families at risk of or infected with COVID-19. To reduce the risk of disease transmission, it is essential that healthcare workers follow strict guidelines for proper hand hygiene, have access to the appropriate level of PPE, and receive adequate supervised training in its use.⁵⁷ Excellent WASH protocols should be in place for the environment the child and family are

in, including toileting facilities.⁶² Hospital cleaners must be trained and supervised in disinfecting patient care areas and equipment, and nursing staff must take particular care in handling patient excreta, soiled bedlinen etc. from patients with confirmed or suspected COVID-19 infection. Similar stringent precautions are required to protect the pediatric oncology clinical area and reduce transmission risks of COVID-19 among its patients. The Lombardy experience recommends the use of masks for all staff in pediatric oncology for all clinical encounters, with surgical masks for non COVID-19 contact, reserving N95 masks for high-risk clinical encounters such as aerosol-generating procedures. Parent and visitor access to clinics and wards should be strictly controlled and limited to one carer, but with compassionate exceptions during end-of-life care so long as measures to protect staff and other patients from infection are observed.

Oncology nurses face a dual hazard: a risk from handling cytotoxic chemotherapy and of contracting COVID-19 from patients or families. Although disruptions in supply chain have threatened the availability of PPE, every effort should be made to preserve appropriate protective equipment for those who are involved in patient care with no possibility to comply with physical distancing recommendations and those who prepare and administer chemotherapy.

Advice on the use of PPE during the COVID-19 pandemic is evolving and differs between countries.⁶³ Reuse of eyewear and N95 masks may be acceptable in certain circumstances, while acknowledging that this may impact on their effectiveness.⁶⁴ The WHO has issued recent advice on the use of masks in communities, during home care, and in healthcare settings.⁶⁵ Healthcare workers, patients, families, and the wider community must, as a minimum, follow their national government guidance.

17.2 | Blood product use and support

Centers are urged to revise their use of blood products and transfusion thresholds while adapting policies for safe and adequate blood supplies because measures to "shelter-in-place" and physical distancing are having a serious impact on blood donations.^{66,67} In many settings, there may be adequate supplies of long-life products such as red cells, but supplies of short life products especially platelets are at risk, and in LMICs, families are resorting to social media to find donors. In asymptomatic children, the safe threshold for red cell transfusion is Hb > 7.0 g/dL. The threshold for prophylactic platelet transfusion in patients with no risk factors for bleeding is recommended as $10 \times 10^9/L$. For procedures, the platelet threshold for lumbar puncture (LP) for a new diagnosis of ALL is recommended at $50 \times 10^9/L$ and $20 \times 10^9/L$ for subsequent LPs; for bone marrow aspirate $10 \times 10^9/L$, and for bone marrow biopsy, it is $20 \times 10^9/L$.⁶⁸ Platelet requirements for surgical procedures vary according to the intervention but should be reviewed with the surgical teams.

17.3 | Procedural support

Centers using general anesthesia for painful procedures should continue to provide these, especially for interventional biopsies, bone

marrow aspirates, and LPs. Where access is limited or compromised by service capacity issues, centers should adopt policies for safe and effective sedation with appropriate patient monitoring and postprocedure supervision.

18 | CARING FOR AND PROTECTING NURSING, MEDICAL, AND SUPPORT STAFF

The high incidence of COVID-19 infection among healthcare professionals working in the frontline of emergency and intensive care highlights the real risk that COVID-19 poses to all healthcare teams, and the need to ensure all practical measures are in place to protect staff. Many institutions have already adopted preclinic screening processes and have limited carers to a single parent (guardian) while a child is in hospital (Supplement II).

The COVID-19 pandemic is a time of great uncertainty with rapidly evolving policies and often conflicting advice from authorities, institutions, and social media. Travel restrictions, “shelter in place” regulations, physical distancing, and other pandemic measures have significantly impacted the general public and healthcare workers. In this context, many patients, parent/caregivers, nursing and medical staff are experiencing significant levels of stress and anxiety. There is a clear need for continuous, unambiguous communication when new institutional practices and guidelines are adopted to avoid confusion, reduce work absenteeism, and mitigate the mental health consequences of long-term stress and anxiety of all staff.

19 | FAMILIES AFFECTED WITH CANCER DURING COVID-19

Parents experience a high level of anxiety due to the lack of specific information on the real potential risk for children and adolescents with cancer as well as the uncertainty related to the continuity of their child’s treatment and care during the pandemic period. It is important that all efforts to avoid delays in treatment administration are put in place and continuous open communication about the situation is provided, while ensuring safety for patients and their caregivers. Implementation of measures to reduce hospital visits such as remote consultation (by telephone or videoconference) and provision of oral medicines (e.g., oral chemotherapy drugs for ALL) through courier service or drive through pharmacy counters are welcomed. However, efforts should be made to improve communication and give parents enough time to ask all the questions they would raise in a face-to-face visit. When hospital visits or admissions are unavoidable, it is very important for parents to be reassured that all health professionals strictly follow all the required safety measures to protect children from infection. Changes that help diminish fears of their child being infected at the hospital include use of staggered appointments and phone check-list on patient/family symptoms administered one to two days prior to attendance to minimize risk of having infected patients

in the waiting room, use of PPE by health personnel, limitation to only one accompanying person, and visit restrictions. It is prudent to advise the use of masks for patients and their parents when attending clinic, on admission, and when in transit, especially on public transport. For masks to be effective, a clear explanation is needed on how to properly wear and remove them.

All services, in cooperation with local childhood cancer parents’ organizations, should provide families with clear, precise, appropriate and accessible information regarding the protective measures to be taken by children and adolescents with cancer and all their household members such as social distancing, proper handwashing, and home hygiene. We recognize that recommended physical distancing and total home isolation may be impractical in many settings and there will remain a real risk of community transmission into the home from parents, grandparents, and siblings. Health professionals should work in cooperation with childhood cancer parents’ organizations, which, in addition to providing psychosocial and financial support to families, can help solve their accommodation needs. Together, these efforts will help to reduce missed appointments and mitigate the long-term risk of treatment noncompletion.

The coronavirus pandemic puts an additional psychological strain on patients, their parents, and their siblings. Their questions and anxieties should be met with understanding and patience. Where available, offering support from the psychosocial team, even if given by phone or video call, can alleviate distress, reduce family anxiety, and improve coping strategies to benefit patient well-being. Helpful guidance for childhood, adolescent, and young adult survivors of cancer has been developed by the International Late Effects of Childhood Cancer Guideline Harmonisation Group and is available in several languages.⁶⁹

20 | ADVICE ON CLINICAL TRIALS FROM COOPERATIVE CLINICAL TRIALS GROUPS

The enrolment of newly diagnosed patients on clinical trials depends entirely on the capacity and resources to support timely informed consent processes, the sustained accrual of clinical trial data, and ongoing research ethics oversight, and institutional governance. Where resources become limited, and the capacity for research-related investigations is compromised, pediatric oncology treatment centers should urgently review their capability, carefully document any changes instituted, and provide timely notification to the relevant regulatory and institutional governance bodies in their country, the clinical trial sponsors, and the collaborative clinical trial group. The Food and Drug Administration,⁷⁰ the National Cancer Institute’s Cancer Therapy Evaluation Program,⁷¹ and the European Medicines Agency⁷² have provided recommendations on conducting research during the COVID-19 pandemic. The principles of these recommendations are captured in guidances provided by the COG and the European Society of Paediatric Oncology (SIOP-E) including provision for telemedicine evaluations in place of clinical visits, remote dispensing of oral investigational agents, and acknowledging minor

protocol deviations to reduce the risk of COVID-19 spread among patients and medical providers. Guidance may vary among disease-specific cooperative clinical trial groups and by pharma sponsor, and maintaining good communication between sites and the trial sponsor is essential.

Many centers have had to suspend enrolment of new patients on open clinical trials during the pandemic. In this case, children should be treated according to disease-specific SOCs, with local modifications where required to reduce risk of exposure to COVID-19. Patients receiving newer therapies (including immunotherapy, molecularly targeted agents, or CAR-T cell infusion) and high-risk procedures (including bone marrow transplantation) require particular attention to maximize the ability to deliver effective therapies while minimizing their risk of exposure to COVID-19.

The longer-term impact of the COVID-19 pandemic on pediatric oncology trials remains to be seen. Many trials will have delayed recruitment and the time to be completed will need to be extended and the impact on trial outcomes of the necessary protocol deviations to protect patient from exposure to COVID-19 will need future evaluation.

21 | COVID-19-RELATED RESEARCH AND THE GLOBAL COVID-19 RESOURCE CENTER AND REGISTRY

There is a paucity of data on the clinical manifestations and outcome of COVID-19 in children being treated for or having recently completed cancer. Given the rarity and spectrum of childhood cancers, it is unlikely that any single center will see more than a few sporadic cases of COVID-19. To address the need for well-curated clinical data, St Jude Global and SIOP have created a global COVID-19 childhood cancer registry to learn more about the impact of the virus on childhood cancer patients worldwide and for us all to be better prepared to meet future similar challenges.⁷³ St Jude Global and SIOP have put out a call for clinicians worldwide to voluntarily report any patient with a malignancy or prior hematopoietic stem cell transplant who is under the age of 19 at the time of a laboratory confirmed SARS-CoV-2 infection. Data requested include nonidentifiable demographics, underlying malignant disease information, limited treatment-related risk factors, and basic outcomes. The survey will be hosted using a freely available web-based data capture tool (REDCap) maintained by St Jude Children's Research Hospital.⁷⁴

Total data entry time requires no more than 15 minutes initially with a second, shorter follow-up survey requested of the original respondent a few weeks later. The collection and storage of all data entered in the repository is entirely deidentified and therefore does not constitute human subjects research. Using the aggregate information from these reported cases, we aim to provide rapid updates to the global pediatric cancer community via the St Jude-SIOP COVID-19 Resource Centre and use the data to support community-initiated online case discussions.

This global effort to accrue and evaluate data on the incidence and clinical course of COVID-19 in children is welcome and essential, and all are encouraged to report their case experience. We are aware of similar registries being set up in some countries and welcome collaboration to develop plans for coanalyses.

22 | DISCUSSION

The global pandemic of infection with SARS-CoV-2 has presented the international childhood cancer community with unforeseen challenges with little time to prepare contingency plans. Ironically, this coincides with only the second year of a global effort, led by the WHO, to improve childhood cancer survival rates in LMICs to 60% by 2030. Even for those countries who had started to implement changes to meet this survival target, their national cancer plans were not written to take account of the possibility of their national healthcare system being overwhelmed by a pandemic such as the world now faces in COVID-19.

We have brought together clinical experts from around the world to provide a "rapid response" to help those caring for children with cancer and their families in the front line. This article and associated supplements are intended to offer temporary pragmatic solutions for clinicians facing constraints in the resources they normally have available, recognizing that almost 90% of the world's children with cancer live in LMICs.² The overall message is that the planned diagnosis and treatment of children with cancer should continue to be delivered in as timely a fashion as possible and with as few modifications as necessary, while taking account of patient safety and service constraints. The message also needs to go out to parents that they should continue to seek medical advice if they have serious concerns about the health of their child. Early evidence is that parents are staying away from emergency rooms and medical assessments, raising the concern that there may be increased toxic deaths on treatment and a future surge in late presentations of new childhood cancers.

In considering treatment modifications for the six most curable cancers that are the focus of the WHO GICC, our contributors drew on their knowledge of the current range of regimens used as "standard of care" in both the HIC and LMIC settings. The first supplement provides consensus opinion formed between tumor type-specific clinical experts from the major clinical trial groups in North America and Europe and the leadership who have developed equivalent adapted treatment regimens for LMICs. The second supplement provides more details on possible modifications to service delivery that have been considered by the leaders of global associations for the full range of pediatric disciplines and staff groups. These are necessarily "broad brush" as healthcare providers will be required to follow national and institutional requirements. The specific examples included from centers with several weeks experience demonstrate what is possible in a high-income context. Those working in more resource-limited settings will have fewer options, but we urge them to prioritize continuing therapy as much as possible for children with highly curable cancers. Also, to work with their public health colleagues to send a

clear message to parents and communities, fear of COVID-19 infection should not prevent seeking medical assessment if they have serious concerns about their child's health.²¹

It is essential that the global pediatric oncology community aims from the outset to learn as much as possible from this pandemic. A full understanding of who is at risk of developing serious COVID-19 disease and how to prevent and treat this can only come from a global effort to capture detailed prospective data. We urge all services to make full use of the St Jude-SIOP platform and registry to achieve this.^{73,74} We hope there will be some positive changes in ways of working that may endure, if they are shown to be better for patients, such as increased use of oral therapies and telemedicine. Careful documentation and prospective evaluation of these treatment and service changes is needed to ensure this. More worrying is the potential for children with cancer to become indirect victims of the COVID-19 pandemic, due to late diagnosis and disrupted therapies. Epidemiological research to monitor incidence and survival across this pandemic will be critical to understanding the extent to which this occurs and to plan actions for recovery. Childhood cancer parents' organizations can play an important role in reassuring parents of children with known or suspected cancer to seek prompt clinical assessment and by disseminating, in cooperation with healthcare professionals, a clear and accessible message.

Finally, we would like to thank all of our colleagues for coming together so quickly to create this publication, and trust that you can all continue care of your patients while staying safe.

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CONFLICTS OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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