The COVID-19 pandemic

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SIOP-E: SIOP Europe
SIOP-PODC: SIOP Paediatric Oncology in Developing Countries
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ABSTRACT (185 words):

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. This Special Report aims to summarise general principles for continuing multi-disciplinary care during the SARS-CoV-2 (COVID-19) pandemic. With contributions from the leadership of the International Society for Paediatric Oncology (SIOP), Children's Oncology Group (COG), St Jude Global programme 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.

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 amongst 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 whilst mitigating against the risk of exposure to COVID19.

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 (LIMC) to 60% by 2030[1] [2]. The GICC has identified 6 common index cancers; Acute Lymphoblastic Leukaemia, Burkitt and Hodgkin Lymphoma, Retinoblastoma, Wilms tumour and Low Grade Gliomas; 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 (Paediatric 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 generalisable 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.

METHODOLOGY:

Over the 3 weeks from 27 March to 17 April 2020, the senior authors consulted and coordinated with the leadership of the principal child cancer organisations; 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) 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 manuscript and two accompanying supplements whose detailed contents are described in table 1.

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 paediatric hospitals. In these centres, 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 centres 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 prioritised approach to review care when normal service capacity resumes.

THE LOMBARDY EXPERIENCE, ITALY:

Colleagues in charge of services in the main childhood cancer centre serving the Lombardy region, Northern Italy, have provided highly practical information on how they have managed to deliver usual anti-cancer care whilst minimising 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 health-care professional had been infected, re-admission to work requires two PCR-negative swabs.

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 is limited and further data are awaited [16]. However, other coronaviruses can produce more severe disease in immunocompromised children with increased risk with co-existing pulmonary disease or concurrent lower respiratory tract infection [17] [18]. While this is not yet proven for SARS-CoV-2/COVID19, 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 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].

RECOMMENTATIONS 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 centres 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 paediatric 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.

New Diagnosis of Childhood Cancer:

All children suspected of having cancer should be investigated without delay. Since 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 maybe a safe approach and permit recovery from COVID-19 before commencing disease-directed treatment. In non-emergency presentations with concurrent COVID-19, such as an abdominal mass, intra-ocular 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. Multi-disciplinary 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].

1. ACUTE LYMPHOBLASTIC LEUKAEMIA (ALL)

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 non-completion.

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 prophase, and commence disease directed therapy on recovery from COVID-19 [22]. If diagnostic flowcytometry 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 minimised 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.

2. 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, Table 2)[25]. The effective chemotherapy regimens in HIC and resource limited settings are summarised in supplement I, Table 2. 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 tumour lysis syndrome.

3. 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 Hodgkin Lymphoma (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. While 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 30,31 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, Table 3.

4. 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 [33,34 6 35 36]. However, in many LMIC settings, retinoblastoma presents with advanced disease, with extra-ocular 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 supplementary table 4. Intraocular retinoblastoma requires access to an experienced ophthalmologist for an immediate examination under anaesthesia (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 anaesthesia, services should consider deferring intraarterial chemotherapy programs. In resource-limited settings, most patients with advanced intraocular disease and no salvageable vison 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, Table 4a and b, for post-treatment surveillance with modified frequency of examination and follow up.

5. WILMS TUMOUR

Pandemic-related service constraints will require a simplified but safe approach to the treatment of Wilms tumour. Sequential clinical trials from SIOP and the COG have adopted a risk-stratified approach to the treatment of Wilms tumour using clinical (SIOP and COG) and molecular (COG) risk factors to minimise 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 tumours are 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 tumours in children (age >6 months) during the pandemic, where the immediate nephrectomy (COG) approach is not possible, we recommend proceeding to SIOP-based pre-operative chemotherapy, based on the best available disease staging, but without biopsy in children aged < 7 yrs [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 pre-operative chemotherapy until surgery can be performed. Post-operative 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 are in Supplement I, Table 5.

6. LOW GRADE GLIOMA

For children with low grade glioma (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, Table 6). Amongst 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 theatre 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. While 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.

7. RADIOTHERAPY:

Radiotherapy plays an essential role in the cure of many tumours in children. The COVID19 crisis is likely to have a grave impact on the accessibility of radiotherapy centres. Because most paediatric 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 paediatric colleagues and to advocate for the treatment of paediatric patients within radiotherapy departments. Where paediatric patients are treated in predominantly adult centres, 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 centres should have a contingency plan in place to deal with revised staffing and workflows at short notice [44-49] [50] and (Supplement II). Consideration to centralising 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 (Table 7) 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.

8. 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 tumour 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 regards 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, post-operative 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 tumours with low metastatic risk should be delayed and reviewed within a planned timeframe. Supplement II (Table 8) provides more detailed considerations from the International Society of Paediatric Surgical Oncology (IPSO).

9. 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 paediatric palliative care that are critically important when contemplating how best to respond to these patients' and families' needs is 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, Table 9.

10. NURSING

Nurses are on the frontlines of treating and preventing the spread of COVID19. The burden of illness during the pandemic simultaneously adds stress to the health system and places health care workers at risk[56], magnifying challenges to the delivery of paediatric 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 COVID19 crisis, including guidelines for hand hygiene, use of personal protective equipment (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 LMIC. During Ebola[58] and H1N1[59] outbreaks, nurses had legitimate

concerns about their occupational welfare, particularly in LMIC, 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.

SUPPORTIVE CARE and PPE CONSIDERATIONS

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 health care 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 paediatric 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 paediatric 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 to 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]. Re-use 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 health care settings [65]. Healthcare workers, patients, families and the wider community must, as a minimum, follow their national government guidance.

2. Blood product use and support:

Centres 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 thresholds for red cell transfusion is Hb >7.0g/dl. The threshold for prophylactic platelet transfusion in patients with no risk factors for bleeding is recommended as $10x10^9$/L. For procedures, the platelet threshold for lumbar puncture (LP) for a new diagnosis of ALL is recommended at $50x10^9$/L and $20x10^9$/L for subsequent LPs; for. bone marrow aspirate $10x10^9$/L, and for bone marrow biopsy it is $20x10^9$/L [68]. Platelet requirements for surgical procedures vary according to the intervention but should be reviewed with the surgical teams

3. Procedural support

Centres using general anaesthesia 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, centres should adopt policies for safe and effective sedation with appropriate patient monitoring and post procedure supervision.

CARING FOR AND PROTECTING NURSING, MEDICAL AND SUPPORT STAFF

The high incidence of COVID-19 infection amongst healthcare professional 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.

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 1-2 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 recognise 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 non-completion.

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 wellbeing. 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[74].

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 are compromised, paediatric oncology treatment centres 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[69], the National Cancer Institute's Cancer Therapy Evaluation Program[70], and European Medicines Agency[71], 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 centres 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 maximise the ability to deliver effective therapies while minimising their risk of exposure to COVID-19.

The longer-term impact of the COVID-19 pandemic on paediatric 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.

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 centre 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 [72]. 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 non-identifiable 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 [73].

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 paediatric 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 co-analyses.

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 low- and middle-income countries 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 manuscript and associated supplements are intended to offer temporary pragmatic solutions for clinicians facing constraints in the resources they normally have available, recognising that almost 90% of the world's children with cancer live in LMICs [2]. The overall message is that 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 HIC and LMIC settings. The first supplement provides consensus opinion formed between tumour 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 low and middle income countries. 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 paediatric disciplines and staff groups. These are necessarily 'broad brush' as health care providers will be required to follow national and institutional requirements. The specific examples included from centres 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 prioritise 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 that 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 paediatric 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 [72,73]. 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' organisations 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 health care 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 whilst staying safe.

Conflict of interest statement:

The authors have no conflicts of interest to declare.

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Table 1.

Table 1: A Global response to pandemic COVID-19, Supplement contents summary	
Supplement I and Tables 1-6	Disease specific guidance for 1) Acute Lymphoblastic Leukaemia, 2) Burkitt lymphoma, 3) Hodgkin Lymphoma, 4) Retinoblastoma, 5) Wilms tumour and 6) Low Grade glioma;
Supplement II Tables 7-9	Specialty and service specific guidance; 7) Radiotherapy, 8) Surgical recommendations, 9) Palliative Care, Infectious Disease Supportive care; Nursing, The Lombardy protocol for pandemic care

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COVID-19 PANDEMIC

SUPPLEMENT I and TABLES

TITLE: Disease Specific Guidance and Supportive Care adapted for children with cancer in response to pandemic COVID-19

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INTRODUCTION:

This supplement (Supplement I) provides detailed disease guidance for adapting services and treatment during the COVID-19 pandemic. Here we advise that wherever possible children presenting with clinical features consistent with a new diagnosis of cancer should undergo investigation as soon as safely possible and within the available resources. Where the completeness of diagnosis and staging investigations are compromised, we advise the commencing treatment according to the best standard of care available. We advise against the elective modification of treatment and chemotherapy, but guidance

is provided for the safe scheduling of surgery and radiotherapy. Table 1-6 summarise the recommended modifications during the COVID-19 pandemic.

1. ACUTE LYMPHOBLASTIC LEUKAEMIA

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

The clinical course of COVID-19 in children with ALL reported to date is of a mild to moderately severe respiratory syndrome although anecdotal reports of severe infections and fatal outcomes are emerging [1] [2] . Thus, the major threat to children with ALL, may be COVID-19 related interruption of treatment, or in some settings, treatment non-completion. We recommend children presenting with ALL undergo full investigation to establish the diagnosis and risk stratification and commence treatment according to institutional standards of care, protocols or clinical trials. Children with concurrent COVID-19 and hyperleukocytosis should commence immediate treatment with supportive care and a steroid prophase, and commence disease directed therapy on recovery from COVID-19 [3]. If diagnostic flowcytometry and/or molecular diagnostics are temporarily unavailable, patients should initiate treatment based on bone-marrow/blood cytomorphology, age and complete blood counts[4]. 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 therapy, stratified by morphological response rather than molecular classification and MRD stratification. We do not recommend any elective modification of maintenance chemotherapy, but in high prevalence regions, clinic visits should be minimised by extended dispensing of maintenance chemotherapy supported by virtual clinical review. Supporting the family in this was way may ensure ongoing treatment compliance and avoid abandonment.

SUPPLEMENT I, TABLE 1: Guidance for adapted diagnosis and treatment for Acute Lymphoblastic Leukaemia during COVID-19 pandemic

PHASE/STAGE	STANDARD OF CARE	POTENTIAL CHALLENGES	COVID-19 ALTERNATIVE OPTIONS	COMMENTS	REF
DIAGNOSTIC INVESTIGATIONS	Bone marrow (or peripheral blood) morphology, karyotyping, flowcytometry, MRD markers, and CSF cytospin, CXR, organ function	Limited capacity for diagnostic investigations for risk stratified therapy. Anaesthetics for procedures	Risk group by age and WBC Store relevant material for later analysis (BM smears for later FISH and PCR).	ALL is very curable cases without molecular genetics and MRD directed therapy	4
INDUCTION THERAPY	Standard 3 or 4 drug induction and IT therapy: Corticosteroids, VCR, ASP, +/- Daunorubicin. IT MTX of ARA-C	Disrupted chemotherapy supply.	Triple induction only and single IT therapy. Equivalent steroid dosing for Prednisone Prednisolone or Dexamethasone. Give ASP later when available.	Triple Induction therapy very effective with single IT therapy. If COVID-19 positive at diagnosis commence supportive care and corticosteroids and await clinical recovery.	5,6
INTENSIVE CONSOLIDATION	MRD risk-based treatment assignment	Resources for supportive care and blood products. Concurrent COVID-19	G-CSF to enhance neutrophil recovery Temporary use of less intense consolidation.	Phasing of consolidation and reinduction phases critical so could be given in least toxic order	
6-MP/6-TG IN CONSOLIDATION		Interrupted supply of 6-MP (or 6-TG) not available	Temporarily substitute 6-MP for 6-TG (or vice versa) dose equivalent	Return to standard of care therapy as soon as supply available	
HIGH-DOSE METHOTREXATE	Protocol defined high dose methotrexate and supportive care	Limited resources for inpatient treatment. MTX levels unavailable; Supportive care for myelosuppression	Postpone or temporary reorder of phasing of therapy. Consider replacing HD-MTX with Capizzi* MTX	With concurrent COVID-19, defer HD-MTX. Consider switch to Capizzi MTX phase if resources not available for standard of care	7
ASPARAGINASE	ASPARAGINASE is an essential chemotherapy agent for ALL treatment and is standard of care	Impaired supply of all forms of ASP; PEG, Leunase and or Erwinase	Use whatever ASP form is available in equivalent dosing. Give PEG-ASP intermittently but to protocol total dosing. Use whatever form available	Potential PEG-ASP toxicity. If deferred, make up to full protocol dosing when available	8
MAINTENANCE THERAPY MTX/6-MP	2 Standard of care protocols with oral Methotrexate and 6-MP for 2-3 years from diagnosis. 2 VCR/Corticosteroid pulses not in	Many patients on active therapy, needing ongoing treatment supervision and	No changes to maintenance therapy advised if at all possible; continue with standard of care. But consider temporary	If COVID-19 positive, withhold maintenance therapy until recovered and virus free. Dispense for longer duration of therapy, follow and support	9, 10, 11,12

+/- VCR and Dexamethasone pulses	all standard of protocols	dispensing of therapy Need for clinic visits for VCR pulses	postponement clinic visits for VCR or maintenance without VCR/Dexamethasone pulses	patients on maintenance via telehealth. Completeness of maintenance therapy is associated with overall outcome. Increased risk of HVOD/SOS with 6-TG	
CNS PROPHYLAXIS WITH CRANIAL IRRADIATION	Not included in many standard-of-care protocols	Service capacity in radiotherapy, anaesthesia the young children	Consider postponing cranial radiation for CNS prophylaxis	Consider standard of care options that omit cranial radiotherapy	13

ASP, Asparaginase; PEG-ASP; pegalated Asparaginase; Capizzi MTX; Capizzi based methotrexate; HVOD/SOS, hepatic veno-occlusive disease/sinusoidal obstructive syndrome; IT. Intrathecal therapy; MRD, minimal residual disease; 6MP, mercaptopurine; 6-TG, 6-thioguanine; MTX, methotrexate; VCR, vincristine;

2. BURKITT LYMPHOMA

Guidance on adapting the care and treatment of child presenting with Burkitt lymphoma (BL) is summarised in Table 2. In resource poor and endemic settings children may present with advanced disease and significant comorbidity especially poor nutrition and concurrent chronic infection [14,15] . 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, Table 2)[16]. Where disease is advanced with concurrent comorbidity, a treatment prephase 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 tumour lysis syndrome.

SUPPLEMENT I, TABLE 2: Guidance for the adapted diagnosis and treatment of Burkitt Lymphoma during COVID-19 pandemic

FULLY RESOURCED AND HIC SETTINGS

PHASE/STAGE	STANDARD OF CARE	POTENTIAL CHALLENGES	ESSENTIAL INVESTIGATIONS and MANAGEMENT	TREATMENT AND ALTERNATIVE OPTIONS	COMMENTS	REF
DIAGNOSTIC INVESTIGATIONS	Guided by standard of care protocol; CT or MRI: neck/chest/ abdomen/pelvis Tissue biopsy; lymph node or other involved site; BMA/Trephine; Flow cytometry, cytomolecular genetics; organ function,	Capacity issues for interventional biopsies, flow cytometry, cytomolecular genetics, and diagnostic imaging. Limited capacity for organ function assessment. Concurrent COVID-19 at diagnosis	CXR, CT staging or US Abdo/pelvis, Biopsy node or other, tissue, FBC, CMP, LDH, Urate, LP and BMA/trephine.	Diagnostic staging for Burkitt Lymphoma should be prioritised. Defer organ function – cardiac echo and GFR if no prior clinical history Diagnosis can be established by morphology of core biopsy of lymph node and IHC	Diagnostic imaging should be prioritized as these determine stage and risk for assigning therapy. Burkitt lymphoma is an emergency and diagnostic investigations and interim therapy should commence even if COVID-19 positive	16 17
SPORADIC BL STAGE I OR II GROUP A (COMPLETELY RESECTED STAGE I/II	Standard of care protocols: either LMB, BFM or COG; approach 2-4 cycles of chemotherapy with response evaluation	Need for inpatient therapy, concurrent COVID-19. Incomplete diagnostic staging	As above, continuous laboratory evaluation for tumour lysis syndrome (TLS): allopurinol and high volume fluids	Commence supportive care, hydration and monitor urine output. COPAD x 2 CHOP or BFM	If limited capacity, or COVID-19 infection, commence stepped steroid prephase and manage for TLS then commence treatment on recovery	18 14 19 17
SPORADIC BL STAGE III/IV GROUP B (UNRESECTABLE ABDOMINAL OF BOTH SIDE DIAPHRAGM)	Standard of care protocol with intensified chemotherapy as per LMB/ COG ANHL1131 protocols +/- Rituximab, Rasburicase for TLS	Unwell at diagnosis, high risk of TLS, urgency to commence treatment, potential concurrent COVID-19. Chemotherapy supply. HD MTX	As above, consider Rasburicase for TLS	COP/COPADMx2/CYMx2 as per LMB/COG ANHL1131	As above, consider stepped steroid prephase if capacity issues. Omit Rituximab risk of impaired B lymphocyte response in COVID-19.	20 14 19 21

STAGE IV GROUP C (+ve BM OR CNS DISEASE)	As above	As above, Supply issues for rituximab – and potential issues with COVID-19 infection	As above, consider Rasburicase for TLS	COP/COPADMx2/CYVEx2 + m1/m2 +/	As above	21 20 19 21
LIMITED RESOURCES AND LIC SETTINGS						
(ENDEMIC) LIMITED STAGE I/II	Malawi protocol – cyclophosphamide based without anthracyclines	Tissue diagnosis by FNA and histology, BMA, LP, US of abdomen, CXR. Remove consultation	TLS investigations and management Early intervention of fever/neutropenia	Malawi/Cameroon protocol (28 days) without anthracyclines. Nutritional support	Initiate steroid prephase and assess response. Management of TLS and nutritional support	22 23
ENDEMIC ADVANCED STAGE III/IV	Malawi protocol including anthracyclines + rituximab clinical trial – none vs 10% dose vs full dose	As above	If neurological symptoms, signs paraparesis, MRI brain + spine	Intensified Malawi protocol with anthracyclines, nutritional support and management of TLS	As above	22 17

COP, cyclophosphamide, vincristine, prednisone and intrathecal methotrexate; COPAD, cyclophosphamide, vincristine, prednisone, doxorubicin +IT; COPADM, cyclophosphamide, vincristine, prednisone, doxorubicin and High dose methotrexate; CYM, high dose methotrexate and cytarabine + IT; CYME cytarabine continuous infusion, high dose cytarabine, etoposide + IT; M1, vincristine, prednisone, high dose methotrexate, cyclophosphamide TLS, tumour lysis syndrome

3. HODGKIN LYMPHOMA

The various options for the management of new and relapsed patients with Hodgkin Lymphoma during pandemic-related resource constrains are summarised in Table 3 . All children and adolescents presenting with progressive lymphadenopathy should have an immediate clinical evaluation, diagnostic imaging and a lymph node biopsy is malignancy is clinically suspected. When treated with chemotherapy alone, or chemotherapy and radiotherapy, classical Hodgkin Lymphoma has an excellent chance of cure (>90%), even in resource limited settings [24] [25]. However, like other childhood cancers with an excellent prognosis, the treatment of Hodgkin lymphoma is risk-stratified, based on disease stage, diagnostic risk factors and the early disease response [26]. The COVID-19 pandemic may compromise the availability and access to the standard of care investigations for a complete diagnosis, staging and response evaluation for risk-based therapy. While multiple treatment approaches are available, we recommend electing for outpatient-based therapy, according to a setting appropriate standard of care or clinical trial, without protocol modification. In HIC settings, patients who are not enrolled on a clinical trial can be treated very effectively with standard of care protocols (Table 3) and safely managed as an outpatient. Contemporary treatment approaches for Hodgkin Lymphoma in HIC settings now use functional imaging with FDG-PET to risk stratify therapy, particularly radiotherapy, after standard initial courses of chemotherapy. Where possible this approach should continue without modification, but where functional imaging is not available due to resource constrains, treatment should be stage based as guided in Table 3. We do not recommend prolonged delays to radiotherapy, especially for patients who have high risk disease and are FDG-PET positive following the initial 2 courses of chemotherapy. The risk bleomycin induced pulmonary toxicity and COVID-19 is unknown, and its use should be reviewed in COVID-19 regions. In high resource settings, regimens with brentuximab vedotin for high risk patients is safe in paediatric and adult patients – see references Table 3).

Relapsed Hodgkin lymphoma remains very curable in HIC settings and we recommend urgent full re-evaluation and access to functional imaging to assess the response of the disease to secondline therapy. Multiple salvage options are available for reinduction chemotherapy and several can be done as an outpatient (Table 3). Consolidation therapy may be required depending on disease response; if accessible, immunotherapy may be an option, but the risk treatment related complications is uncertain especially in the setting of high COVID-19 prevalence. Similarly, autologous stem cell transplant should /could be delayed until resources and capacity are available. Therapy for biopsy proven localized nodular lymphocyte predominant HL (nLPHL) can be delayed, if necessary, without affecting prognosis (Table 3).

In LMIC settings during the pandemic access to functional imaging for response-based treatment stratification and access to radiotherapy may be very limited or compromised. In these settings, a chemotherapy only approach to treatment without radiotherapy is safe and reasonable, especially for low and intermediate risk disease [24,27] [28,29] [30]. 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.

SUPPLEMENT I TABLE 3; Guidance for adapted diagnosis and treatment of Hodgkin Lymphoma during COVD-19 pandemic in HIC and LMIC settings

PHASE/STAGE	STANDARD OF CARE	POTENTIAL CHALLENGES	ESSENTIAL INVESTIGATIONS AND MANAGEMENT	TREATMENT AND ALTERNATIVE OPTIONS	COMMENTS	REF
DIAGNOSTIC INVESTIGATIONS	Guided by clinical trial if open, or according to standard of care protocol such as EuroNet PHL-C1 (OPEA/COPDAC) ABVD or COG. History and examination, CXR, and CT or MRI neck to pelvis. In HIC settings - FDG-PET. Core of surgical biopsy of lymph node. FBC, CMP, LDH, ESR, Urate and organ function.	Capacity issues for evaluation and investigation of child with progressive lymphadenopathy. Limited procedural access for core or surgical node biopsy. Diagnostic imaging and limited access to PET scans in HIC settings. Limited capacity for organ function assessment. Concurrent COVID-19 at diagnosis.	History of symptoms and detailed physical examination to document nodal sites and size. CXR, US scan abdomen and pelvis. Core biopsy of involved node (not FNA). Organ function assessment. If limited PET scans, one scan after 2 courses of chemotherapy.	As majority of patients are well, investigate as outpatient. If concurrent COVID-19, assess clinical disease urgency, if stable and not compromised may defer investigations till recovered from COVID-19 Defer organ function prior to treatment. Not PET based response evaluation.	For a patient with clinically stable HL at diagnosis (on biopsy), safe to defer commencing treatment until COVID-19 resolved, then elect for outpatient-based therapy. Minimum diagnostic imaging would establish Ann Arbor staging for treatment assignment but not functional response-based therapy.	26 31
LOW RISK Classical Stage I/II A, no B symptoms, E lesions, or bulk and ESR<30	Treatment guided by clinical trial or standard of care protocol. Stage and risk group-based therapy with response-based chemotherapy and radiotherapy. 1. OEPA x 2 with response adapted RT, or 2. ABVD x 2-4 cycles with response adapted RT, or 3. AVPC x 3	Capacity issues for inpatient treatment. Limited access to FDG-PET in all settings. Limited capacity for organ function assessment. Limited capacity for radiotherapy. Capacity issues for enrolment, and support for ongoing clinical trials. Concurrent COVID-19 at diagnosis.	Response evaluation; clinical examination, US scan neck and abdomen, CXR. FDG-PET optional unless enrolled on clinical trial. Monitor pulmonary function with use of bleomycin.	If non-clinical trial, recommend outpatient-based therapy OEPA/COPDAC or ABVD without PET response. ABVD option has less clinic visits. OEPA very effective in low stage without radiotherapy.	If non-clinical trial, consider a non-radiotherapy-based standard of care, especially if PET remains available. If ABVD, and a negative course 2 PET can omit further bleomycin. If radiotherapy indicated, consider dose fractions. RT can be delayed until end but not beyond 3 months.	32 25 33 34

INTERMEDIATE RISK Classical Stage IB or IIB or bulk disease, or E lesions	As above 1. OEPA x 2 + COPDAC x 2 + with response adapted RT 2. ABVD x 4-6 or 3. ABVE-PC x 4 with response adapted RT	As above Limited access to FDG-PET Limited access to radiotherapy	Anatomical imaging following 2 courses of chemotherapy. CXR and US scan, or CT/MRI. Monitor pulmonary function with use of bleomycin.	If non-clinical trial, safe to treat with standard or care without functional imaging response. Safe to omit radiotherapy if complete anatomical response or PET response	ABVD x 6 courses is safe option for LMIC settings without PET and no radiotherapy. If RT indicated, proceed as soon as scheduled or available, and avoid long delay.	32 27,35
HIGH RISK: Classical Stage IIB with bulk, III or IV	As above 1. OEPA x 2 + COPDAC x 4 + with response adapted RT 2. ABVD x 6 + radiotherapy Or 3. ABVE-PC x 5 with response adapted RT 4. Brentuximab-AVDx6	As above Limited access to FDG-PET Limited access to radiotherapy	No BMA for stage IV if PET available. Anatomical imaging with CT or MRI essential to evaluation of treatment response and to guide radiotherapy.	Recommend PEG-GCSF PET response if possible. Monitor pulmonary function with use of bleomycin	ABVD x 6 is safe outpatient - based therapy + RT if indicated. Where indicated avoid delayed radiotherapy for all standard of care therapy treatment.	32 36 24,37,38
NODULAR LYMPHOCYTE PREDOMINANT: Stage I or II without B symptoms or bulk	1. Single node complete resection: Observation only. 2. Bulky Stage I/II, CVP x 3 3. Rare advanced disease Stage III/IV; OPEA/COPDAC	As above Limited access to FDG-PET	Anatomical imaging, CXR, US scans or CT	In low stage disease, safe to defer therapy, with clinical review and reassessment.	Low stage disease is slow growing and usually associated with asymptomatic lymphadenopathy	39,40
RELAPSED: REINDUCTION	Multiple options, see below ICE, or GV, IGV or G + Bv Brentuximab + Bendamustine, Brentuximab + Nivolumab	Full disease restaging, priority for access to FDG-PET is available. Limited access to high dose or SCT supported therapy	Anatomic imaging with CT or MRI essential to assess extent of disease.	Multiple options for therapy. Risk of immunotherapy unknown if COVID-19 develops – best avoid.	2-4 cycles of Bv + bendamustine for outpatient administration Reserve ASCT for later relapse	41-45 46-48

ABBREVIATIONS: ABVD, Adriamycin, bleomycin, vincristine, Dacarbazine; AVPC, Adriamycin (doxorubicin), vincristine, prednisone, cyclophosphamide; ABVE-PC, doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide; COPDAC, prednisone (prednisolone), Dacarbazine, vincristine, cyclophosphamide; ICE, Ifosfamide, carboplatin, etoposide; IGV, Ifosfamide, gemcitabine, vinorelbine; GV, gemcitabine, vinorelbine; G+Bv, gemcitabine, brentuximab; Bv+Bn, brentuximab, bendamustine; OEPA, prednisone (prednisolone), vincristine, doxorubicin, etoposide (etopophos).

4. RETINOBLASTOMA

The management of retinoblastoma includes the clinical evaluation of laterality, the extent of disease, and genetic predisposition. Delay in diagnosis and progression of disease can lead to loss of vision, loss of the eye, and possibly loss of life. Recommendations for adapting the care of children with various intra and extraocular stages of retinoblastoma in LIMIC are in Table 4a, and recommendations for adapting care in HIC settings from the European Retinoblastoma Group (EURbG; http://www.eurbg.org/) are set out in Table 4b.

An ophthalmologist is essential for the diagnosis, staging, and formulation of treatment in coordination with a paediatric oncologist [49] [50]. Assessing *Rb1 germline* mutations guides therapy, aiming to preserve vision and avoid radiation therapy (and future second cancers). Intraocular staging (cT1-cT3) drives treatment: with local (laser, cryotherapy, intravitreal) control or chemo-reduction [49] [51].

If there is no vision and enucleation is not favoured, other modalities are available to preserve the globe when there is no evidence of extraocular spread. In most resource-constrained settings: enucleation with adjuvant chemotherapy according to histopathology risk factors is recommended [52] [50]. When extraocular disease is suspected, evaluation of optic nerve, regional and systemic spread, and central nervous system (CNS) should be completed to deliver appropriate therapy. Regional spread and metastatic disease are curable (if not involving the CNS) [53] [54]. Adjustments to therapy during COVID-19 can be done with careful follow-up according to local human resources and availability of proper staging, medications and radiation therapy. Patients presenting with cough+/-fever on the day of EUA must be postponed according to current protocols Local systematic screening procedures for COVID-19 should be applied.

SUPPLEMENT I TABLE 4a; Guidance for adapted diagnosis and treatment of Retinoblastoma during COVD-19 pandemic in LMIC settings						
PHASE AND STAGE	STANDARD OF CARE	POTENTIAL CHALLENGES	ESSENTIAL INVESTIGATIONS AND MANAGEMENT	TREATMENT AND ALTERNATIVE OPTIONS ESSENTIALS	COMMENTS	REF
DIAGNOSTIC INVESTIGATIONS	EUA Ex under anaesthetic MRI/CT orbit and brain RB1 gene mutation analysis	Limited access to theatres and anaesthesia for EUA Access to diagnostic radiology. Concurrent COVID-19 infection	EUA without delay MRI orbit and brain in selected cases	Defer RB gene analysis until after COVID-19 pandemic	For intra-ocular disease may need to defer until recovery from COVID	50 49
TREATMENT (OVERALL)	1. Local disease control either; laser, cryotherapy, intravitreal therapy or brachytherapy 2. Enucleation 3. Intra-arterial therapy 4. Expert histopathology	As above with limited access to operative resources. Chemotherapy supply. Interventional radiology services.	Immediate Enucleation where indicated. An option for local control of intra-ocular disease, Intravenous chemotherapy	See stage and risk-based recommendations below	Limited access to interventional radiology may preclude intra-arterial therapy. Access to operating theatres may limit regular planned EUA and local therapy.	49,50
GROUP A-C UNILATERAL OR BILATERAL (IRSS 0)	Local treatment and standard of care chemotherapy with CEV or CV	As above, access to timely local therapy and chemotherapy	CT/MRI orbit/brain EUA, and standard blood tests (CBC and coagulation, CMP etc)	Consider single agent carboplatin with local therapy in young infants.	Delay routine surveillance Carboplatin single chemotherapy in infants. Defer RB gene analysis until after COVID-19 pandemic	55 56 57
GROUP D-E UNILATERAL NO BUPHTHALMOS (IRSS I)	Enucleation and chemotherapy CEV or VDC according to histopathology	As above. Access to EUA, enucleation, chemotherapy Timely access to expert pathology	As above – MRI or CT orbit and brain essential EUA and retinal images	Interim chemotherapy options depending on availability of drugs	Do not delay enucleation. Delay surveillance if no pathological risk factors	49 50 52 58 59

UNILATERAL & BILATERAL WITH BUPHTHALMOS (IRSS I)	1. Enucleate upfront if surgically appropriate 2. Or immediate neoadjuvant chemotherapy and delayed surgery after 2-3 cycles. 3. Complete 8 cycles of chemotherapy regardless of pathology. 4. Radiotherapy for marginal resection	As above and access to chemotherapy, EUA, PE, CBC and coagulation CT/MRI orbit. Timely access to expert pathology	Imaging as above of brain and orbit. LP for cytospin cytology Retinal images EUA, PE, CBC and coagulation, CMP	Expert or external opinion for histopathology Chemotherapy – either options CEV or VDC for 8 cycles. CV if no etoposide	Pre-operative chemotherapy cycles 2 or 3 depending on service capacity Radiotherapy – if indicated for marginal resection could be delayed if service capacity issues Safe to defer surveillance Safe to defer RB testing	60 53
BILATERAL, WITH AT LEAST 1 EYE **GROUP D** (IRSS 0 OR I)	Local therapy and chemotherapy with CEV or VC Group D eyes. Enucleation if fellow eye is A-C. Consider initial eye preservation in cases of bilateral group D eyes with vision.	As above Timely access to expert pathology Access to theatre for EUA and enucleation	CT/MRI orbit/brain EUA, and standard blood tests (CBC and coagulation, CMP etc)	Enucleate if indicated after 2-3 cycles	Complete chemotherapy 6 cycles if secondary enucleation regardless of pathology. Safe to defer RB testing	61
ORBITAL DISSEMINATION (+/- RONE) (UNI OR BI) (IRSS III)	Neoadjuvant chemotherapy Enucleate after 2-3 cycles Radiotherapy after local control.	Complex cases management Access to theatre for EUA and enucleation	Imaging as above of brain and orbit. LP for cytospin cytology Retinal imaging, EUA, PE, CBC and coagulation, CMP, BM	Chemotherapy with CEV or VDC And Radiotherapy	Neoadjuvant chemotherapy for high risk disease Delayed enucleation 2-3 cycles XRT after local control May delay surveillance	53 61
METASTATIC (IRSS IV) Distant metastatic disease (uni- or bilateral)	As per standard of care for metastatic solid tumour in the treatment setting. Palliative care an appropriate option for poor prognosis	Challenging case management in context of COVID-19 Access to home palliative care and support	Thorough disease evaluation and staging to determine resource appropriate management	Consider counselling family and offer palliative care	Palliative care with appropriate family support	62

Abbreviations: BM, bilateral bone marrow biopsies; CBC, complete blood count; CEV, carboplatin, etoposide, vincristine; CMP, complete metabolic panel; CT, computerized tomography; CXR, chest x-ray; EUA, exam under anaesthesia by ophthalmologist with indirect ophthalmoscope; IAC, intra-arterial chemotherapy; IVi, intravitreal therapy; LP, lumbar puncture; MRI/CT,

magnetic resonance imaging and/or computerized tomography; PE: physical exam; RB1: molecular testing to evaluate RB germline mutation; RONE: radiographic optic nerve enlargement; VDC; vincristine, doxorubicin, cyclophosphamide;

SUPPLEMENT I TABLE 4b: Guidance for adapted diagnosis and treatment of Retinoblastoma during COVD-19 pandemic in HIC settings; European RB Group (EURbG) and Children's Oncology Group (COG)	
PHASE AND MODALITY OF CARE	**RECOMMENDED CHANGES TO STANDARD OF CARE for European RB group (EURbG) (on behalf of members of EURbG)**

DIAGNOSIS	• ***No delay in diagnosis*:** if clinical symptoms (leukocoria, strabismus, others) or in case of screening for subjects that are genetically at high-risk. • Screening of siblings or offspring of affected unilateral cases without a proven Rb1 mutation, decrease frequency. • Families not at high risk from a proven/or assumed germline mutation but still at above population risk as somatic aetiology has also not be proven. Screening of siblings or offspring of affected unilateral cases without a proven genetic cause maybe be reduced in frequency. This applies to families not at high risk from a proven/or assumed germline mutation but still at above population risk as somatic aetiology has also not be proven. • Orbit and brain imaging when optic nerve head is involved by EUA, fundus not visible and in case of suspicion of extraocular disease (MRI or CT scan according to availability) • Consider delay of MRI brain (pineal), if asymptomatic and unilateral or non-familial RB
CONSERVATIVE MANAGEMENT OF INTRAOCULAR RETINOBLASTOMA	• Restriction of conservative treatment approaches in unilateral retinoblastoma: conservative treatments should only be attempted in children with TNMH cT1 and selected cT2* • For bilateral cases: initiation of intravenous chemotherapy with further treatment adapted according to response and initial staging • Intra-arterial (with single agent or a two or three drug combination of melphalan, topotecan, and carboplatin) versus intravenous chemotherapy (Etoposide+Carboplatin±Vincristine): according to local practice, laterality and availability of anaesthesia/OR/interventional neuroradiologist • No restriction on focal treatment including cryotherapy, hyperthermia, intra-vitreal chemotherapy and brachytherapy • Avoid long anaesthesia procedures for diagnosis and follow-up using a simplified protocol excluding non-essential exams • For patient under active therapy: no delay of EUA for evaluation or therapeutic interventions • If patient cannot travel during conservative treatment, it is recommended to give additional intravenous chemotherapy course(s) • For patient in remission since < 6 months, follow-up with EUA should **not** be delayed more than 4-6 weeks • For patients in remission since > 6 months, follow-up wit EUA should not exceed 6-8 weeks. • Restrict use of MRI in follow-up (perform *only* if optic nerve head is involved, or when the ocular fundus cannot be evaluated fundoscopically because of intraocular haemorrhage or cataract) • Screening other eye in unilateral Rb, depending on risk (Rb1 germline mutation and age): try to postpone
IF FIRST LINE ENUCLEATION	• No staging after enucleation, **except** in high risk patients (pT3)* • Adjuvant systemic chemotherapy when retrolaminar ON involvement ± massive choroidal and isolated choroid involvement equal to or greater than 3 mm • Adjuvant systemic chemotherapy and orbit radiation in patients with pT4 pathologic staging • No MRI for follow-up
EXTRAOCULAR	• Full staging recommended including bone marrow, bone scan, CNS imaging and CSF cytology • Orbit and lymph node pN1: conventional chemotherapy and radiotherapy • Metastatic disease outside CNS (pM1a*): according to local resources. Conventional chemotherapy in all cases. High-dose chemotherapy if possible. Radiation therapy as per response and presence of residual tumour • Palliative approach in CNS disease (pM1b*) should be strongly considered • Only clinical follow-up after treatment

Abbreviations: EUA: exam under anaesthesia, Rb1: MRI: magnetic resonance imaging, CT: computerized tomography,

*Mallipatna A et al. Retinoblastoma. AJCC Cancer staging system, 8th Edition, 2018, Springer International Publishing AG, Switzerland

5. WILMS TUMOUR (Nephroblastoma): Guidance on how to adapt diagnostic work-up and treatment protocols during COVID-19 pandemic.

Wilms Tumour (WT) or nephroblastoma is a highly curable childhood cancer with cure rates around 90% as shown by the SIOP Renal Tumour Study Group (SIOP-RTSG) and the Children's Oncology Group (COG) [63]. During the last decades treatment is stratified according to clinical (SIOP and COG) and molecular risk factors (COG) to avoid under- and overtreatment. This resulted in curing patients by minimizing acute toxicities and late effects and in avoiding as many relapses as possible. To provide this standard of care will be a specific challenge during the COVID-19 pandemic as the ability to deliver adequate diagnosis, treatment and supportive care for patients with WT will vary from country to country and even from region to region depending on the overload of the health care system caused by COVID-19.

Diagnosis.

WT in general is a fast growing tumour with a doubling time between 2 – 3 weeks [64]. A comparison between UK and Germany showed that a delay in diagnosis between first symptoms and tumour diagnosis should be avoided [65]. To avoid sedation of small children for MRI, a CT scan of the abdomen and the lung should be carried out as soon as clinical signs of a tumour mass in the abdomen are palpated and ultrasound shows a kidney tumour. Imaging studies need to be of high quality and should be performed at a paediatric cancer centre. Exact staging at the time of diagnosis needs to rule out bilateral tumours, vena caval thrombus and metastatic disease to the lungs and / or liver. In pandemic circumstances or settings with more limited resources, consideration may be given to staging with US and Chest Xray (CXR). These provide less detail and it is known treatment based on CXR compared to CT findings results in inferior EFS [66]. Nevertheless, whenever available thoracic CT should be done, as it may recognize COVID-19 infection in asymptomatic children and avoid spread of the infection by adopting adequate isolation of infected children. Bone and brain metastasis at diagnosis are rare and further imaging studies are only needed if there are specific symptoms or histology shows clear cell sarcoma (CSSK) or rhabdoid tumour of the kidney (RTK). Given the fast doubling time, patients with predisposition syndromes should maintain diagnostic imaging surveillance frequency, if feasible [67] [68], and parents should be taught how to examine the abdomen of the child for a mass. After discussion with parents, relaxation of the stringent frequency of follow up may be considered in patients with a predisposition syndrome with a relatively low risk of developing WT, balancing the risk of community or hospital exposure to COVID-19.

Start of Treatment

There are differences in treatment protocols between COG and SIOP regarding the start of treatment. COG recommends primary nephrectomy if thought feasible on imaging, with biopsy, chemotherapy and delayed nephrectomy only used for patients not amenable to resection up front. If primary surgery or

biopsy in the COG setting is not possible secondary to operating room limitations under COVID-19, strong consideration should be to start with pre-operative chemotherapy according to SIOP protocols. If neoadjuvant chemotherapy is initiated using a SIOP protocol, the full SIOP approach should be applied. Tumour nephrectomy after pre-operative chemotherapy should be planned from the day of treatment start. If using COG neoadjuvant therapy of regimen DD4A, the feasibility of tumour nephrectomy should be assessed at 6 weeks. If using SIOP induction therapy, tumour nephrectomy should be done at week 5 but could be delayed by up to a further four weeks in non-metastatic tumours providing response was seen during the first 4 weeks. In SIOP 9 it was demonstrated by randomization that a second cycle of AV over 4 weeks resulted in further tumour volume shrinkage, if this was the case during the first cycle. Those without shrinkage were not randomized [69]. In patients with metastatic disease prolongation of preoperative chemotherapy was not tested in the SIOP setting, thus resulting in a maximum of 6 weeks in unilateral metastatic tumours as standard. In bilateral tumours, response to treatment needs to be followed by at least ultrasound. After 6 weeks of chemotherapy the tumour should be re-evaluated and in case of shrinkage chemotherapy can be prolonged up to 12 weeks. In both COG and SIOP settings, every effort should be made to avoid delaying definitive tumour nephrectomy beyond 12 weeks. In case of tumour progression despite pre-operative chemotherapy, immediate surgery should be attempted despite the pandemic situation.

Note that stage I FHWT patients less than 2 years of age had similar EFS and OS if treated with single agent vincristine for 10 weeks compared to the COG regimen EE4A [70]. Observation only after tumour nephrectomy in stage I FH WT with a tumour weight of < 550 g and negative lymph nodes is also a validated strategy [71]. Extension of this to older ages and bigger tumour weights is the subject of an upcoming COG study and would not be considered standard of care, although in pandemic situations a mild relaxation of the age and tumour weight restrictions could be considered after careful discussion with the family. There is recent evidence showing very good outcomes for patients with stage I epithelial tumours of any age irrespective of use of chemotherapy [72]. Observation alone in this cohort is also being considered in the next generation of COG trials but may be considered in pandemic settings with limited resources.

Surgery

Tumour nephrectomies should be done as soon as there is enough capacity to anticipate the possible need for post-operative high dependency/intensive care unit for such a child and that there is an assurance of adequate blood product support given the current pressures on the blood donation system. Avoidance of sharing a critical care unit with ventilated COVID-19 patients is highly recommended. It is also recommended that, in general, surgeons should not perform laparoscopic tumour nephrectomies due to the prolongation of the surgical time. (Please see related IPSO guidelines discussion in this manuscript). The need for resection of lung metastases needs to be balanced on an individual basis if further

intensification of chemotherapy may avoid lung surgery [73]. In case of high risk or unfavourable histology, metastasectomy should be performed in the context of SIOP protocols, if no CR can be achieved by chemotherapy alone but may be achievable by additional surgery [74]. In children younger than 6 months, where international consensus currently advises direct surgery in COG and SIOP, pre-treatment with chemotherapy may be seriously considered over the age of 2 months in COVID-19 situation if operating theatre access is restricted.

Postoperative chemotherapy

Chemotherapy in low and intermediate risk favourable tumours should always be given according to the current treatment plan, with permitted modifications in patients with toxicities. Severe side effects of chemotherapy are rare in these patients [75]. In the setting of adequate resources, it is recommended not to empirically reduce the dose or duration of established chemotherapy protocols, as the impact of such a reduction on risk of recurrence is untested. Treatment for relapse will be more challenging as it will be more intensive and may cause more acute toxicity, including need for transfusion support, and more hospital stays for supportive care. In case reference pathology or central surgical or diagnostic imaging review is not possible, then treatment needs to be given according to locally assigned stage and pathology recognizing that there is a discrepancy in histology and staging between 10 and 15% on central review [76]. If molecular biomarkers are not available for risk stratification purposes in COG, then consideration may be given to initiating chemotherapy solely based on stage and histology. Combined LOH1p and 16q is present in 5% of patients and intensification of treatment has demonstrated a reduced risk of relapse, so if available should be utilized for treatment stratification [77]. 1q gain is an adverse biomarker present in approximately 25-30% of FH WT patients but there is insufficient evidence to recommend intensification for this biomarker outside of a clinical trial.

In patients with high risk or unfavourable histology, treatment is much more intensive resulting in more hospital stays caused by the treatment itself but also because of more acute toxicities, mainly febrile episodes due to neutropenia. As such side effects may also result in treatment delays, one can consider using G-CSF during treatment episodes. Reduction of dosage of drugs should only be considered if episodes of acute toxicities were life threatening in preceding treatment courses. The risk of poorer outcome in this group of patients is not outweighed by sparing toxicity. Patients with relapsed FH WT have an approximately 50% salvage rate whereas those with diffuse anaplastic WT are unlikely to survive a relapse. In the event of overwhelmed critical care infrastructure, palliation of the latter patients in considering prioritization to ventilator access should be consistent with local, established pathways of COVID-19 care.

Radiotherapy

The start of radiotherapy may be possible to delay for not longer than 10-12 weeks if the local situation does not allow a faster start. Such a delay should be avoided in high risk tumours. Dosing, fractionating and radiation fields should not be changed. In case of the need for lung irradiation this should always be considered, if it can be prevented by intensification of chemotherapy using SIOP protocols.

Follow-up

Visits to hospitals should be reduced to the minimal need. Telemedicine may help in this respect. This reduction also includes the frequency of imaging studies after the end of treatment. This frequency should depend on the risk of the patient and the local COVID-19 situation. Parents should be taught to examine the abdomen for masses. CT should not be used for routine surveillance post completion of therapy based on findings from Mullen et al showing no difference in EFS or OS based on imaging modality [78]. Consideration for rapid point of care Ultrasound may be adopted in the absence of access to more routine diagnostic imaging. Brok et al. have called for cessation of diagnostic imaging after 2 years of follow up in the SIOP setting although this has not been widely adopted in COG [79].

Table 5 summaries the options for adapting the treatment of Wilms tumour during the COVI-19 pandemic in UMIC and LMIC settings.

In summary, only a few changes are recommended for the treatment of Wilms tumour compared to standard treatment protocols. They are mainly dependent on the pressure of the local COVID-19 situation and leverage established evidence from the two major cooperative group approaches to renal tumours. Adherence to full dose, timing and duration of evidence-based chemotherapy, surgery and radiotherapy schedules are strongly recommended.

SUPPLEMENT I, TABLE 5: Guidance on the management of paediatric renal tumours during COVID-19npandemic-related resource limitations

PRESENTATION	STANDARD OF CARE	MINIMUM WORKUP	OPTIONAL	ESSENTIALS	COVID ALTERNATIVE OPTIONS	REF
NEW PATIENT WITH SUSPECTED RENAL TUMOUR Either COG or SIOP Standard of Care approaches	1. Immediate nephrectomy (COG) Or	1. Chest X-ray 2. Abdominal ultrasound 3. CT chest for staging where feasible, and assesses risk of concurrent COVID-19 infection	Anatomical Staging CT chest CT or MRI abdomen	Surgery Histology and tumour pathological stage on nephrectomy specimen	1. COG: primary nephrectomy; Where primary nephrectomy is not possible, delay surgery (max.1 month for small tumours), or start pre-op chemo without biopsy if typical clinical and radiological presentation for Wilms	63, 69 80
	2. Pre-operative chemotherapy and delayed nephrectomy (SIOP)				2. SIOP: Delayed nephrectomy; Safe to prolong pre-op chemo (aim for surgery within 6-8 weeks, maximum delay for nephrectomy of 12 weeks)	
POST-OPERATIVE TREATMENT, LOCALISED WILMS TUMOUR (WT)	1. Observation alone for selected Stage I FHWT 2. VCR-ACT-D (VA) or 3. VA + Dox High risk 4, Flank or Whole abdomen radiotherapy	1. Histological subtype 2. Tumour Stage	Molecular analysis for LOH 1p and 16q	Chemotherapy +/-RT according to tumour stage and histology and LOH status if available	1. Restart chemotherapy within 3 weeks of nephrectomy 2. Multi-drug regimens should be given with G-CSF if feasible. 3. Flank/Abdo RT, if required, may be delayed if chemo continuing until facilities to deliver XRT are available and safe. Such a delay should be avoided in high risk tumours, wherever possible.	75-77
POST-OPERATIVE TREATMENT, METASTATIC WILMS TUMOUR (WT)	1. Post-op chemo with 3 drugs (AVD) if complete pulmonary metastatic response to pre-op chemo. 2. Change to 'higher risk' drug regimens if diffuse	1. Chest X-ray 2. Abdominal ultrasound to assess metastatic response prior to nephrectomy	CT chest CT/MRI abdomen Molecular analysis for LOH 1p and 16q if available	1. Imaging for metastatic response assessment (CT preferred) 2. Chemotherapy 3. Radiotherapy if slow metastatic responder	1. As above 2. Defer surgery to metastases 3. Whole lung RT may be delayed if chemotherapy continuing 4. Not recommended to delay flank/abdo RT to stage III high risk histology (anaplasia or SIOP	66,73,74

	anaplasia, slow FHWT responder or in COG regimens positive for LOH 1p and 16q. 3.Consider surgery to metastasis 4. Whole lung RT for slow metastatic responders			4.Surgery with metastasectomy if slow metastatic responder	blastemal type)	
INFANT AGED <6 MONTHS WITH UNILATERAL INTRA-RENAL MASS	Immediate nephrectomy	1. Chest X-ray 2. Abdominal ultrasound, 3. Family history	1. CT chest 2. CT/MRI abdomen preferred if available	1. Surgery 2. Histology and tumour stage on nephrectomy specimen	If surgical access an issue; safe to delay surgery until progression is seen on weekly US, or start weekly vincristine monotherapy on progression	70-72, 63 81
CHILD ANY AGE WITH BILATERAL INTRA-RENAL MASSES	Empirical pre-op chemo & delayed nephron sparing surgery until week 6 to 12 Chemotherapy (Vincristine, Actinomycin-D, consider Doxorubicin, carbo, etoposide or regimen UH2 if high risk histology or suboptimal response	As Above Renal function/BP Family history	As above	Advanced planning for nephron-sparing surgery Histology and tumour stage on (partial) nephrectomy specimens	Pre-op chemo should not be prolonged beyond 12 weeks as increased risk of anaplasia	63-65

COMMENTS: The above guidance is aimed at high and upper middle-income country settings. It is recommended that clinicians maintain as much as possible the dosing strategy and radiotherapy timings related to the cooperative group regimen that is initiated for the patient. For example, if the patient starts with a COG protocol this should be continued and if the patients starts with a SIOP protocol, this strategy should be continued.

Countries who use the SIOP PODC clinical guidelines for the management of children with Wilms tumour in a low-income setting will already apply some of these modifications as part of usual care [23]. There is no published evidence base regarding the potential impact on clinical outcomes of making further adaptations and clinicians working in these settings should be guided by their local experience and resources if the COVID-19 pandemic demands further

changes. Chemotherapy for Wilms tumour is largely deliverable in a day care setting; hence we recommend that scheduling of attendance within the clinic aims to minimise the time the patient is in contact with hospital staff and that they maintain social distancing from other patients in day care. Providing financial support for travel, accommodation and treatment costs to enable parents to complete the treatment of their child may become even more important. If funds allow and wherever possible, accommodation should be provided close to the hospital to reduce costs and also to reduce the use of public transport.

6. LOW GRADE GLIOMAS

Recommendations for adapting the treatment of children with low grade glioma is summarised in Table 6.

For children with low grade glioma receiving chemotherapy, the recommendation is to continue the planned treatment without modification. However, some changes could be considered in order to reduce hospital visits. Amongst the different LGG protocols, monthly carboplatin and TPCV are the most suitable in this context [82] [83] [84].

For newly diagnosed patients, situations are closely related to the resources available. As the diagnosis of low-grade glioma is generally only suspected on imaging studies, this raises more broadly the issue of the management of a child with newly diagnosed brain tumour [82] . In high income countries most children with a suspected diagnosis of intracranial brain tumour will be managed urgently and undergo immediate surgery. This may not be the case in countries with limited resources or in areas were access to operating theatre and ICU is affected by the COVID-19 situation. For these reasons, a number of centres are recommending an immediate shunt or third ventriculostomy only approach when signs and symptoms of increased intracranial pressure can be controlled by CSF diversion. This allows for prompt discharge within 24 hours and planned delayed resection when the epidemic situation is improving.

For children without neurofibromatosis type 1 (NF1) with a suspected diagnosis of low grade glioma 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.

While 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 clinical decision making.

SUPPLEMENT I TABLE 6. Guidance on the management of paediatric low grade gliomas during pandemic-related resource limitations

CLINICAL PRESENTATION	STANDARD OF CARE	MINIMUM WORKUP	ESSENTIAL	COVID ALTERNATIVE	REFs
Resectable tumour; **-no hydrocephalus,** **-mild clinical symptoms**	Elective surgery	1. Clinical assessment and physical examination 2. MRI scan or CT scan if MRI not accessible	Histology, postoperative scan (can be delayed)	Safe to delay surgery with regular contact; consider steroids	82
Resectable tumour; **- no hydrocephalus,** **- but significant signs or symptoms**	Urgent surgery	1. Clinical assessment and physical examination 2. MRI scan or CT scan if MRI not accessible	Histology, postoperative scan (can be delayed)	No alternative, needs urgent admission, investigation and surgery	
Resectable tumour, **- with hydrocephalus**	External ventricular drain (EVD) or other CSF diversion, and Surgery for resection of tumour	1. Clinical assessment and physical examination 2. MRI scan or CT scan if MRI not accessible	Histology, postoperative scan (can be delayed)	- CSF diversion and regular follow-up if no other option (i.e. limited access to OR and ICU)	82
Unresectable tumour, **- no hydrocephalus,** **- minimal neurology or** **- no significant threat to vision**	1. Biopsy only followed by adjuvant chemotherapy treatment 2. Standard of care chemotherapy	1. Clinical assessment and physical examination 2. MRI scan or CT scan if MRI not accessible 3. Visual assessment if OPG	1. VCR/Carboplatin 2. TPCV 3. Vinblastine (weekly) 4. Carboplatin (monthly)	- No biopsy - Careful wait and see if clinically indicated (repeat visual assessment if OPG) - Neoadjuvant chemotherapy or radiotherapy, without biopsy	82 85 86 84

Unresectable **- with hydrocephalus** **- or significant neurology** **- or significant threat to vision**	1. CSF diversion if hydrocephalus , 2. biopsy followed by 3. adjuvant treatment	1. Clinical assessment and physical examination 2. MRI scan or CT scan if MRI not accessible 3. Visual assessment if OPG	1. VCR/Carboplatin 2. TPCV 3. Vinblastine (weekly) 4. Carboplatin (monthly)	- Urgent CSF diversion for hydrocephalus - No biopsy - Careful wait and see (repeat visual assessment with OPG unless significant threat to vison - Neoadjuvant treatment (Chemotherapy or radiotherapy) without biopsy	As above

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COVID-19 PANDEMIC SUPPLEMENT II

TITLE: Specific advice for adapting care for children with cancer in response to pandemic COVID-19: Radiotherapy, Surgery, Palliative Care, and Infectious Disease; the Lombardy Centre and the St Jude Global COVID-19 Observatory

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INTRODUCTION:

Multidisciplinary care is the cornerstone of paediatric oncology, from diagnosis, therapy and supportive care. The coordination of services in a timely fashion has resulted in improvement in outcomes throughout all childhood cancers. Here we present extended advice for the sustained provision of cancer care during the COVID-19 pandemic from radiotherapy, surgery, palliative care and infectious disease.

We have also included unpublished experience on the provision of care during the COVID-19 in the paediatric haematology oncology service in Monza, Lombardy, Italy.

Finally, we have included details on the Global COVID-19 Observatory and Registry, a joint collaboration between St Jude Global and SIOP.

RADIOTHERAPY: (PROS CONTRIBUTORS :

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1. Radiotherapy for Children - Advocacy Needs in times of COVID-19:

Radiotherapy plays an essential role in the cure of many tumour types in children. The current COVID-19 crisis may significantly impact on the accessibility of radiotherapy. Paediatric cancers, when managed appropriately, are more likely to be curable compared to many cancers that occur in adults. Therefore curative cancer treatment in children should be given a high priority. Radiation oncologists treating children have a heightened responsibility to triage and coordinate cases with their paediatric oncology colleagues and to advocate for the treatment of paediatric patients within their radiotherapy department.

2. Impact of COVID-19 on Radiotherapy Resources:

The COVID-19 pandemic may have a direct impact on radiotherapy resources, primarily from the depletion of staff infected with the virus or deployed to another area in their institution where shortage of staff may have occurred [1] [2] [3]. Additionally, there may be disruption in equipment supplies and machine maintenance. Radiotherapy centres should have a contingency plan in place to deal with these situations. Such a plan should include revising the staffing model and workflows. Given the limited number of radiation oncologists skilled in the treatment of paediatric patients at any given centre or even at the country level, it will be preferable to protect them for exposure risks by avoiding cross-coverage of adult services. Radiation oncologists may also need to refer children to a different facility, if available and if travel allows it, if their own is no longer able to treat children.

3. Impact of COVID-19 on Treatment Regimens:

There are currently no specific data nor recommendations for paediatric radiation oncology care in the setting of the COVID-19 pandemic. In principle, the majority of recommendations and guidelines for infection risk mitigation in radiotherapy centres for adults will be applicable to children needing radiotherapy. The overarching goal for any radiotherapy facility is to reduce the risk of transmission of COVID-19 to patients and staff without compromising the clinical benefit and outcome of all patients. Nonetheless, in the context of an active COVID-19 pandemic, it may be acceptable to omit or defer radiotherapy for some paediatric tumours with the use of chemotherapy, without significantly affecting survival probability. Centres will need to develop more specific plans and flexibility for treatment regimens based on current threat levels from

COVID-19 and staff availability. As a general principle, but particularly for paediatric cancers, radiotherapy plans/decisions should not be made in isolation but need to be closely coordinated with paediatric haematology/oncology and surgery colleagues. In all cases, the current pandemic calls for an extra layer of care coordination for triaging of cases for urgency for treatment.

Disease-specific radiotherapy adaptation recommendations for adult tumours have started to emerge from various societies and organizations [4] [5] [6]

Similar efforts are underway for paediatric tumours (personal communications Boterberg et al.). Many treatment protocols for childhood tumours from cooperative groups in Europe and North America dictate specific radiotherapy timing based on clinical rationale or published evidence. In an environment of depletion or limitation of radiotherapy resources, centres may need consider deferral options for certain tumours. In some diseases, there may be some historical or other level of evidence that suggests that delays in radiotherapy will not negatively affect the outcome. Centres may need to take decisions on which tumours will be appropriate for delay/deferral of radiotherapy based on the local environment and current scenario.

There may be some 'low grade' tumours with more indolent behaviour where radiotherapy can be safely deferred or even omitted. For example, low-grade gliomas of the brain are often observed for a long period of time in the absence of progressive or impending symptoms. There are also effective chemotherapy regimens that can be used initially instead of radiotherapy. However, in such diseases, there may be a scenario where a patient will require urgent local intervention when presenting with acute symptoms where surgical intervention should be considered. The decisions for those urgent or emergent cases will need multi-disciplinary discussion with the priority given to the modality most readily accessible. Haematological malignancies will be often successfully treated with chemotherapy alone.

Another important consideration is the possibility of shortening treatment courses for all patients, including children. Most tumours are currently treated with 1.5 to 1.8 Gy per fraction which allows for better tolerance with concurrent chemotherapy. This conventional dose fractionation is also favoured in order to minimise the risk of late effects. It may be a safe approach to increase the daily dose to 2 Gy in order to reduce the treatment duration by a few days, and thus also the burden on the department. In extreme situations, one may consider increasing the daily dose to 2.5 or even to 3 Gy while delivering a biologically equivalent dose.

One important consideration with altered fractionation is to try to administer radiotherapy without full overlap with concurrent chemotherapy, particularly those drugs known to cause significant radiosensitization (e.g Adriamycin, Dactinomycin).

Palliative cases may present different challenges. Commonly, they present with more urgent symptoms, often in patients in with very advanced disease, immunosuppression from chemotherapy and other needs. Initially, the decision depends on whether symptoms can be managed medically by the paediatric oncologist, palliative care or other services. In case where radiotherapy is still the best option, there should be very strong consideration for hypofractionated courses. There is a substantial evidence, primarily in adults, but also applicable in children, for effective palliation of bone metastases using a single fraction. Other accelerated fractionation regimens can be used for palliation of metastasis in the brain, liver, lungs, etc. For the treatment of DIPG, an aggressive brain tumour which needs prompt initiation of radiotherapy, there is a randomized controlled study using accelerated fractionation which resulted in a similar response and outcome compared to the more protracted course of radiotherapy.
Cooperative group SIOPE Radiation Oncology Working Group had come up with recommendations on modification of radiotherapy treatment regimens during constrained resources.

4. Impact of COVID-19 on Radiation Treatment Delivery and Follow up care:

The impact of COVID-19 on the clinical course and outcome of children receiving radiotherapy and/or concurrent chemo-radiotherapy is not yet known; however, emerging data suggest that cancer patients in general, both on active treatments and in survivorship phase, are more vulnerable to complications from COVID-19 infection [7 8 2 6]. When making decisions on embarking on radiotherapy for children, providers need to be extra vigilant in the screening of patients for suspected COVID-19 infections and taking proactive measures and protocols for interventions. Immunocompromised children need particular attention, especially younger children (<6 years) who may be at higher risk for COVID-19 complications. As such, some centres have advocated for routine testing of all patients, including children, prior to the start of radiotherapy. Having all patients and the accompanying parent wear masks has been implemented in some centres. Overall, the symptomatic presentation of COVID-19 in children is fairly low, and it is reasonable to assume that children during radiotherapy may stay asymptomatic or exhibit only mild symptoms. This should not prevent vigilant screening of symptoms for all children undergoing radiotherapy, especially ones who are already

significantly immunocompromised. Moreover, some side effects of radiotherapy and chemotherapy can mask or mimic COVID-19 symptomatology, like respiratory symptoms, fatigue, diarrhoea and sore throat. Providers should have a very low threshold for testing for COVID-19. All centres recommend screening of symptoms for all patients undergoing daily treatment, but routine testing may not be practical in the setting of low testing capacity. In the case of proven COVID-19 positivity, clinicians may face a bigger dilemma in light of lack of evidence as to whether it is safe to continue the treatment of the patient. Borrowing from adult experience [6 9], patients with asymptomatic disease may be safe for continuation of the radiotherapy course when a treatment gap will significantly affect local control and/or prognosis. If the patient becomes symptomatic, it is best to make treatment decisions weighing the risks and benefits based on the severity of symptoms, the risk from treatment break or discontinuation. Patients with high-grade symptoms/toxicity will require a treatment break. The decision to resume treatment may be equally as challenging. Some experience suggests that patients are safe to resume treatment only after they become COVID-19 test negative. However, whether asymptomatic patients who still test positive have any increased risk is currently unknown.

During the treatment delivery phase, it is very important to plan the feasibility of the treatment of a child (and caregiver) in the setting of social distancing and/or isolation measures. The data suggests that, compared to adults, children may remain asymptomatic or mildly asymptomatic from COVID-19 infections and may shed virus for longer periods than adults (especially if they have been on steroid medication). This may pose an additional risk for exposure to adult oncology patients and to staff in the radiotherapy centre which needs to be taken into account in infection prevention measures. However, this should not be a reason for omitting or delaying curative radiotherapy for children during COVID-19 pandemics.

Families should be provided with resources to be able to adhere to the treatment regimen. Infection prevention measures within the treatment facility and during transfer between various care facilities should be upheld to the highest standards and may involve infectious disease and appropriate specialists.

After completion of radiotherapy, follow up care for children may need to be provided with the goal of limiting exposures and spacing out tests and appointments. The use of telemedicine tools is also reasonable for such visits.

There is a hope that radiotherapy centres will be able to resume usual operations after an epidemic is over; however, lessons learnt from epidemics will impact future care delivery models.

5. Sedation and Anaesthesia need in time of COVID-19:

Centres which regularly treat children generally have paediatric anaesthetic services available for daily intravenous sedation or anaesthesia of younger children. During the earlier stages of the pandemic, daily radiotherapy anaesthetic services may still be available. Use of intravenous sedation is preferred over inhaled anaesthetics in order to prevent anaesthetic machine contamination. Where the extent of the COVID-19 pandemic has affected staffing and anaesthetists are required to staff intensive care units, then a daily anaesthetic service for radiotherapy may become problematic. Transfer of all paediatric cases requiring radiotherapy to a single centre per city may help to limit the numbers of required anaesthetists. Where necessary, use of older mild to moderate intravenous, intramuscular or oral sedation methods by radiation oncology or paediatric staff without the presence of an anaesthetist could be considered. These techniques have been practiced safely and with good outcomes in many low and middle income countries [10] [11].

6. COVID19: General Mitigation Measures for Radiotherapy:

Table 7 summarises recommendations from PROS for the mitigation of the impact of COVID-19 on the provision of paediatric radiation services.

SUPPLEMENT II Table 7: Recommended general measures for mitigation of Paediatric Radiation Services during COVID-19 pandemic	
GENERAL MEASURES APPLICABLE PAEDIATRIC RADIATION ONCOLOGY SERVICES	• Decrease patient numbers by prioritization and triaging of cases based on acuity, curability, etc. Investigate options of delaying treatment, alternative modalities and condensed regimens, when feasible • Screening of patients prior to their appointments (some recommend testing of patients, especially if anaesthesia and intubation required, prior to commencement of treatment, if testing is readily available, with a policy to delay patients with active COVID-19 infection where it will not influence prognosis). • Strict adherence to social distancing standards in patient waiting rooms. • Limit foot traffic into the department by allowing a single patient escort. • Restrict entry to children (siblings or multiple family members) who may be vectors of the virus without being symptomatic. • Strict adherence to enhanced cleaning and sanitation of surfaces between cases, with approved disinfectants (particular attention to high touch surfaces like treatment equipment, immobilization devices, keyboards, doors, etc.) • Identification of high-risk areas within the radiotherapy department; and use of PPE in areas where aerosolization procedures may be done, including ear nose and throat examinations, making of thermoplastic masks, and during the fitting of masks and positioning for radiotherapy treatment • Safeguarding the levels of staffing, especially in a high community transmission environment, by implementing a shift system for therapists, nurses and other clinic personnel where possible • Allocation of a specific machine for treatment of patients with known positive COVID-19, who cannot be delayed, treating those patients at the end of the

	day with strict zoning. During later stages of the pandemic where rising numbers of community-acquired infections are seen, measures such as full PPE for staff is required • Use of telemedicine/telehealth tools for appropriately selected patient encounters • Deferral of routine long-term follow-up, survivorship and screening visits

PAEDIATRIC SURGERY: IPSO COVID-19 STATEMENT

Jonathan Karpelowsky (Lead), Simone Abib, Abdelhafeez Abdelhafeez, Jörg Fuchs

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-CoV2 transmission is highest when intervening in the airway or respiratory system due to dense viral load aerosolization [12]. 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 Personal Protective Equipment (PPE) and care for patients with suspected or confirmed COVID-19 cases in designated operative and perioperative area[13-15]. The risk of transmission of infection during tumour 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-CoV2 transmission[16,17], but extra care should be taken in regards smoke and gas evacuation if the surgeon chooses minimal invasive access.

During this evolving pandemic, surgery scheduling and prioritization is a shared decision involving 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, post-operative critical care is needed, patient infection with SARS-CoV2 or hospital resources would not enable an optimal surgical outcome. Elective procedures and surgery for benign or low-grade tumours with low metastatic risk should be delayed and reviewed within a planned timeframe.

Table 8 below summarises IPSO recommendations for general service provision and surgical intervention in children with cancer during the COVID-19 pandemic.

SUPPLEMENT II TABLE 8; IPSO STATEMENT, Guidance for the provision of surgical services during COVID-19 Pandemic		
SERVICE	GUIDANCE AND RECOMMENDATIONS	Refs
COVID-19 RELATED SURGICAL ISSUES	1. Patients with COVID-19 may present more unwell 2. COVID-19 may present with abdominal pain, mesenteric adenitis or diarrhoea leading to delayed diagnosis of acute abdomen/peritonitis 3. Delayed presentation to hospital surgical services with acute surgical problems (acute abdomen) may be delayed due social isolation, hospital capacity issues or family reluctance to present acutely to hospital	
CLINICAL SERVICE PRIORITIES	1. Non-urgent in-person clinic/office visits should be minimized, postponed, or offered via tele/videoconferencing when available 2. Only one person stays with the child throughout the period needed for treatment – as per institutional policy 3. Review frequency of catheter flushing to q3 monthly	18
PRE and PERI-OPERATIVE MANAGEMENT	1. If readily available and practical, surgical patients should be ***tested pre-operatively for COVID-19*** for staff safety, intraoperative and postoperative care and possible complications. 2. If testing is not available, consider the patient COVID-19 positive for the procedure. 3. Anaesthesia for cross sectional imaging (CT/MRI) should avoid intubation, if possible. 4. Performing aerosol-generating procedures in negative pressure rooms, if available.	
GENERAL OPERATIVE GUIDANCE	1. Airborne precaution PPE including whether a PAPR or P2 / N95 mask and face shield with impervious gown 2. Performing **endotracheal intubation** on patients with COVID-19 or suspected COVID-19 we **suggest** using video-guided laryngoscopy, over direct laryngoscopy, if available; (low quality evidence). 3. Designated COVID-19 operating rooms, if feasible 4. Only essential staff should be participating in the surgical case with minimal staff change over. 5. Clear briefing as to adequate PPE during the pre-surgical briefing and checking availability prior to surgery as recommended by national or international organizations including the WHO or CDC 6. Clear donning and doffing areas and procedures as recommended by national or international organizations including the WHO or CDC . 7. If available, monopolar diathermy pencils with attached smoke evacuators should be used. 8. Surgical equipment used during procedures with COVID-19 positive suspected COVID patients should be cleaned separately from other surgical equipment. 9. The operating room to remain closed for 30 minutes for air exchange after the patient leaves the room.	12,13,15

POST OPERATIVE CARE	1. Aerosol-generating procedures should occur in negative pressure rooms with adequate PPE . 2. Post-operative activities considered aerosol-generating include high flow oxygen, CPAP , suctioning and respiratory physiotherapy to clear secretions	15
MINIMALLY INVASIVE PROCEDURES (MIS)	1. Small incisions for ports to allow for the passage of ports but not allow for leakage around ports. 2. CO2 insufflation pressure kept to a minimum and ultra-filtration (smoke evacuation system or filtration) should be used, if available. 3. Safe evacuation of all pneumoperitoneum via a filtration system before closure, trocar removal, specimen extraction or conversion to open.	
DISEASE SPECIFIC RECOMMENDATIONS	1. **Vascular Access:** Vascular access should still be offered where feasible, if not, PICC lines or peripheral IV access may be considered. Removal of vascular access may be delayed where this poses minimal risk to the patient. 2. **Surgical biopsy:** Avoid any delays for surgical tumour biopsy where indicated, to establish a safe and reliable diagnosis especially if interventional biopsies unavailable. 3. **Wilms Tumour:** delay nephrectomy or elect for start pre-operative chemotherapy without biopsy if clinical presentation for Wilms; Prolong pre-op chemotherapy up to a maximum 8 weeks for localized tumours and up to 12 weeks for bilateral. 4. **Neuroblastoma:** Low-risk and resectable tumours; proceed to surgery as clinically indicated; High-risk tumours consider delayed surgical resection with prolonged chemotherapy or consider altered sequence of treatment phases in consultation with oncology team. 5. **Hepatoblastoma**: Standard of care timing of surgery. Where primary resection is indicated (PRETEXT I/II) and feasible proceed to surgery; If primary surgery not feasible commence stage and PRETEXT specific pre-operative chemotherapy and delayed resection. Prolonged pre-operative chemotherapy is safe if AFP and anatomical response up to 6 cycles. 6. **Germ cell tumours**: If tumour marker positive, commence pre-operative chemotherapy and delayed surgery. If clinical features and location suggest benign consider postponed surgery unless tumour-related compromise (massive mediastinal or pelvic locations). 7. **Lymphoma**: Urgent surgery indicated for diagnosis and surgery is urgent for diagnosis and complications. 8. **Bone and Soft Tissue Sarcoma**: Plan local therapy as per standard of care. Where chemotherapy sensitive and responding to pre-operative chemotherapy safe to delay until surgery safe and possible. For relatively chemotherapy insensitive tumours (osteosarcoma) and soft tissue sarcomas, proceed to surgery where possible according to standard	

	of care protocol. 9. **Surgery for palliative care**: maintain non-invasive supportive approach, but operate if surgically urgent and clinically indicated.	

PALLIATIVE CARE AND FAMILY SUPPORT DURING COVID-19 PANDEMIC

Justin Baker (Lead), Marisol Bustamante

Children with high-risk cancer 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 paediatric palliative care that are critically important when contemplating how best to respond to these patients' and families' needs is the midst of this pandemic [19]. The World Health Organization defines palliative care for children as the active total care of the child's body, mind, and spirit while giving additional support to the family. This approach uses early identification and treatment of sources of physical, psychosocial, and spiritual distress to prevent and relieve suffering in patients with life-threatening illnesses and their families. The early integration of this approach is standard of care [20] and must be instituted when a high-risk cancer is diagnosed and should continue throughout the course of illness, regardless of whether or not a child receives treatment directed at the disease. Children with cancer suffer from a distinct and significant constellation of symptoms secondary to both the primary disease and the toxicities of treatment, and these adversely affect the quality of life for both patients and their families [21]. Symptoms at end-of-life related to COVID-19 have not been described in this population, but dyspnoea and delirium are highly prevalent in children with cancer at end-of-life [22]. These and other symptoms are likely to be exacerbated by the virus. Additionally, the negative effects on parents' and caregivers' long-term emotional and psychological well-being of witnessing significant suffering [23] and experiencing poor communication/insensitive delivery of bad news are well documented [24].

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 Table 9.

SUPPLEMENT II TABLE 9; Guidance for the provision of palliative care services during COVID-19 Pandemic	
Area	Recommended adapted care
CORE ATTRIBUTES OF PAEDIATRIC PALLIATIVE CARE	1. The WHO defines palliative care for children as the active total care of the child's body, mind, and spirit while giving additional support to the family: 2. Identification and treatment of sources of physical, psychosocial, and spiritual distress • prevent and relieve suffering in patients with life-threatening illnesses and their families. • early integration of this approach should be seen as standard of care 3. Institute palliative care when a high-risk cancer is diagnosed and should continue throughout the course of illness, • regardless of whether or not a child receives treatment directed at the disease • mitigate symptoms of primary disease and toxicities to improve quality of life 4. Symptoms at end-of-life related to COVID-19 have not been described in this population, but dyspnoea and delirium are highly prevalent in children with cancer at end-of-life 5. Other symptoms are likely to be exacerbated by the virus, including negative effects on parents' and caregivers' long-term emotional and psychological well-being of witnessing significant suffering and consider appropriate/sensitive communication
ROLE AND RESPONSE OF PALLIATIVE CARE AND HOSPICE SERVICES	1. Respond rapidly and flexibly to suffering 2. Ensue symptom management protocols are available 3. Distressing symptoms in can usually be managed in a step-wise fashion • Step 1: Evaluation • Step 2: Treat underlying causes • Step 3: Integrative & rehabilitative/supportive therapies • Step 4: Pharmacological therapy • Step 5: Re-evaluation at regular intervals and following interventions 4. Educate generalist providers in paediatric symptom management 5. Aid in triage and decision-making of patient treatment priorities and resource allocation 6. Assist in shifting resources and patients and families into the community setting 7. Facilitate redeployment of volunteers to aid in psychosocial and bereavement care 8. Facilitate support among the healthcare staff and introduce measures to promote resilience and help cope with the additional stress 9. Implement technological strategies to communicate with patients and caregivers and protect healthcare providers

INFECTIOUS DISEASE and SUPPORTIVE CARE FOR COVID-19

Title: SARS-CoV-2 infection and COVID-19 in children with cancer

Sheena Mukkada and Miguela Caniza

INTRODUCTION

The objective of this supplemental material is to describe what is currently known about SARS-CoV-2 as it relates to other respiratory viral diseases in the paediatric oncology and HSCT population; also, to highlight risk factors associated with severe outcomes which may guide focused interventions. As SARS-CoV-2 recently emerged, there are multiple evidence gaps which would benefit from further investigation. As clinical trials continue to accrue and clinical experience grows, our understanding of recommended treatments and the patient population which could most benefit from them will continue to evolve.

CLINICAL CHARACTERISTICS AND SIGNIFICANCE

The clinical spectrum of confirmed or suspected SARS-CoV-2 infection in children was described by Dong et al in a retrospective review of 2135 paediatric patients reported to the Chinese Centre for Disease Control and Prevention from January 16, 2020, to February 8, 2020 [25]. COVID-19 severity was classified as asymptomatic, mild, moderate, severe and critical based on clinical manifestations and the healthcare support required. Among confirmed cases, over 50% were classified as either asymptomatic or mild. Of patients that required medical interventions, 93.4%, were moderate infections; very few were severe and critical and required advanced medical care.

Since 14 April 2020, the Global Registry of COVID-19 in Paediatric Cancer has been collecting clinical characteristics of children with cancer and laboratory confirmed SARS-CoV-2 infection. This registry has the largest number of reported information of children with cancer and SARS-CoV-2. Actualized descriptive statistics and summary reports are available in the site; preliminary analysis shows that children with hematologic malignancies are the most affected group (possibly due to the frequency of the disease and the length of treatment), that most were receiving cancer directed therapy and were symptomatic when they were tested, that the most frequent symptoms were fever and cough; and imaging reported in those patients with positive findings indicates similar findings as those reported in the literature in immunocompetent children [26]. At this moment, it is unclear whether a more severe disease can occur in these patients and what risk factors (use of high dose of steroids, radiation, and organ dysfunction conditions) may determine clinical severity[27].

Most of what we know of the clinical characteristics and severity of coronavirus in immunocompromised children is based on our knowledge of other coronaviruses[28] . Ogimi et al, described 85 patients who were immunosuppressed due to cancer treatment (hematologic and solid organ malignancy), transplant (HSCT and solid organ), chronic use of immunosuppressive drugs, and primary immunodeficiency. The most frequent clinical symptoms of these patients included fever, cough, and sore throat; and in those who had imaging, abnormalities were found in about half of them[28] .

Based on knowledge of other respiratory viral diseases in children with cancer, it is imperative to assess the risk for progression of SARS-CoV-2 infection to more severe clinical manifestations and assess the risk for mortality. Risk factors identified in other viral illnesses include T-cell lymphopenia, presence of organ dysfunction including pulmonary, cardiac and renal comorbidities and their functionalities. Coinfections are also risk factors for severe disease, and accurate diagnosis may enable the use of targeted therapy for coinfections. A diagnosis of SARS-CoV2 does not exclude other infections in children with febrile neutropenia, and antibiotic therapy should be administered as per institutional guidelines.

In children with risk factors for progression of SARS-CoV-2, and in those who present with moderate to severe infection, it might be prudent to withhold intensive immunosuppressive therapy until clinical improvement occurs, and possibly until there is viral clearance. In children with severe and critical disease, one should assess the effect of SARS-CoV-2 on other organs including the heart as that will impact supportive measures such as fluid resuscitation; and the emerging information of the effects on coagulation and renal function[29] . Antiviral therapies may be indicated for patients at high risk for progression to severe disease but the literature at this time is inconclusive as to which therapy should be routinely recommended[30]. Risk factors for progression and severe outcomes are summarized in Table 10.

MANAGEMENT PRINCIPLES

Management of SARS-CoV-2 in children, as in adults, is rapidly evolving with the understanding of the pathophysiology of this infection. Use of new or repurposed drugs with antiviral effects and immunomodulators will be guided by the results of clinical trials [31]. A listing of registered open trials can be found on clinicaltrials.gov. When using medications, one must be mindful of drug interactions and coexisting medical conditions. Recommendations to treat the SARS-CoV-2 infection and its complications in this population, for now, are extrapolated from what is known for other non-SARS-CoV-2 respiratory viral infections [28 32].

The severity (Box 1) and day of illness are important pieces of information that could guide care providers. SARS-CoV-2 can progress to a more severe condition toward the end of the first week[33]. Therefore, plans for further medical assessment, diagnostics and therapeutics can be affected by knowing the day of illness, and length of isolation can be anticipated.

For patients with asymptomatic and mild disease, decision making may be affected by assessment of risk factors for progression requiring interventions (Table 10). If no risk factors are present, these patients can be managed as outpatients; or through telephone follow ups.

For patients with moderate disease, evaluation of pulmonary, cardiac, and renal function will assist in anticipating the medical support that will be needed and the selection of medications, avoiding those that can interact with each other and have toxic effects on some organs. If patients are not admitted, they should have frequent clinical evaluations.

For patients with severe and critical disease, efforts should be directed at preventing organ damage and mortality. Most of these patients will need critical care support and those with ARDS may need ventilatory support to maintain appropriate oxygenation. Cardiac, renal and coagulation functions should be monitored and may require separate intervention. Antibiotics might be indicated for possible co-infections. Administration of antivirals, intravenous immunoglobulins and convalescent plasma must be guided by careful evaluation of other medications and overall fluid requirements in order to prevent adverse effects. These patients can have prolonged hospital stay and usually need a multidisciplinary care team. Prolonged shedding, and if on ventilatory support, aerosolization of SARS-CoV-2 and contamination of healthcare personnel are a real threat.

DIAGNOSTICS CONSIDERATIONS

As the pandemic advances, there is a need to provide reliable recommendations on diagnosis that can help rapidly and accurately diagnose infected patients, optimize resources, and aid in the development of hospital practices.

Diagnostic testing modalities: Nucleic acid detection is the recommended diagnostic approach, including for immunocompromised paediatric patients. Adequately obtained samples from the nasopharynx and oropharynx are validated specimen types for less ill patients, whereas sputum and bronchoalveolar lavage specimens may be obtained in patients with lower respiratory tract infection [34]. Nasopharyngeal (NP) washes, which were preferred for detection of other respiratory viruses at many centres before the COVID19 pandemic, may expose healthcare workers to greater risks of aerosol generation. The use of NP swabs instead of NP washes may preserve PPE and protect healthcare workers. RT-PCR using rectal swab has also been used and there are suggestions

that this method may remain positive longer than samples of respiratory origin[35]. Testing methodologies employed also depend on availability of testing swabs, and alternative testing methodologies, including salivary self-collection methods, may gain popularity due to reagent availability and testing volumes [34]. Use of antibody assays in immunocompromised hosts will remain limited by impaired antibody production due to primary disease and its associated treatment. Furthermore, even in immunocompetent hosts, it is not yet known whether antibodies are protective against repeat infection challenge.

Who to test: When determining who to test, centres must consider the availability of diagnostic testing. At minimum, symptoms-based screening is recommended targeting patients presenting with fever, including patients presenting with febrile neutropenia, and patients presenting with respiratory symptoms with or without fever. If resources are adequate, screening all patients before procedures requiring anaesthesia may protect healthcare workers with high exposure risk. In centres with high community population prevalence and adequate testing capacity, it may be rational to screen all patients before admission due to the potential for asymptomatic infection. This could be useful both for prevention of asymptomatic transmission and for anticipating risks associated with further chemotherapy in a high-risk host. When performing respiratory viral testing, it is important to test for other respiratory viruses in addition to SARS-CoV2. Currently utilized assays have a range of manufacturers and performance characteristics vary by assay, but the possibility of false negatives does exist. Retesting parameters for patients who initially test negative are not well established. If a patient persists with or develops new signs or symptoms concerning for COVID19, it is reasonable to consider retesting.

Prolonged viral shedding: While concern has been raised over the detection of SARS-CoV-2 RNA by PCR in stool for prolonged amounts of time even in immunocompetent paediatric hosts[35], the significance of this positive result is unknown at this time. Detection of viral nucleic acid confirms that the virus was once present but does not prove replication fitness or ability to infect a new host. A recent publication shows that stool and sputum specimens in 2/3 of immunocompetent young adult subjects had detectable RNA at 3 weeks post infection despite resolution of clinical symptoms[36]. Nevertheless, despite high RNA concentration, virus was detectable in culture only through day 8 of symptoms in this epidemiologically linked cluster and was never cultured from the stool [36]. Discerning the location and duration of shedding of replicable virus has implications for infection prevention, as the nature and duration of precautions used should be based on assessment of transmission potential.

Box 1. COVID-19 Disease Severity[25]	
Severity Level	**Description**
Asymptomatic	Patient has no symptoms, positive SARS-CoV-2 diagnostic test taken for other reasons
Mild	Patient might have fever or not; has some upper respiratory symptoms (cough, sore throat, rhinorrhoea, stuffy nose), chest is clear to auscultation; or has some gastrointestinal symptoms (nausea, vomiting, diarrhoea) or some generalized symptoms (fever >100.4 F / >38 C, headache, body aches or myalgia, chills), or other mild symptoms such as loss of sense of smell, loss of sense of taste.
Moderate	Patient might have signs and symptoms of lower respiratory tract infection (e.g. pneumonia / bronchiolitis), fever, cough, but does not have increase work of breathing, does not require oxygen, the chest radiograph or computed tomography has abnormal findings attributed to SARS-CoV-2
Severe	Patient has respiratory distress (shortness of breath, tachypnoea) and requires oxygen administration via nasal cannula/facemask, high-flow nasal cannula. Patient might require intravenous fluid support.
Critical	Patient requires ventilatory support (CPAP/BiPAP; Intubation); patient might have one or multiple organ dysfunction (cardiac, renal, neurologic, liver).
(Dong et al Pediatrics 2020)	

SUPPLEMENT II TABLE 10; COVID-19 Risk factors [32]	
Risk factors for progression to LRTI	**Mortality risk factors**
• **Lymphopenia (RSV), other cytopenias (PIV)** • **Exposure to pulmonary toxins (smoke, total body irradiation at high doses)** • **The APACHE II score** • **The presence of co-pathogens** • **High doses of steroids**	• Stem cell source • Oxygen requirement • High-dose steroid use • APACHE II score • Cytopenias
(Waghmare et al Blood, 2016)	

THE MONZA, LOMBARDY EXPERIENCE

Professors Balduzzi and Biondi have described the observations and the approach of their service in the short manuscript kindly contributed below;

Title: Pediatric Hematology Oncology management in Monza, Lombardia, Italy

Authors: Adriana Balduzzi[1], Andrea Biondi

Affiliations: Clinica Pediatrica Università degli Studi di Milano Bicocca, Fondazione MBBM, Monza, Italy

SERVICE PROVISION:

- All childhood cancer service activities should continue and be reorganized during the COVID-19 emergency.
- Patients candidate for transplantation, hematopoietic stem cell donations, surgery, apheretic procedures undergo a diagnostic swab and wait for a negative result before undertaking the procedure
- Selection of visits to delay and reschedule (maintenance, long-term follow-up, non-malignant haematology cases).
- Provide remote management with teleconferences.

- Visits of sickle cell patients, at highest risk of complications and unreliable self-management, are usually maintained
- Chemotherapy delay is discussed on a case to case basis
- Maintain MDT and tumour boards by teleconference to maintain social distancing
- Transplantations are rescheduled to make sure that cryopreserved grafts are available in-house prior to the start of conditioning regimens
- Transplantations in most non-malignant diseases, apart from life-threatening disorders, are postponed
- CAR-T deferred to limit the potential pressure on ICU
- COVID-free and COVID specific pathways to reach the radiology department are set-up and shown in maps and specific signs clarify risk areas
- Procedures involving anaesthesiologists, who bear an increased workload, are carefully planned
- COVID-19 related research projects encouraged, whenever possible.

STAFF AND STAFF PROTECTION:

- Hospital staff members are at very high risk of viral infection and transmission, so surgical masks are worn at all time
- Physicians and nurses dedicated to Hematology and Stem Cell Transplant Units do not attend any COVID-19 patients
- Symptomatic staff members (fever, respiratory symptoms, myalgia, weakness, diarrhoea, dysgeusia, anosmia) come back to work after two negative swabs
- Hand washing and correct use of masks is monitored by healthcare professionals
- Physicians not required for Haem/Onc service reassigned/redeployed to new COVID-dedicated units.
- No students or volunteers are allowed in the hospital (child-life specialists, and so on);
- Residents staff continue with rostered care in cancer unit
- Psychological support for health-care professionals deal with psychological distress within the COVID-19 Units

PPE:

- Personal protective equipment (PPE) are stocked within the unit and continuously replaced

- FFP2 masks in case of invasive procedures or procedures causing nebulization, including swabs
- FFP3 masks and facial screen and specific gown are worn during COVID patient assistance

PATIENT AND CAREGIVER SCREENING AND UNIVERSAL MASKS:

- Patients and caregivers wear surgical masks all the time
- Active screening with PCR analyses of nasal-pharyngeal swabs for all admissions help if laboratory capacity available.
- Employees at the reception desk are trained to administer specific screening checklist.
- Symptomatic patients may not enter the Hematology Units but be evaluated and admitted elsewhere
- One caregiver only is allowed with the patient, both In- and Outpatient
- No visits are allowed in the Wards

ST JUDE GLOBAL AND SIOP
COVID-19 RELATED RESEARCH AND THE GLOBAL COVID-19 RESOURCE CENTER AND REGISTRY

Title: Global COVID-19 in Pediatric Oncology

Coordinating Center MNEMONIC: G-COPO –**G**lobal **CO**VID-19 in **P**ediatric **O**ncology

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The G-COPO data repository is a collaboration between St. Jude Global and SIOP for the development of a voluntary anonymized reporting database for cases of COVID-19 occurring in children with cancer that can serve as a resource to the global pediatric oncology community.

Primary objective: To collect baseline and follow up clinical characteristics of COVID-19 infection amongst children with cancer or recipients of bone marrow transplants at globally.

Secondary objective: To share de-identified data summaries of the clinical characteristics of subjects with COVID-19.

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 centre 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. 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 [37]. Data requested include non-identifiable 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 [37] [27].

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 paediatric 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 co-analyses.

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