Victorian paediatric oncology care pathway: Providing optimal care for children and adolescents

Acute leukaemia

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Disclaimer: The information in this pathway is considered to be true and correct at the date of publication, however, changes in circumstances after the time of publication may impact on the accuracy of this information. The pathway is intended to support health services to decide how best to organise service delivery to achieve the best outcomes. The pathway is not intended to constitute medical advice or replace clinical judgement.
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Foreword

Childhood cancer is by definition rare, and treatments are complex. Surveillance and follow-up are a lifelong process. Clinical management is characterised by the diversity of disease presentation, lead coordination by tertiary centres with higher case volumes, and the central role of clinical trials. The care experience is profoundly impacted by the patient’s age, developmental stage and disease risk profile as well as the need for parents/guardians to act as decision makers.

Treatment and care for children diagnosed and treated for cancer is complex and challenging for all those involved. It involves multiple professionals and sometimes multiple services that may be close or distant to home. Best outcomes demand a timely, multidisciplinary, collaborative approach.

Documented cancer care pathways map the journey for specific disease/tumour types, aiming to foster an understanding of the whole pathway and its distinct components to promote quality cancer care and patient experiences. These pathways act as a reminder that the patient and family is the constant in the care continuum and that the health system has a responsibility to deliver the care experience in an appropriate and coordinated manner.

To be useful, a paediatric oncology care pathway needs to encompass the specific challenges of childhood cancer management. The Victorian Paediatric Integrated Cancer Service (PICS), supported by the Victorian Department of Health and Human Services, developed these oncology care pathways explicitly tailored for the care of children and adolescents. We acknowledge with gratitude the model provided in the adult cancer sector by the Optimal Care Pathways for Cancer Program, auspiced by the National Cancer Expert Reference Group.

The purpose of the paediatric oncology care pathways initiative is to improve children’s outcomes by facilitating consistent cancer care based on a standardised pathway of care. The principles and the standards of good cancer care are not expected to differ from service to service, even though treatment regimens may vary from patient to patient for a variety of reasons.

A wide range of multidisciplinary clinicians and stakeholders in paediatric cancer were consulted or participated in the care pathway development including parent representatives. We want to thank all involved for their generous contributions. We are sure those providing paediatric cancer care will find the specific pathways useful in deciding how best to organise service delivery to achieve the best outcomes for those we care for. Importantly, readers should note that the pathway is not intended to constitute medical advice or replace clinical judgement.

The PICS is a partnership between the health services that deliver care and treatment to children and adolescents with cancer in Victoria. The paediatric oncology care pathways have been adopted by the PICS partners. Other jurisdictions are invited to adopt and co-badge these for their local use.

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Background

Paediatric oncology care pathways are intended to guide the delivery of consistent, high-quality, evidence-based care for patients with cancer. The pathways align with key service improvement priorities including providing access to coordinated multidisciplinary care and reducing unwarranted variation in practice.

The paediatric oncology care pathways are modelled on the adult Optimal Care Pathways developed by the Victorian Department of Health and Human Services and the Cancer Council Victoria (via the National Cancer Expert Reference Group). These are accessible at www.cancer.org.au/ocp

Each care pathway outlines seven critical steps:

1. Prevention and early detection
2. Presentation, initial investigations and referral
3. Diagnosis, staging and treatment planning
4. Treatment
5. Care after completing therapy and survivorship
6. Managing refractory disease or relapse
7. End-of-life care
**Purpose**

Oncology care pathways can be used by health services and professionals as a tool to identify gaps in current cancer services and to inform quality improvement initiatives across all aspects of the care pathway. Clinicians can also use the pathways as an information resource and tool to promote discussion and collaboration between health professionals and families affected by cancer. The pathway can also be very helpful for health professionals who may only have discrete involvement at one step in understanding the whole continuum of care.

The paediatric oncology care pathways are also intended to provide a reference point for general practitioners (GPs) and paediatricians to guide decision making regarding referral to a paediatric cancer service and supporting shared care arrangements. They also provide guidance for the paediatric cancer service in the referral process to survivorship clinics and transition to adult healthcare.

This document is not intended to be a clinical practice guideline (CPG) and does not replace expert, multidisciplinary professional advice or clinical trial demands.

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**Scope**

The paediatric oncology care pathways are intended as a resource in managing children and adolescents diagnosed with cancer from birth to 18 years of age.

**Critical time points**

The blue clock symbol is used throughout this document to highlight a critical time point that has a specific timeframe attached to it.

**How to navigate the paediatric oncology care pathway**

There are unique challenges in caring for children and adolescents with cancer that are distinct from the adult population. These include:

- the different disease types and prevalence
- the rarity and complexity of childhood cancer
- the impact of treatment on the developing child and the risk of significant late effects
- the increased role of clinical trials and need for international collaboration
- the family-centred versus patient-centred model of care.

The ‘fundamentals of care’ section covers key principles and fundamentals of paediatric oncology practice that underpin the care of all children and adolescents with cancer. Following that, disease/tumour specific pathways are outlined in separate sections. A summary is provided at the beginning of each disease/tumour specific pathway to highlight key aspects of each stage of care and emphasise critical time points.
VICTORIAN PAEDIATRIC ONCOLOGY CARE PATHWAY FUNDAMENTALS OF CARE

The ‘fundamentals of care’ section covers key principles and fundamentals of paediatric oncology practice that underpin the care of all children and adolescents with cancer. Following that, disease/tumour specific pathways are outlined in separate sections.

Why an oncology care pathway for children and adolescents with cancer?

• Cancer in children is rare and treatments are often complex.
• The types of childhood cancer differ greatly from those experienced in adults.
• Early diagnosis is important but can be challenging due to the rarity of the disease and diversity of presentations.

Safe and quality care

Health policy in Victoria is firmly anchored in principles of safety and quality. The State government has clearly outlined its vision for delivering better, safer care across the health system. The vision includes the following aspirations:

• “World-class care patients receive is supported by a world-class system of quality and safety assurance
• Patient views and experiences are heard and shared at every point of the health system to drive continuous improvement
• Frontline healthcare workers have a real say on how to make the system safer and lead the way on improvement and best practice
• Individual safety and quality success is shared and built into the state-wide system”.

The Victorian paediatric oncology community shares this vision for better, safer care and recognises the adoption of care pathways as a tool for achieving service improvement.

Service capability — minimum standards

The paediatric oncology care pathways will be delivered by appropriately trained and credentialed clinicians within hospitals and health services that meet the minimum standards articulated in the Victorian Paediatric Integrated Cancer Service (PICS) documents:

• Service capability framework: a guide for Victorian health services providing primary treatment and shared care to children and adolescents with cancer (2014)

The objectives of these two frameworks are to:

• describe a coordinated system of state-wide paediatric oncology care
• support a sustainable model of care with efficient use of resources across health services
• support and advocate for patient safety through describing minimum recommended capability while providing care as close to home as possible
• provide clear and consistent language across state-wide services.

The emphasis of these frameworks is to define the minimum level of service capability required of health services across different time points in a child’s care. The frameworks support health services to plan, develop and deliver a high level of safe and effective paediatric cancer care within an agreed scope of practice. By documenting minimum requirements, health services will be assisted to deliver services that meet the local needs of the community and build confidence in shared care referrals between health services.
The service capability framework for primary treatment and shared care identifies six paediatric cancer service levels, as outlined in Figure 1. The frameworks are described in terms of the following dimensions:

- time points and level of complexity of care
- infrastructure
- speciality services
- workforce
- education and research
- quality and clinical governance
- service links and networks.

**Figure 1: The levels of paediatric cancer services**

**LEVEL 6** Specialist – high complexity

**LEVEL 5** Specialist – moderate to high complexity

**LEVEL 4** Moderate complexity – Regional (higher critical mass, limited chemotherapy)

**LEVEL 3** Low to moderate complexity – Regional Shared Care (supportive care only)

**LEVEL 2** Low complexity inpatient (excluded)

**LEVEL 1** Low complexity ambulant (excluded)

Whilst the service capability frameworks define the minimum requirements for health services, this document builds on these requirements by defining optimal paediatric cancer care.
Principles of care

Family-centred care

In Australia, family-centred care is a philosophy of care endorsed by the paediatric healthcare community.6,7 It has been defined across eight elements:6

- the family is central and constant in the child’s life, while healthcare services change
- the facilitation of family-professional collaboration at all levels of healthcare, including program development, implementation and evaluation
- the exchange of complete and unbiased information between families and professionals, in a supportive manner
- recognition of cultural diversity across and within all families
- provision of developmental, educational, emotional, environmental and financial supports to meet the diverse needs of families
- encouragement of ‘family-to-family’ support and networking
- ensuring systems for children needing specialised care, and their families, are flexible, accessible and comprehensive
- the appreciation that children and families possess a wide range of strengths.

A family-centred care philosophy is required in the design, promotion, communication and delivery of all aspects of the care pathway for children and adolescents with cancer.

Multidisciplinary care

A centralised multidisciplinary approach to paediatric oncology care forms the basis of leading institutional recommendations5,10,11 and has been demonstrated to improve patient outcomes.12,13,14 The expertise within a disease-specific multidisciplinary team (MDT), usually located within a tertiary referral centre, is of particular importance in the field of paediatric cancer due to the rarity and complexity of management. The ‘high-volume effect’ within tertiary referral centres has been shown to improve survival outcomes in the paediatric oncology population.15

Multidisciplinary care is one of the key areas of reform for the Integrated Cancer Services in Victoria. Effective MDTs can support:

- improved treatment
- improved communication
- improved coordination of care
- improved access to clinical trials
- reduced service duplication
- better consideration of patient (and family) needs
- better promotion of shared learning and professional development.

- It is a requirement that all children with a provisional cancer diagnosis be discussed at a paediatric oncology multidisciplinary meeting (MDM), with definitive diagnosis and prospective treatment planning forming the core themes.
- Core attendees of the MDM include all experts who are appropriate to the diagnosis.
- Documentation and dissemination of meeting outcomes are shared with key stakeholders including the family, the child or adolescent’s GP and, if applicable, their paediatrician.
Care coordination

Care coordination is a comprehensive approach to achieving continuity of care, ensuring that care is delivered in a logical, connected and timely manner to meet the needs of the patient. In the context of a child or adolescent with cancer, this approach incorporates both the child and their family and includes MDMs, supportive care screening/assessment, referral practices, data collection, clinical trial participation, information provision and individual clinical treatment.

There should be a designated nurse within the MDT allocated to the child or adolescent with cancer with the responsibility to coordinate and communicate care.

Consistency of care

The primary oncologist should provide direct clinical consultation at all critical timepoints during the child or adolescent’s treatment. These timepoints include:
- at diagnosis
- following investigations measuring response to treatment
- prior to each new cycle of treatment defined by the protocol
- following any significant morbidities
- at the end of treatment

and, if applicable:
- at relapse
- during the transition to treatment with a primarily palliative intent
- during the transition to end-of-life care
- during bereavement.

Communication

Communication with children and adolescents with cancer and their families should be:
- individualised
- candid and transparent
- consistent
- in plain language (avoiding complex medical terms and jargon)
- culturally sensitive
- active, interactive and proactive
- ongoing
- delivered in an appropriate setting and context
- offered in a variety of means such as printed and electronic media.

For the child or adolescent, information should also be tailored to their age and/or level of cognitive development. Medical play may support the needs of younger children, while opportunities for ‘time alone’ with the healthcare provider may benefit adolescents.

Place of care

Definitive diagnosis, staging/risk assessment and treatment planning for all children and adolescents aged 15 years or younger is made at a level five or six paediatric cancer service.

Adult health services managing patients with ‘paediatric-type’ cancers should have links to and advice from a level five or six paediatric cancer service, and relevant MDTs.

Children and adolescents with ‘adult-type’ cancers should have links to and advice from an adult oncology service and relevant MDTs.

The child or adolescent’s usual place of residence should be considered when determining the most suitable place of care. For patients living in outer metropolitan and regional areas, efforts should be made to support localised and home-based care when it is safe to do so.

Adolescent care

Adolescence is a time of considerable growth and development. These changes are characterised by physical, psychological, social, emotional and sexual maturational processes and can pose significant challenges. The normal developmental process will be significantly harder for adolescents with a serious illness. Additional challenges include:
- difficulty fostering and maintaining peer relationships
- potential loss of autonomy and independence and the need for increased parental support
- sexual and reproductive health
- potential emerging mental illness
- education and vocation challenges
- the concept of assent and/or consent to treatment.
The health service needs to be cognisant of the needs of adolescents by:

- ensuring access to expert adolescent health professionals with knowledge specific to the biomedical and psychosocial needs of the population
- understanding the biology and current management of the disease in adolescence
- considering clinical trials accessibility and recruitment for each patient
- engaging in proactive discussions and management of fertility preservation and the late effects of treatment
- providing treatment in an adolescent and young adult (AYA) friendly environment
- acknowledging the importance of educational support in this age group
- fostering opportunities in adolescents for ‘time alone’ with health professionals where applicable
- promoting normality.

Core principles for transitioning to survivorship programs should include the following:

- the survivorship healthcare setting should be appropriate to the patient’s age and cognitive development
- common concerns of young adulthood should be addressed in addition to speciality care. These include fertility, sexual health, contraception, self-management, psychosocial and emotional risk factors and access to healthcare
- transition should promote autonomy, personal responsibility, self-reliance and a healthy lifestyle in young adults
- transition programs should be flexible to meet the changing needs of the young adult
- the process should be planned with the young adult and their family.

Fundamentals of paediatric oncology practice

Effective transition of adolescent survivors of cancer is an important part of the care continuum. As the incidence of late effects following treatment for childhood cancer has been shown to increase with age, it is important that effective transition to adult care takes place to enable ongoing surveillance and earlier detection and intervention of late effects.

Challenges include the adolescent adhering to ongoing appointments when the focus of those appointments has moved from treatment to surveillance, often in a different healthcare setting and with reduced parent involvement. Oncology services have limited involvement once the adolescent no longer has cancer. These patients may also require expertise from several specialties in the long term, making the transition more complex.

The model of care for transition will also depend on the availability of resources, the risk stratification of the individual and the complexity of care required. This means that some patients will remain in the tertiary adult healthcare sector rather than with their GP. Regardless of risk, a model that incorporates the person’s GP will reduce the potential for patients to be ‘lost in transition’ and is recommended.

Transition from paediatric to adult care

As the number of children and adolescents diagnosed with cancer is small, participation in collaborative international clinical trials (CTs) is essential. This allows patients access to a wide range of trials and also enables the trials to recruit the critical mass of participants needed to deliver outcomes in the shortest possible timeframe. Outcomes may include improvement in overall survival or reduction in therapy, toxicities and/or late effects, as well as improved quality of life. CTs may also enable access to off-label emerging therapies that would otherwise be unavailable to the clinician and patient. It is important to note that as more personalised, individual approaches to treatment increase the number of subpopulations of each disease, the already small disease population will become smaller.
Eligibility for CT enrolment should be considered for and offered to all children and adolescents diagnosed with cancer.

For children who do not meet eligibility criteria, where enrolment is declined, or where a CT is not open, the patient should follow the most recently completed and published ‘standard of care’ treatment protocol offering the best possible outcome (this may not be the current open trial).

The cancer service should maintain a database of CT enrolment for each diagnosis.

Reasons why eligible patients are not enrolled and why patients come off study should be collated and any identified issues examined.

Trials in other disciplines in child and adolescent cancer care
Participation in CTs and research should be encouraged in areas other than primary treatment. These include:

- supportive care – for example, infection control and prevention strategies, palliative care, complications of therapy, nutrition, antiemetic control and fertility
- epidemiology – for example, investigation of genetic causes to develop preventative measures
- behavioural science – for example, neurocognitive batteries and assessment, identification of at-risk families and children, and psychological and behavioural interventions
- nursing – for example, efficacy of patient and family education and reducing illness-related distress

Research and data collection
Other initiatives that should be encouraged include participation in a state-wide approach to trials and participation in national and international cancer registries and survivorship registries.

Supportive care
Supportive care is an umbrella term used to refer to services that may be required by those affected by cancer. Supportive care meets the needs across the following five domains:

- physical needs – for example, symptom management, managing and preventing infection, the impact of therapy on growth and development, physiotherapy, occupational therapy
- psychological needs – for example, the impact on cognition and education, managing stress and anxiety
- spiritual needs – for example, meaning-making in the context of illness
- social needs – for example, the child’s access to their community, school and social networks
- information and communication needs of both the child and family.

Supportive care interventions in the paediatric context
Cancer affects the emotional, financial, social, physical and cognitive vulnerability of children and adolescents and their families. Treatment of childhood cancer occurs in the context of a family and, as such, health services are required to ensure they meet the needs not only of the child or adolescent but of their family as well. This includes parents, siblings, guardians and care providers. Health services are required to provide access to appropriate information for parents and caregivers to effectively participate in treatment decisions with the healthcare team.

Risk groups
Patients and families that have a greater need for supportive care may include:

- infants
- children and adolescents receiving therapy for high-risk disease with significant toxicities from either therapies or underlying cancer
- children and adolescents who develop refractory disease or relapse
- children and adolescents with types of cancer for which there is no curative treatment available
- children and adolescents with pre-existing co-morbidities
- single-parent and/or blended families
• families with mental health issues
• families with significant financial distress
• issues of child protection within the family
• families from regional and remote areas
• families with cultural and linguistic diversity.

Supportive care assessments are shared with the MDT, documented and actioned at critical time points during and after treatment, including:
• at diagnosis
• following risk assessment
• during treatment
• at the end of treatment
• during the transition to survivorship
• during the transition to the adult healthcare sector
• at relapse
• during the transition to treatment with a primarily palliative intent
• during the transition to end-of-life care
• during bereavement.

Supportive care tools
Recommended tools for supportive care assessment are evidence-based, validated and age-appropriate. Tools may include:
• a validated psychosocial assessment tool for the patient and family (for example, PAT 2.0™)
• a pre-chemotherapy nursing assessment tool (for example, SISOM or the memorial symptom assessment scale)
• a performance status tool used prior to each treatment encounter (for example, the Karnofsky or Lanksy score)
• survivorship guidelines in assessing late complications of therapy (for example, the Children’s Oncology Group survivorship guidelines)
• a visual analogue score for chemotherapy-induced nausea and vomiting (for example, the BARF™ scale)
• a visual analogue score for pain assessment (for example, the FACES™ pain scale)
• validated tools for assessing mucositis in children and adolescents (for example, ChIMES)
• a nutritional screening tool for children with cancer (for example, SCAN)
• an AYA psychosocial screening tool (for example, HEADSS assessment).

Clinical practice guidelines
The development and utilisation of clinical practice guidelines (CPG) in supportive care is essential to provide optimal care and reduce morbidity and treatment related mortality. Paediatric cancer services should ensure they are following evidence-based supportive care CPGs and should aim to promote national and international collaboration in their development.

Neuropsychological demands
A risk algorithm for managing the neuropsychological effects of childhood cancer, and its treatment, is outlined in the PICS document *A compendium of evidence and framework for neuropsychological services in paediatric cancer (2015)*.

This compendium was written with the aim to establish a risk algorithm using international guidelines and local data that could inform workforce requirements for neuropsychology services. It is recommended that health services use this framework.

Risk factors for neuropsychological morbidity in children include, but are not limited to:
• diagnosis of a central nervous system tumour
• cranial irradiation (with higher intensities correlating with poorer outcomes)
• central nervous system (CNS)-directed chemotherapy such as intrathecal chemotherapy
• chemotherapy agents such as high-dose methotrexate
• young age at diagnosis or during treatment
• co-existing neurocognitive morbidities
• perioperative complications related to neurosurgery.

Access to neuropsychology services should be risk-adapted and when required, be performed routinely at diagnosis and again at completion of therapy. Neuropsychology assessments should continue to be undertaken in survivorship.
Psychosocial standards of care

Psychosocial standards for paediatric oncology care are summarised below.35

- Patients and their families should receive routine psychosocial assessments.
- Patients in survivorship should receive yearly psychosocial screening.
- Patients and their families are at high risk of financial hardship, and targeted referral for supports should be made.
- Parents and carers are a psychosocially at-risk group and should have early and ongoing assessments.
- Siblings are an at-risk group and should be provided with appropriate supportive services.
- Patients and their parents should receive school re-entry and ongoing support to ensure the child remains on track academically.
- Patients should be provided with opportunities throughout treatment for social interaction.
- Patients and their families should be provided with psychoeducation, information and anticipatory guidance related to diagnosis, treatment and adaption.
- Patients should be referred to pain and palliative care services to reduce suffering throughout the disease process.
- A member of the healthcare team should provide bereavement management support following a child’s death.

Every family should be seen by a social worker within one week of diagnosis.

A validated psychosocial screening tool is required to be completed at the time of diagnosis with the results (and ongoing actions) communicated to the MDT and documented in the medical record.

Nutritional needs of children with a cancer diagnosis

For many childhood cancers, there is a risk of malnutrition during therapy.36 In survivorship, there is a risk of obesity and developing metabolic syndrome.37 These risks have the potential to be controlled with dietary and exercise interventions. Using a nutritional screening tool (both during and after treatment) can provide a way of identifying those patients at risk and offering early intervention.31

Health services treating children and adolescents with cancer should adopt a validated tool for nutritional assessment as part of ongoing care during and after therapy, with referral to speciality services for those at risk.

Paediatric cancer services should give consideration for a nutritional assessment to be undertaken for all new diagnoses to guide the number and type of interventions required and further assessments during treatment.

All patients should have a nutritional assessment undertaken at each survivorship consultation.

Infection prevention and management

Infection is one of the most common complications in treating childhood cancer.

Recommendations for infection prevention and management in paediatric oncology are summarised below.

- Patients are required to undergo appropriate infection screening.
- Febrile neutropenia (FN) must be managed according to evidence-based guidelines.
- Families must receive information and education concerning the prevention and management of infection.
- Antimicrobial prophylaxis (viral and fungal) must be prescribed according to trial protocol or institutional guidelines.
- Household contacts should be up to date with vaccinations (including live vaccines).
- Annual influenza vaccinations should be provided to the patient and household contacts.
- The paediatric cancer service is required to demonstrate access to an infectious diseases consultant with experience in paediatric oncology.

In children with FN, antibiotics must be administered within one hour of presentation to hospital, or within 30 minutes for inpatients.
All patients should be identified as standard or high risk of FN and be provided with documentation at diagnosis that identifies their risk category to streamline any required emergency care. This documentation should be updated according to the degree of perceived toxicity during each phase of treatment by a member of the MDT.

**Palliative care**

Palliative care needs should be assessed at all stages of a child’s cancer diagnosis. Palliative care can be integrated into the child’s management alongside disease-modifying therapy including chemotherapy, radiotherapy, bone marrow transplant and clinical trials. Specialists in palliative care are able to assist the oncology team with advance care planning, symptom management, spiritual care, psychosocial support, linking with community palliative support services, end-of-life care and bereavement support.

Timely referral to palliative care promotes:
- the opportunity to focus on enhancing quality of life and reducing symptoms
- time to develop a tailored palliative approach to the evolving needs of the individual child and family
- the avoidance of crisis-oriented management, which exacerbates the family’s sense of vulnerability and helplessness
- a framework for preventive, proactive interventions and decision making
- support for the family’s strengths and capacity to cope.

**Fertility**

Reduced fertility and infertility are potential consequences of many cancer treatments in children and adolescents and can result from:
- exposure to selected systemic chemotherapy agents or radiation to reproductive organs
- high-dose radiation to the hypothalamic-pituitary axis, causing secondary hypogonadism
- selected pelvic, abdominal or neurosurgeries.

These different aspects of impaired fertility should be discussed and reinforced at different time points as appropriate throughout the diagnosis, treatment, surveillance and survivorship phases of care. These ongoing discussions will enable the family and, if applicable, the patient to make informed decisions.

**Communicating fertility options**

Discussing the impact of cancer treatment on fertility is an international standard of care. Infertility is acknowledged as a side effect of child and adolescent cancer treatment. Discussions should be standardised and follow institutional guidelines. If a procedure is deemed inappropriate due to medical risk or lack of efficacy in some patients, it is advised to have that discussion prior to treatment.

Communicating the options and potential risks to fertility should be discussed at diagnosis, coming off treatment and entry into the survivorship program.

**Prevalence**

Rates and degree of infertility vary greatly and are dependent on a number of risk factors, including the location of the disease, treatment regimen, treatment dose and pubertal status, which should be taken into consideration when discussing fertility options in children and adolescents with cancer. Prediction of risk is difficult and outcomes vary amongst individual patients.

**High-risk groups**

The following interventions place young people at high risk for infertility:
- treatment with high-doses of alkylating agents such as cyclophosphamide, busulfan, ifosfamide, Carmustine and procarbazine
- high-dose radiation to the pelvis, abdomen or hypothalamic axis, particularly in combination with alkylating agents
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- total body irradiation for children and adolescents undergoing transplant conditioning
- testicular and ovarian radiation.

In discussing the late consequences of emerging therapies for childhood cancer such as immunotherapy, patients and families should be advised about the lack of conclusive data of the impact of these treatments on fertility, particularly in sperm production.

Education and information should include the enhanced risk of premature ovarian failure and/or early menopause faced by female survivors of childhood cancer.\(^{40}\)

These different aspects of impaired fertility should be discussed and reinforced at different time points as appropriate throughout the diagnosis, treatment, surveillance and survivorship phases of care. These ongoing discussions will enable the family and, if applicable, the patient to instigate coping mechanisms and make informed decisions.

Fertility recommendations are outlined below.\(^ {41}\)

- An assessment of the risk of infertility is made by the MDT and documented at diagnosis for all patients.
- Families and, where appropriate, the child or adolescent, should be educated on the potential fertility-related effects of the treatment delivered.
- Discussions about fertility preservation and why it may or may not be deemed appropriate should occur as early as clinically possible and prior to treatment commencing.
- Information should be provided in both verbal and written form regarding potential options, risks and benefits.
- Families who express an interest in fertility preservation should be referred and, where clinically feasible, be seen by a fertility service.
- In those preservation techniques where efficacy for future fertility cannot be adequately demonstrated, this should be clearly communicated to the child, adolescent and/or family.
- Families should be aware of the ongoing costs involved in preservation.
- All discussions should be documented in the patient’s medical record.
- Clinical and ethical governance is required in centres offering fertility preservation.
- Results regarding semen analyses and tissue biopsies should be communicated to the family as soon as possible, in case the potential for a secondary procedure is possible.
- Appropriate follow-up during treatment and survivorship is important to discuss results and legalities regarding tissue storage and to monitor reproductive function.
Complementary and alternative medicine in childhood cancer

Complementary and alternative medicine (CAM) refers to a diverse group of practices and products not considered part of evidence-based conventional medicine. CAM is not a substitute for conventional therapy and is not overseen by any health regulating body. In most situations, CAM is integrated into healthcare.

The ever-growing access to information has made parents, patients and families increasingly aware of CAM. How the role and potential benefits of CAM are presented in social media and online (often with limited objectivity) will drive an increase in its use. Caution must be used in supporting or advocating the use of CAM in children and adolescents with cancer, particularly the use of unproven medicines or supplements during therapy. This requires an open, effective relationship between the consumer and the healthcare clinician.

The most common complementary health approaches used in children are:

- dietary supplements (not including multivitamins)
- chiropractic or osteopathic interventions
- yoga
- deep breathing
- homeopathy
- meditation
- guided imagery
- massage
- special diets.

The main reasons cited for use of CAM in children and adolescents with cancer are:

- help fight/cure the child’s cancer (with the concurrent use of conventional therapy)
- provide symptomatic relief
- support ongoing use of chemotherapy.

Some of the main reasons cited for CAM by adult cancer patients and their families are to:

- improve physical and emotional wellbeing
- ‘boost’ the immune system
- reduce the side effects of conventional treatment
- improve quality of life.

- Patients should be encouraged to discuss all CAM with the treating team.
- Health services should have a policy governing the use of CAM.
- All discussions of CAM should be shared with the patient’s oncologist and/or pharmacy and documented in the patient’s file.

Genetic predisposition to cancer

Background

Common genetic variations are associated with a proportion of childhood cancers and inherited genetic traits (germline mutations) currently account for about 10 per cent of all new diagnoses. Many cancer predisposition genes continue to be discovered across adult and paediatric cancers highlighting the need to develop specific services to address and provide reliable information about future risks faced by patients, as well as advice and strategies to lower the risk.

Genetic testing allows children and adolescents with a predisposition to developing cancer to be identified early. The potential clinical utility of identifying cancer predisposition genes in individual patients includes:

- providing an assessment on the likelihood of disease development
- altering treatment
- identifying targeted therapies
- using screening and prevention guidelines.

The number of patients with some underlying level of cancer predisposition is underestimated and underreported. The addition of a genetic counsellor to the MDT has been shown to significantly increase the identification of such patients who could benefit from genetic evaluation.
Genetic counselling, screening and prevention may ‘greatly improve either the chance of avoiding the further onset of cancer or the outcome of the disease’\(^46\). However, health services need to also acknowledge the impact of results on the siblings and other family members, for example, where some germline mutations may be shared within the family.

Children and adolescents with cancer predisposition syndromes should be considered for referral to a genetic service.

- There should be access to a genetic service with experience in oncology.
- There should be access to a genetic counsellor in the health service with experience in oncology.
- All children with cancer should have a complete family history of cancer of at least three generations documented at diagnosis.
- The emerging family history of cancer should continue to be documented as part of the survivorship program, and consideration of referral to a genetic clinic where new family cancer histories in children or young adults are reported.
- The health service should have a management strategy that covers the ethical implications of genetic testing in other family members.
- The genetic clinic should continue to measure the efficacy and yield of findings of referrals to genetic services.

### Coming off treatment

The coming off treatment and surveillance phase has been identified as one of the most difficult periods faced by parents in their child’s treatment.\(^49\) There are significant psychosocial and educational pressures encountered by patients and families during this critical time point.

Some of the major considerations for the cancer service to address with the patient and family coming off treatment include:

- education and learning requirements to be identified and tailored to the specifics of the child’s cancer treatment
- that education requires the parent’s readiness to learn during this point in care

- that the child’s primary oncologist should remain responsible for managing cancer-related issues during the surveillance phase
- discussion with and assistance for the child/adolescent and parents in dealing with the fear of relapse
- education in differentiating significant from non-significant symptoms
- review of the initial diagnosis, the side effects and the follow-up care required
- review of any CT demands during surveillance
- interventions that meet educational and psychological needs of the child and adolescent not be delayed until referral to survivorship
- referral or reintroduction to psychosocial services.

- All patients should attend a formal, multidisciplinary end-of-treatment review.
- Every patient coming off treatment should be given a full summary of the diagnosis, staging, treatment received and any complications of treatment.
- Every patient should also receive a tailored surveillance roadmap. The roadmap should identify the recommended timings for clinical tests and investigations as well as referrals to the necessary support services. This should be tailor-made to the individual patient and cover the period from the end-of-treatment to entry into a survivorship program.
- Copies should be provided to the child/adolescent and their family, as well as their GP and paediatrician as appropriate.
Survivorship

Currently, more than 80 per cent of Australian children and adolescents diagnosed with childhood cancer will be cured. A substantial proportion will have adverse late effects requiring ongoing medical and psychological care. A system/service should be in place to support survivors of childhood cancer into adulthood and transition into adult healthcare services when necessary.

- All children and adolescents who have been treated for cancer or who have undergone an allogeneic stem cell transplant should be referred to a survivorship program two to three years after completing treatment.
- Patients in the survivorship program should follow an approach such as the Children’s Oncology Group 2013 Long-term follow-up guidelines to ensure access to appropriate services.
- The survivorship program should undertake a risk-adapted approach to all patients entering the service for appropriate allocation of resources for those at higher risk of late effects.
- Paediatric oncology healthcare staff should be available, with access to clinical expertise and resources dependant on the child’s risk and current guideline recommendations. This may include representation from areas such as cardiology, endocrinology, fertility, physiotherapy, nutrition, education, psychology, dental, social work, occupational therapy and rehabilitation.
- All patients should receive tailored educational material in a format appropriate to their level of understanding and language type.
- The summaries developed at the end-of-treatment must be updated with new information.
- The surveillance roadmap provided should be updated with new information on entry to the survivorship program, in line with current guidelines and recommendations. This should be made available to the patient and their GP and, if applicable, their paediatrician.

Relapse

Disease recurrence is a distressing experience as survivors and their families once again face the psychosocial effects of cancer: uncertainty, distress and concerns about death.

Treatment protocols for relapse can still provide a realistic chance of cure. However, in some diseases, the prognosis following relapse is poor. Relapsed treatment plans, by nature, are very distinct from the original treatment plan as the initial therapy has failed the patient. The treatment is generally more complex and intensive and the outcomes are more uncertain.

Recommendations for patients with relapsed or refractory disease are summarised below.

- All patients with relapsed disease are required to be discussed at a paediatric oncology MDM to develop appropriate treatment planning, including decisions about potential clinical trial availability and possible referral to other specialty services including palliative care.
- The team should present all the information regarding the success rate of conventional relapse treatment plans, regardless of prognosis, and be available to discuss CAM options.
- The MDT should maintain open and candid communication at all times.
- Information is sensitively provided to the child/family, in plain language and in a supportive environment.
- There should be an increased focus on psychosocial support, including exploration of the family’s strengths, a focus on enhancing quality of life, ongoing discussion within a multidisciplinary structure and an awareness of maladaptive behaviour, such as emotional or physical withdrawal and refusal to follow through with medical care.
- Due to the toxicities of many relapse protocols, referral to fertility services should be considered.
End-of-life care

The Victorian Department of Health and Human Services has developed the Victoria’s end of life and palliative care framework: A guide for high-quality end of life care for all Victorians, available at www.health.vic.gov.au. There is also the National consensus statement on end-of-life care for paediatric patients developed by the Australian Commission on Safety and Quality in Health Care, which should guide practice in this area.51

Each child dealing with an incurable cancer will have different needs, priorities, goals and wishes as they approach the end of their life. The needs of their families will also differ. Supportive care interventions should aim to honour and facilitate the individual’s preferences, which should be elicited with sensitive, open and candid communication.

Informational needs

Children with incurable cancer, and their families, have a high need for communication and support. Discussion regarding approaching end-of-life is likely to require an iterative approach and should be tailored to the individual and their family. Plain language should be encouraged, and euphemisms avoided. Discussions may encompass:52

- prognosis
- rationale for decisions to change the focus of therapy
- explanation of and plans for addressing and preventing symptoms
- referral to community palliative care supports
- advance care planning including place of care
- explanation of the dying process.

The family should be supported and encouraged to involve the child in discussions and decision making in a developmentally appropriate manner.

Symptom management

Symptoms at end-of-life should be vigorously managed using both pharmacological and non-pharmacological measures. This may include the use of palliative chemotherapy or radiotherapy.

Place of care

As the end-of-life phase approaches, clinicians elicit the family’s preferences for ongoing care and preferred place of death. Some families prefer to continue to have regular hospital visits for support. Others favour exclusive home-based care. Similarly, the choice between death at home, in hospice or in hospital is highly individual and may change as the disease evolves.

The dying process

Families should be guided in preparation for and recognition of the dying process. Signs of approaching death, including increasing fatigue, reduced conscious state, reduction in appetite and changes in temperature and breathing, should be described.
ONCOLOGY CARE PATHWAY FOR CHILDREN AND ADOLESCENTS — ACUTE LEUKAEMIA

This oncology care pathway outlines seven critical steps for children diagnosed with acute leukaemia. While these steps are portrayed in a linear time model, in practice, patient care is rarely straightforward and predictable. The critical steps will require realignment and adjustment to best meet the needs of patients and their families as well as care providers without undermining the effectiveness of the treatment and supportive care program. The pathway describes the optimal cancer care that should be provided at each step.

The key principles and fundamentals of paediatric oncology practice outlined in the ‘fundamentals of care’ section underpin the oncology care pathway for acute leukaemia.

Scope

This oncology care pathway is intended as a resource in managing children and adolescents diagnosed with acute leukaemia.

Critical time points

As mentioned at the beginning of this document the blue clock symbol is used to highlight a critical time point that has a specific timeframe attached to it.

A red clock symbol indicates the time point is part of an urgent pathway. A precis of these time points are found in the summary of optimal timeframes (figure 3, page 22).
## Step 1: Prevention and early detection

**Risk Factors.** There is currently no known cause of childhood leukaemia. There is a peak in incidence for acute lymphoblastic leukaemia (ALL) in early childhood and some genetic disorders increase the risk of developing leukaemia in childhood. There is a link between developing acute myeloid leukaemia (AML) and prior chemotherapy exposure. There is no evidence that lifestyle plays a role in developing leukaemia. There are no preventative or screening programs for childhood leukaemia.

## Step 2: Presentation, initial investigations and referral

**Signs and Symptoms.** Clinical presentation is dependent on the level of leukemic infiltration in the marrow and extramedullary sites at the time of presentation, resulting in a wide spectrum of signs and symptoms. Signs and symptoms that warrant a full blood examination and peripheral film include:

- a persistent unexplained fever
- diffuse bone pain with no obvious history of trauma and/or refusal to walk
- generalised lymphadenopathy
- pallor or unexplained bruising
- unexplained bleeding
- extreme fatigue
- recurrent respiratory tract infections.

Signs that warrant an immediate referral to a paediatric tertiary referral centre include:

- hepatosplenomegaly
- unexplained petechiae.

**Parental Concern.** Escalation for further investigations is also warranted if there have been repeated GP visits or a high level of parental anxiety.

**Referral.** All children and adolescents with a suspicion of leukaemia on clinical or laboratory grounds will be discussed on the same day with a level five or six paediatric cancer service. Paediatric tertiary referral centres should provide clear routes of rapid access for GPs to specialist evaluation.

## Step 3: Diagnosis, staging and treatment planning

**Diagnosis.** A diagnosis of leukaemia will require laboratory testing on both peripheral blood and bone marrow and include:

- assessment of morphology
- immunophenotyping, karyotyping and fluorescence in situ hybridisation (FISH) analysis
- molecular genetic analysis.

Tissue must be collected as a baseline at diagnosis to define markers that can be used for risk stratification, such as minimal residual disease (MRD) testing.

A lumbar puncture must be obtained at diagnosis to check for CNS disease.

**Treatment Planning.** Optimal treatment planning includes presentation to and consideration within a paediatric leukaemia MDM when all necessary tests and investigations have been completed.

**Clinical Trials.** CT enrolment should be offered to all children and adolescents with leukaemia. For patients who do not meet trial eligibility criteria, the most recent, evidence-based and published study protocol offering the best outcomes must be used.

**Communication.** The lead clinician should discuss the outcomes of the MDM with the patient and family, including the diagnosis, risk assignment, treatment plan and access to clinical trials, if appropriate. The plan should be communicated with the GP and/or paediatrician.

## Step 4: Treatment

**Treatment.** Treatment protocols used must offer the best curative approach.

- Chemotherapy is the key component of treatment, prescribed within validated treatment protocols.
- Targeted therapies are also increasingly being utilised in leukaemia.
- Radiotherapy. Any consideration for radiotherapy will be discussed within the paediatric leukaemia MDM.
- Immunotherapy, including haematopoietic stem cell transplant (HSCT), may be required in some circumstances.

**Communication.** The lead clinician should discuss the treatment protocol, including risks and benefits and supportive care measures, with the patient and family. The care plan should also be communicated with the GP and/or paediatrician.
<table>
<thead>
<tr>
<th>STEP 5</th>
<th>Care after completing therapy and survivorship</th>
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<tbody>
<tr>
<td><strong>COMING OFF TREATMENT.</strong> All patients will be provided with a surveillance roadmap covering the first three to five years after treatment.</td>
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<tr>
<td><strong>SURVIVORSHIP.</strong> All patients completing treatment for childhood leukaemia will be referred to a survivorship program following surveillance.</td>
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<tr>
<td>Minimum documentation should include:</td>
<td></td>
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<tr>
<td>• a treatment summary</td>
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<tr>
<td>• a patient-specific roadmap for future tests and investigations.</td>
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<tr>
<td><strong>TRANSITION OF CARE.</strong> Transition to adult care should be supported by the survivorship program or the cancer service, via a referral and documentation to the patient’s GP. In selected patients having specialised therapies such as HSCT, referral to more specialty adult services may be warranted.</td>
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<thead>
<tr>
<th>STEP 6</th>
<th>Managing refractory disease or relapse</th>
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<tbody>
<tr>
<td><strong>DETECTION.</strong> Most instances of relapse or recurrence are identified through routine clinical examination or laboratory findings.</td>
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<tr>
<td><strong>TREATMENT PLANNING.</strong> Optimal treatment planning requires presentation to and consideration within a paediatric leukaemia MDM. Early integration with palliative care should be considered.</td>
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<tr>
<td><strong>TREATMENT.</strong> Children with relapse ALL are often eligible for enrolment in CTs evaluating the effectiveness of chemotherapy alone, or in combinations of therapies including HSCT, chemotherapy and targeted therapies. For patients with relapsed AML, treatment with chemotherapy may be an option, though chemotherapy followed by HSCT is currently the most common modality. Services should continue actively pursuing new treatment modalities for relapsed and refractory leukaemia such as targeted therapy and immunotherapy.</td>
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<tr>
<td><strong>COMMUNICATION.</strong> The lead clinician should discuss the outcomes of the MDM with the patient and family, including treatment options, potential CT enrolment, prognosis and risks and benefits of treatment. The plan should be communicated with the GP and/or paediatrician.</td>
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<tr>
<th>STEP 7</th>
<th>End-of-life care</th>
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<tbody>
<tr>
<td><strong>PLANNING.</strong> Discussion should be held within the paediatric leukaemia MDM to determine those patients for whom no further disease-modifying therapy is warranted and to identify those approaching end-of-life.</td>
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<tr>
<td><strong>COMMUNICATION</strong> of advance care planning, including preferred site of ongoing care and preferred location of death, must be undertaken with all families with primarily palliative goals of care. Referral to palliative care must be implemented, if not already undertaken. The plan should also be communicated with the GP and/or paediatrician.</td>
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</table>
### Summary: Optimal timeframes

Figure 3 summarises the recommended timeframes across two pathways at critical time points in the management of acute leukaemia in children and adolescents. All other timings of care for treating acute leukaemia can be found within the document.

**Urgent pathway:** Some patients may present with oncological emergencies including, but not limited to, hyperleucocytosis, tumour lysis syndrome, mediastinal mass and coagulopathies. Urgent, same-day emergency assessment and diagnosis needs to be completed to allow rapid commencement of therapy to manage these emergencies.

**Standard pathway:** If the patient is stable and/or enrolled in a CT, protocol requirements and institutional resources should guide timing for optimal diagnosis and treatment planning.

### Figure 3: Recommended timeframes in managing acute leukaemia

<table>
<thead>
<tr>
<th>STEP IN PATHWAY</th>
<th>CARE POINT</th>
<th>TIMEFRAME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presentation, initial investigations and referral</td>
<td>GP investigations and referral</td>
<td>All children and adolescents with a suspicion of leukaemia on clinical or laboratory findings must be discussed on the same day with a paediatric tertiary referral centre and, if required, referred to a level five or six paediatric cancer service within 24 hours.</td>
</tr>
</tbody>
</table>
| Diagnosis, staging and treatment planning | Diagnostic interventions | **Urgent:** Diagnostic investigations need to occur on the day of presentation  
**Standard:** Diagnostic investigations need to occur by the next business day in clinically stable patients; however, CT requirements, as well as the level of institutional resources, should also guide timings. |
| Central venous access                  |                                   | **Urgent:** Central venous access should be established on day of presentation when it is safe to do so.  
**Standard:** A central venous access device should be placed prior to beginning intravenous chemotherapy. |
| Multidisciplinary meeting              |                                   | A referral for discussion at an MDM will be made within a week of diagnosis. Discussion at the MDM will also take place at the end of induction therapy. |
| Treatment                              | Chemotherapy                      | **Urgent:** Chemotherapy commenced on the day of presentation  
**Standard:** Chemotherapy commenced by the next business day in clinically stable patients; however, CT requirements, as well as the level of institutional resources, should also guide timings. |
**STEP 1: Prevention and early detection**

**1.1 Prevention**

Although risk factors have been identified, the cause of childhood leukaemia remains unknown.

There is no evidence that lifestyle plays a role in childhood leukaemia. It is important to ensure the patient and their family are aware of this to avoid feeling responsible for their child’s illness.

**1.2 Risk factors**

**Genetic predisposition**

Some genetic disorders may increase the likelihood of developing leukaemia in childhood or adolescence. These include Down syndrome, neurofibromatosis type-1, ataxia telangiectasia and Fanconi’s anaemia.

**Siblings**

Siblings of children and adolescents with leukaemia have an increased risk compared with the general population, although the risk is still very low. In identical twins, the non-affected twin has an increased risk of developing leukaemia, occurring in approximately 15 per cent of cases when the first twin develops leukaemia between two and five years of age. Generally when the second twin develops leukaemia, this occurs within six months of the first child.

**Environmental factors**

There is evidence to suggest that radiation exposure including from medical imaging sources, particularly during pregnancy and early childhood, may increase the risk of childhood cancer, including leukaemia. However, the cumulative absolute risk is very small. Computed tomography/CT scans in children and adolescents should be limited to situations where there is a definite clinical indication, with every scan using the lowest possible dose of radiation. Other environmental factors, such as electromagnetic fields, parental smoking habits and paternal workplace exposures, have not been able to yield strong aetiological associations.

There is a link between the use of chemotherapy (particularly topoisomerase-II inhibitors) for childhood malignancies and secondary leukaemia, particularly treatment-related AML.

**1.3 Screening and early detection**

There are no effective screening tools for detecting newly diagnosed leukaemia in children and adolescents. Most children present with an array of non-specific symptoms that prompt the parent or guardian to seek medical attention. These signs and symptoms can be quite varied and are listed below in step 2. Screening individual symptoms has been shown to have low positive predictive values for leukaemia in primary care. Despite this, there is a need to educate GPs to appreciate the potential significance of these symptoms and make appropriate referral. Delays in diagnoses can adversely affect outcome and have major implications on the acceptance of a cancer diagnosis and a patient and family’s subsequent health-seeking behaviour.

Children who have a higher predisposition to develop cancer, such as a genetic risk or previous treatment for cancer, should have regular medical consultations. Children with identified bone marrow failure syndromes should have annual bone marrow evaluations to identify potential leukaemia.

**STEP 2: Presentation, initial investigations and referral**

Childhood cancer is rare. This represents a major diagnostic challenge for GPs.

This step outlines the process for establishing a provisional diagnosis and appropriate referral for a child or adolescent suspected of having leukaemia.

In isolation, alert symptoms do not have a strong positive predictive value but nevertheless should be used to guide early referral to a level five or six paediatric cancer service. One identifying factor that supports referral is repeated visits with the same symptoms but without a clear diagnosis. Similarly, parental ‘insight’ and anxiety should be a strongly noted and sufficient reason for referral.

This is in line with the National Institute for Health and Care Excellence’s (NICE) recommendations.

Specific ‘alert symptom’ guidelines should be encouraged in primary care to overcome the issue of rarity, including education for adolescents and parents and guardians.
2.1 Presenting signs and symptoms
The clinical manifestations of leukaemia are dependent on the level of leukaemic infiltration into the marrow and extramedullary sites at the time of presentation, resulting in a wide spectrum of signs and symptoms. It is important to recognise parental concern; escalation for investigations should be warranted after repeated visits or high levels of parental anxiety.

- The following symptoms may warrant the consideration of a **full blood examination and peripheral film**: persistent unexplained fever, diffuse bony pain with no obvious trauma and/or refusal to walk, generalised lymphadenopathy, pallor, unexplained bruising, unexplained bleeding or extreme fatigue, persistent respiratory tract infections.

- The following signs warrant **immediate referral and presentation to a paediatric tertiary referral centre**: hepatosplenomegaly and/or unexplained petechiae.

2.2 Referral
All children and adolescents with a suspicion of leukaemia on clinical and/or laboratory findings will be discussed on the same day with a level five or six paediatric cancer service, and if required, referred to the service within 24 hours.

The GP should have a clear and timely process for paediatric referral.

The minimum documentation for referral should include:
- a referral letter, including the patient’s demographics, relevant medical history, medications and allergies
- results of clinical investigations (including imaging and pathology reports)
- the need for interpreter services and other recognised significant psychosocial issues.

The GP should aim to provide electronic or printed confirmation of tests and investigations, but availability should not delay the referral or assessment.

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**STEP 3: Diagnosis, staging and treatment planning**
Step 3 outlines the process for confirming the diagnosis, risk stratification and treatment planning of leukaemia in children and adolescents.

It is a requirement that all children and adolescents with leukaemia are managed by a level five or six paediatric cancer service.

**Urgent pathway:** Some patients may present with oncological emergencies including, but not limited to, hyperleucocytosis, tumour lysis syndrome, mediastinal mass and coagulopathies. For these patients, **urgent, same-day emergency assessment and diagnostic interventions** need to be completed to allow early commencement of therapy.

**Standard pathway:** diagnostic interventions should be planned for the next business day in clinically stable patients; however, clinical trial requirements, as well as the level of institutional resources, should also guide timings.

---

3.1 Diagnostic work-up and pre-treatment investigations

**Physical examination and history**
- A thorough physical examination and history is important to identify co-existing organ dysfunction and the extent of infiltration, such as the clinical effects of bone marrow disease and extent of extramedullary disease, as well as potential features of underlying genetic predispositions and pre-existing comorbidities.
- Once a diagnosis is confirmed, a comprehensive family cancer history of at least three generations’ pedigree will help further identify patients and families with potential cancer predisposition or inherited syndromes. This may in turn help guide treatment or provide support to the extended family.

A physical exam and history is required on the day of presentation to the level five or six paediatric cancer service.
**Pre-treatment laboratory examinations**

- Full blood examination and film review
- Urea and creatinine, electrolytes, liver function tests
- Uric acid and lactate dehydrogenase
- Blood group, antibody screen and red blood cell phenotype
- Coagulation studies

**Pre-treatment medical imaging**

A chest x-ray will provide evidence or confirmation of mediastinal masses, particularly in patients with T-cell ALL.

Pre-treatment investigations will be performed on the day of presentation to the level five or six paediatric cancer service.

**Diagnostic laboratory investigations**

Laboratory diagnostic work-up includes the following “tests, performed on bone marrow and, at times, also on peripheral blood: 61

- morphology
- immunophenotyping, karyotyping and FISH analysis
- molecular genetic analysis.

All diagnostic tests should be ordered in such a way as to reduce the number of investigative procedures requiring general anaesthesia, improve workflow and support CT enrolment. One such example may be in the use of upfront flow cytometry on peripheral blood.

A lumbar puncture (LP) is performed to establish whether there is any CNS disease. It is a requirement that the initial LP be performed with adequate platelet cover and performed by an experienced clinician to avoid trauma, and the subsequent need to deliver increased therapeutic lumbar punctures.

A bone marrow aspirate (BMA) and LP should be performed under a general anaesthetic.

**Urgent pathway:** For urgent cases, if it is safe to do so, the diagnostic BMA and LP should be performed on the day of presentation. Urgent patients include, but are not limited to, those who present with hyperleucocytosis, tumour lysis syndrome, mediastinal mass and coagulopathies.

**Standard pathway:** The diagnostic BMA and LP should be performed by the next business day; however, CT requirements, as well as the level of institutional resources, should also guide timings.

**Infection screening**

It is important that infection screening is undertaken at diagnosis and prior to treatment. Screening should include:

- routine serology – HBV, HCV, HIV, HSV, VZV (for all patients prior to receiving blood products)
- EBV, CMV and toxoplasma (as indicated but particularly for patients that may require haematopoietic stem cell transplantation (HSCT))

For patients born or who have travelled overseas, particularly to tropical regions or tuberculosis endemic countries, consultation with infectious diseases must be sought.

Other investigations are as clinically indicated and on discussion with the infectious diseases service.

**Comorbidities**

Due to the toxicities of therapy, baseline organ function should be assessed at diagnosis. A thorough medical history will also help identify any pre-existing comorbidities.

**Biobanking**

Consent for biobanking of diagnostic material should be sought. In many upfront CTs in leukaemia, biobanking is a prerequisite to enrolment.

**Minimal residual disease (MRD)**

A MRD level is a strong and independent predictor of relapse in childhood leukaemia and widely used for risk stratification.62,63 This requires a diagnostic marrow or peripheral blood specimen to enable identification of leukaemia-specific markers.

**MRD testing in childhood leukaemia should occur at the time points listed on the next page.**64
For ALL:
• diagnostic (baseline MRD panel) specimen
• following induction therapy
• end of consolidation for those who are positive at end of induction
• following re-induction therapy in relapse
• prior to a transplant for relapsed patients proceeding HSCT.

For AML:
• diagnostic (baseline MRD panel) specimen
• end of the first course of induction
• consideration at end of subsequent course if positive at end of induction.

These time points will vary according to the protocol and may be overruled by CT requirements.

Clinical trial investigations
Further laboratory tests may be required to enable enrolment onto CTs.

3.2 Staging and risk stratification
Stratifying risk according to evidence-based criteria ensures that patients at the highest risk of relapse receive appropriately intensified therapy while those with more favourable prognosis (the lowest risk of relapse) receive therapy of reduced intensity to reduce complications.

Risk stratification at diagnosis must be assessed by a current, internationally recognised, peer-reviewed classification tool.

Acute lymphoblastic leukaemia\textsuperscript{60,65,66}
There are four main pillars that underpin risk stratification in ALL: host factors, disease presentation, disease biology and, most importantly, response to treatment.

ALL favourable prognosis:
• Host factors – for example, age older than one year and younger than 10 years
• Presentation – for example, peripheral white cell count at diagnosis of less than 50,000/µL
• Biology – for example, favourable genetic and biological features such as hyperdiploidy or ETV6-RUNX1 (TEL-AML1) positive
• Response – for example, negative MRD at the end of induction therapy.

ALL unfavourable prognosis:
• Host factors – for example, age younger than one year and older than 10 years
• Presentation – for example, peripheral white cell count greater than 50,000/µL at diagnosis, presence of extramedullary disease (CNS and testicular)
• Biology – for example, hypodiploidy and BCR/ABL
• Response – for example, positive MRD following first cycle of therapy.

Acute myeloid leukaemia\textsuperscript{56,67,68}
Risk stratification in AML is primarily related to the disease biology and response to treatment.

AML favourable prognosis:
• Down syndrome-associated less than four years of age
• Acute promyelocytic leukaemia (these patients generally have t(15;17))
• Negative MRD at the end of induction chemotherapy
• Specific genetic and biological features such as translocation t(8;21).

AML unfavourable prognosis:
• Extremely high or low body mass index at diagnosis
• Positive MRD at the end of induction therapy
• Specific genetic and biological features of the leukaemic blast cell such as FLT3 mutations and monosomy 5 and 7.
Application of new diagnostic techniques in the biology of childhood leukaemia continue to develop at a great pace.\textsuperscript{69,65} The MDT needs to be aware of these changes and advances and ensure they are translated to the bedside.

### 3.3 The multidisciplinary team and treatment planning

Optimal treatment planning includes presentation at a paediatric leukaemia MDM. It is a requirement that the MDT include all the experts required for the diagnosis and treatment planning of childhood leukaemia including:

- paediatric oncologist with a subspecialty in leukaemia*  
- haematopathologist with experience and expertise in paediatric haematological malignancies*  
- nurse consultant with experience and expertise in paediatric haematological malignancies*  
- paediatric clinical trials coordinator  
- paediatric oncology pharmacist  
- paediatric infectious diseases consultant  
- social worker with experience in paediatric oncology.

*Core members of the MDT who will be represented in person or remotely at the time of the meeting.

Administrative support should also be sought for documentation and dissemination of meeting recommendations.

- Discussion at an MDM should occur within one week of diagnosis.  
- All patients will be discussed at the MDM at the completion of induction therapy.  
- All new diagnoses are reported to the state cancer registry.

### 3.4 Supportive care considerations

Supportive care demands in all children and adolescents with cancer is discussed in the ‘fundamentals of care’ section. The success in childhood leukaemia over the past 40 years has led to a stronger emphasis on health status and health-related quality of life. Enhancements in supportive care and better measures of short- and long-term health-related quality of life are essential and are increasingly being embedded into the primary aims of new leukaemia clinical trials.\textsuperscript{70}

Supportive care requirements in the context of children and adolescents with leukaemia include:

- managing acute symptoms in newly diagnosed patients (including coagulopathies), providing blood product support and managing electrolyte abnormalities, including preventing tumour lysis syndrome  
- managing other clinical symptoms at diagnosis due to extramedullary disease  
- nutritional assessment at diagnosis and for all patients requiring HSCT as part of their treatment, though the risk of malnutrition in leukaemia in much less than in other types of childhood cancers\textsuperscript{36} (there is a risk of obesity both during treatment and in survivorship)  
- physiotherapy support in managing chemotherapy-induced peripheral neuropathy  
- management and prevention of infection  
- neuropsychology supports – referral to neuropsychology should be made for children who have experienced potential neurocognitive insult from triggers such as CNS-directed therapy (cranial radiation and intrathecal chemotherapy), those patients receiving high-dose methotrexate and patients who experience any significant CNS morbidity during treatment such as cerebral bleed, stroke, acute meningitis and encephalopathies  
- consideration of palliative care referrals for patients with a high symptom burden.

### 3.5 Communication with the patient and family

Lack of access to information has been identified as a cause of stress and conflict with the healthcare team for families of children with cancer.\textsuperscript{71} The family and patient (if appropriate) will be provided with both verbal and written information, specifically for consumers, on the following topics as a minimum:\textsuperscript{72}

- diagnosis, treatment plan and prognosis  
- management of fever and neutropenia  
- side effects of treatment  
- who/how to call their hospital and/or treating team  
- clinical trials  
- managing medications and compliance at home  
- central line care

\textit{Continued next page}
• caring for the child at home
• supportive care
• orientation to the hospital and overview of the healthcare team (key members)
• preventing infection
• blood counts
• follow-up appointments
• fertility preservation options
• psychosocial issues.

Information specifically targeted to children with acute leukaemia immediately following diagnosis include:
• neutropenia precautions
• medication adherence
• steroid side effects
• chemotherapy side effects
• bleeding precautions
• managing procedures
• nutrition
• anaemia.

Family education information is provided as part of the discharge plan following diagnosis.

Considerations must be made and strategies in place for communicating with families with cultural and linguistic diversity, including providing access to interpreter services and translated educational materials.

Age and developmentally appropriate information should be available for children and adolescents.

The paediatric cancer service should be able to demonstrate a process for providing timely and consistent remote support and monitoring via the telephone for patients and their families at home.

STEP 4: Treatment
Step 4 outlines a framework for delivering treatment for leukaemia in children and adolescents.

Effective strategies to improve overall survival in childhood leukaemia are identified through international collaborative CTs.

4.1 Treatment intent
The intent at diagnosis for all children and adolescents with leukaemia is cure. Children who develop refractory or relapsed disease are discussed in step 6.

4.2 Timing of therapy

[Urgent pathway:] Treatment must begin on the day of presentation immediately following diagnostic interventions. Urgent patients include, but are not limited to, those who present with hyperleucocytosis, tumour lysis syndrome, mediastinal mass and coagulopathies.

[Standard pathway:] Treatment for leukaemia should commence by the next business day following diagnosis. In clinically stable patients, CT requirements and the level of institutional resources available on the day to provide optimal care should guide timings.

4.3 After-hours admission of newly diagnosed patients
In some settings, paediatric patients admitted with newly diagnosed acute leukaemia on a weekend have been shown to have prolonged length of stay, increased time to chemotherapy and higher risk of organ failure. The timing of diagnostic and therapeutic interventions should be flexible and reflect clinical need, particularly for patients who present with oncological emergencies.

4.4 The role of clinical trials and research in childhood leukaemia
The five-year overall survival rate in ALL for children and adolescents has increased to 92 per cent in 2013. There has also been an improvement in AML survival, with current overall survival at 70 per cent. In 1960 nearly all children with AML and ALL succumbed to their disease. To date, this dramatic reduction in mortality has largely been a result of collaborative research.
The low incidence of childhood leukaemia in the general population requires active participation in national and international CTs to achieve statistically significant numbers for research.

CT enrolment should be offered to all children and adolescents with a leukaemia diagnosis where open trials are available. For children who do not meet eligibility criteria, or where a CT is not open, the patient should be treated according to the most recent, evidence-based and completed study protocol (this may not be the current open trial).

Clinical trials for leukaemia are risk-stratified and coordinated and managed within international collaborative studies.

4.5 Chemotherapy

Chemotherapy is the key component for treating childhood leukaemia. Due to the complexity and toxicity of administering cytotoxic agents to children, adherence to medication safety standards (such as mini-bag vincristine infusions) and the demands for supportive care, intravenous chemotherapy should be delivered via a central venous access device (CVAD).

**Urgent pathway:** Central venous access should be established on the day of presentation.

**Standard pathway:** Insertion of a CVAD should be undertaken prior to initial treatment.

- Chemotherapy should be prescribed with the use of validated protocols within an electronic prescribing system.
- A documented procedure that is strictly followed on the prescribing, dispensing and administering of chemotherapy must be used.

Minimum requirements for delivering chemotherapy are defined in the PICS 2014 document *Service capability framework: a guide for Victorian health services providing primary treatment and shared care to children and adolescents with cancer.*

4.5.1 Treatment for acute lymphoblastic leukaemia (ALL)

Most treatments for patients with standard-risk leukaemia are delivered in the outpatient setting. At this point in time, treatment lasts between two and three years and is dependent on risk stratification.

Treatment (includes CNS directed therapy throughout)

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>(includes CNS directed therapy throughout)</th>
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</thead>
<tbody>
<tr>
<td><strong>INDUCTION</strong></td>
<td>Goal: Achieve rapid remission. Length: 4 weeks (high-risk period)</td>
</tr>
<tr>
<td><strong>CONSOLIDATION</strong></td>
<td>Goal: Strengthen depth of remission and systemic treatment for sanctuary sites. Length: variable, weeks to months</td>
</tr>
<tr>
<td><strong>DELAYED INTENSIFICATION</strong></td>
<td>Goal: Strengthened pulse of intense therapy. Length: 8–12 weeks (high-risk period)</td>
</tr>
<tr>
<td><strong>MAINTENANCE THERAPY</strong></td>
<td>Goal: Provide a prolonged period of low-risk treatment to eliminate MRD. Length: 2–3 years</td>
</tr>
</tbody>
</table>

4.5.2 Treatment for acute myeloid leukaemia (AML)

All treatment for AML is intensive and is delivered within the inpatient setting. At this point in time, total duration is four to six months, dependant on risk stratification. Some children may progress to HSCT as part of the protocol.

Treatment (includes CNS-directed therapy throughout, cycles may be repeated)

<table>
<thead>
<tr>
<th>TREATMENT</th>
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<tr>
<td><strong>INDUCTION I</strong></td>
<td>Goal: Achieve rapid remission. Length: 4 weeks</td>
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<td><strong>INDUCTION II</strong></td>
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<td><strong>CONSOLIDATION/INTENSIFICATION I</strong></td>
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<td><strong>CONSOLIDATION/INTENSIFICATION I</strong></td>
<td>Goal: Strengthen pulse of intense therapy. Length: 4 weeks</td>
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</tbody>
</table>
4.5.3 Treatment for infant leukaemia
Infants diagnosed with ALL remain a high-risk subset with significantly inferior outcomes. Current event-free survival remains at 50 per cent, despite best-practice international collaborative trials. Treatment is intensive and predominantly inpatient-based. New therapies are examining the addition of specific targeted therapies, as current treatment regimens have reached dose-limiting toxicities.

It is important that infants with a leukaemia diagnosis are enrolled in CTs to provide optimal therapy.

4.5.4 Acute promyelocytic leukaemia (APML)
Although paediatric APML is rare, many children at diagnosis develop significant coagulopathy. Because of this, these patients are managed at diagnosis in the inpatient setting with ready access to intensive care. At this point in time, following induction, treatment is outpatient-based and specific to these patients, including the use of all-trans retinoic acid and arsenic trioxide.

4.5.5 Targeted therapy
The addition of tyrosine kinase inhibitors (a targeted therapy for specific high-risk subsets of ALL) has improved outcomes in recent international studies from a three-year survivorship of 35 per cent to 80 per cent.

Cancer services should continue to search new targets in treating childhood leukaemia, particularly in the high-risk groups. Personalised medicine should stay within the framework of robust collaborative CTs.

4.6 Radiotherapy
The use of radiotherapy (RT) for CNS prophylaxis has been one of the most important advances in the treatment of leukaemia. Intrathecal prophylaxis and intensified systemic chemotherapy have now reduced the need for RT without any impact on long-term outcomes, reducing the incidence of late neurological sequelae traditionally associated with cranial RT.

Currently, the use of cranial radiotherapy (CRT) in treating leukaemia is generally restricted to patients with overt CNS disease at diagnosis, and prophylaxis CRT is used in some patients with T-cell disease and other high-risk features. Internationally, protocols have drastically reduced the incidence of CRT and continue to do so.

Radiotherapy also has a place in some patients for the treatment of testicular disease, salvage treatment in patients with isolated CNS relapse, as well as a part of the conditioning regimen for some children undergoing HSCT (total body irradiation). It can also be very useful in palliating symptomatic masses in advanced disease.

Patients receiving radiotherapy are usually treated outside of the level five or six paediatric cancer service. It is important that these patients are managed under the recommendations outlined in the PICS service capability framework for children and adolescents receiving radiotherapy for cancer, which describes the minimum service requirements for providing a coordinated, sustainable and consistent model of care for delivering radiotherapy to children and adolescents with cancer.

Referral to radiotherapy services should be made once the treatment plan is confirmed.

4.7 Place of care
Treatment for childhood leukaemia is managed by a level five or six paediatric cancer service, in line with the document Service capability framework: a guide for health services providing primary treatment and shared care to children and adolescents with cancer. Consideration for supportive care and some aspects of treatment such as administering chemotherapy in shared care centres outside the level five or six paediatric cancer service should be made after consultation with the patient’s MDT. Shared care centres are required to adhere to the standards outlined in the service capability framework. Episodes of chemotherapy in regional shared care centres should be conducted with the use of telehealth between the local health service and the child’s oncologist.

The child or adolescent’s usual place of residence should also be considered when determining the most suitable place of care. For children living in outer metropolitan and regional areas, efforts should be made to support localised and home-based care, when it is safe to do so.
At a time when cure is agreed not to be the primary goal of care, the child and family’s preferences for site of ongoing care and site of end-of-life care should be explored.

4.8 Managing and preventing infection

Treatment-related mortality in AML in children and adolescents has been shown to be as high as 10 per cent.\(^6\) Time to antibiotics greater than one hour in managing FN in high-risk groups has been shown to have negative outcomes in paediatric studies.\(^80,81\) Children and adolescents with Down Syndrome ALL are also at increased risk of treatment related mortality and morbidity.\(^82\) In addition to the infection recommendations in the ‘fundamentals of care’ section, strategies to mitigate infection risk in children or adolescents with leukaemia are identified below.

- Mandatory hospitalisation should be considered for all patients with AML and those patients with Down Syndrome-ALL during induction and periods of neutropenia.
- Consideration for hospitalisation during induction for non Down Syndrome-ALL should be made based on clinical and social/compliance factors.
- Patients undergoing HSCT or treatment for AML must be treated in facilities appropriate to provide sufficient isolation from airborne pathogens, particularly fungal disease (such as HEPA filtration and positive pressure rooms).
- Strategies and policies should be in place for the management of infectious patients within the oncology clinical environment and waiting areas.
- For patients with febrile neutropenia, antibiotics must be administered within an hour of presentation to hospital, or within 30 minutes for inpatients.
- Patients with AML/ALL during the induction and intensification phases of treatment or those immediately (+ 30 days) post HSCT are at high risk of sepsis. They must be identified as such and follow a high-risk pathway for FN.

4.9 Role of haematopoietic stem cell transplantation and other cell therapies

HSCT is an established treatment regimen for haematological malignancies in children. HSCT should be considered in selected patients at greatest risk of relapse where there is evidence that this modality improves outcome. As the understanding of the biology of leukaemia and treatment with chemotherapy and targeted therapy has improved, the indication for HSCT has reduced. HSCT is more widely used as a salvage where primary treatment has failed.

4.9.1 Indications for haematopoietic stem cell transplantation in leukaemia

The indications for HSCT in leukaemia should be reassessed continuously by the cancer service.\(^83\) At this point in time, consideration for HSCT may include:

- ALL with high-risk features, for example, t(4:11), hypodiploidy and/or induction failure
- AML patients with high-risk features
- Mixed-phenotype acute leukaemia
- infant leukaemia with poor prognostic criteria
- relapse during or shortly after first remission
- persistent positive minimal residual disease.

All patients being considered for HSCT will be discussed at a leukaemia MDM.
4.10 Adherence and compliance to treatment for leukaemia

Treatment for childhood leukaemia can be up to three and a half years, with much of the treatment (oral chemotherapy) delivered in the home. The rate of medication errors in the home for children with cancer have been shown to be very high.\textsuperscript{84,85} Non-adherence to oral chemotherapy in ALL has been demonstrated to occur due to practised restrictions placed upon families.\textsuperscript{86} Cancer services are required to demonstrate strategies to support patients, families and caregivers in adhering to the treatment plan, particularly the role of long-term oral chemotherapy in the home.

The cancer service should have in place a mechanism to measure and record compliance with home-based oral medication administration, including how changes to oral chemotherapy doses are communicated to families in both written and verbal forms.

Step 5: Care after completing therapy and survivorship

5.1 Coming off treatment and surveillance in leukaemia

All patients are required to attend an end-of-treatment consultation following completion of treatment for leukaemia. This should be a multidisciplinary episode of care, including their primary oncologist, nurse consultant (with expertise in managing childhood leukaemia) and, if enrolled in a CT, their study coordinator.

A referral to a survivorship program should occur at completion of treatment with the view of transition to the survivorship program at the completion of surveillance.

All patients with a leukaemia diagnosis should be provided with a treatment summary, surveillance roadmap and educational material specific to coming off treatment at their end-of-treatment consultation. The summary should also be sent to the child’s GP and if applicable to the paediatrician.

The surveillance roadmap is sourced from the study protocol delivered for that individual disease and should be strictly followed, regardless of clinical trial enrolment. This roadmap should be prepared in collaboration with the survivorship program.

Surveillance includes:
- full blood examination and peripheral film
- Alanine Aminotransferase (ALT) and Urea, Electrolytes and Creatinine (UEC) testing on blood until normal recovery
- physical examination and history.

Echocardiograms will be undertaken routinely during surveillance for patients treated with chemotherapy for AML and ALL, as defined by the clinical trial protocol.

Planned episodes of surveillance following treatment for leukaemia are, at a minimum:
- first year – every four to six weeks
- second year – every eight weeks
- third year – every 12 weeks
- fourth year – every six months.

For patients enrolled on clinical trials, timings will be determined by the study protocol.

The length of surveillance for leukaemia usually lasts between three and five years. The medical management during the surveillance period should be directed by the primary paediatric oncologist. However, if provided with the adequate information and escalation criteria, consideration of the GP or paediatrician undertaking a portion of this under a shared care arrangement should be considered. Families from regional centres should be encouraged to conduct reviews under a telehealth model with the regional healthcare team, as deemed appropriate by the MDT. The demands for managing children enrolled in a CT should be met prior to shared care being discussed.

5.2 Haematopoietic stem cell transplant

Children and adolescents who received a HSCT as part of therapy for leukaemia should follow a specific evidence-based surveillance roadmap, including routine bone marrow evaluation, designed by the transplant team, tailored to the patient’s level of immunocompetence.
5.3 Survivorship

All patients who have been treated for leukaemia should be referred to a survivorship program at the completion of treatment with the view of transition to the survivorship program at the completion of surveillance.

All patients who have been treated for leukaemia should be participating in a survivorship program from three to five years after completing treatment.

All patients should be given an updated treatment summary and a roadmap for late effects surveillance on entering the survivorship program.

Patients and their families should also be provided with educational material about survivorship, including adopting a healthy lifestyle.

Large cohort studies show there is a low prevalence for significant adverse long-term outcomes in ALL and recommend regular, primary care consultations.

Late complications specifically related to childhood leukaemia may include:

- deficits in neurocognitive functioning, particularly with CNS-directed therapy
- impaired cardiac function due to the use of anthracycline chemotherapy
- neuropathy
- risk of obesity and metabolic syndrome, particularly in those patients treated with cranial radiation.

Increased support in survivorship is necessary for children with AML, particularly due to the risk of cardiotoxicity, secondary to the use of anthracyclines.

Increased surveillance and monitoring is also necessary for those who have undergone a transplant due to the increased toxicities of therapy, particularly during conditioning and any graft versus host disease.

See the ‘fundamentals of care’ section under ‘survivorship’ for more information.

5.4 Transition from paediatric to adult care

Most survivors of childhood leukaemia will be transitioned to a GP with a treatment summary and roadmap outlining investigations and surveillance required. For patients who have undergone a transplant, transition to an adult transplantation service may be appropriate. See the ‘fundamentals of care’ section for more information on transition.

STEP 6: Managing refractory disease or relapse

Despite approximately 90 per cent of children with ALL being cured of their disease, relapse remains the most common cause of treatment failure, occurring in 15–20 per cent of all patients. Of those children who relapse, cure only occurs in about 50 per cent of patients.

In AML, 30 per cent of all patients will relapse, and recent studies show only 30–40 per cent of those patients survive.

6.1 Signs and symptoms

Most cases of disease recurrence or relapse are identified through routine investigations or follow-up. Relapse may be discovered by peripheral blood examination (ordered during or after treatment) or via routine examination of bone marrow at critical time points during the child’s treatment. Extramedullary relapse may be made during physical examination (such as testicular relapse or hepatosplenomegaly) or via routine cerebrospinal fluid examination during therapy.

Factors contributing to prognosis in relapsed ALL include:

- marrow relapse less than three years from diagnosis (poor)
- extramedullary relapse (for example, CNS) less than 18 months from diagnosis (poor)
- marrow relapse longer than three years since diagnosis (favourable)
- extramedullary relapse longer than 18 months since diagnosis (favourable)
- response to initial therapy.

In AML, the length of time from the first remission is a major predictor of survival (with longer periods more favourable).
6.2 Multidisciplinary team

There should be immediate referral to a leukaemia MDT at a level five or six paediatric cancer service for all children with suspected or confirmed relapse.

6.3 Treatment

Children with relapsed ALL are often eligible for enrolment in relapsed protocols, often involving the delivery of systemic chemotherapy and the use of HSCT for selected patients. Transplant remains an option in relapsed ALL where chemotherapy resistance has been established, particularly if there is a matched sibling donor available.

In relapsed AML, achieving rapid remission via systemic chemotherapy followed by HSCT is currently the most effective curative strategy.

Immunotherapy

New immunotherapy agents continue to show promise in early clinical trials in refractory leukaemia. The health service should continue to look to enrol patients in early clinical trials investigating immunotherapy agents in children and adolescents with refractory leukaemia where standard therapy has failed the patient or the patient has been unable to meet eligibility criteria.

Chimeric antigen receptor T-cell therapy

Despite significant risk of morbidity during treatment requiring high dependency or intensive care, this emerging therapy has shown promising results. Chimeric antigen receptor T-cell therapy should continue to be investigated in children and adolescents with refractory leukaemia.

6.4 Supportive care in relapsed leukaemia

Treatment for relapsed leukaemia is associated with a high risk of treatment-related morbidity and mortality, particularly infectious complications. HSCT, novel agents and cell therapies used in refractory leukaemia may also be associated with significant treatment-related side effects.

Families from regional centres may need to reside near the level five or six paediatric cancer service due to the toxicity of therapy.

Support of the patient and family, including access to information, should be managed under the family-centred care principles discussed in the ‘fundamentals of care’ section. Further information on relapse in children and adolescents is discussed in the ‘fundamentals of care’ section.

6.5 Palliative care in relapsed leukaemia

Therapies such as HSCT, treatment for high-risk AML and targeted therapies within the context of CTs can result in high levels of physical, psychological and existential distress, despite having curative intent. Children and adolescents with an uncertain prognosis and high symptom burden should be able to access palliative care support alongside curative-intent therapies.

Cases of relapse should trigger a referral to palliative care services, unless there are strong, family-centred reasons to decline referral. The principles of a palliative care approach need to be documented and shared with the team. The decision should be made in collaboration with the child or adolescent, and their family.

Discussion should be held within a paediatric leukaemia MDM to offer the family referral to palliative care where there is a likely need to escalate care to manage symptoms and distress in high-risk curative regimens such as HSCT, as well as support when cure is no longer the intent of the MDT.

Scenarios that should prompt the discussion of early referral by the MDT to palliative care include:

- infant leukaemia, particularly associated with mixed-lineage leukaemia and hypodiploidy
- allogeneic HSCT, particularly in high-risk leukaemia
- AML expressing high-risk criteria
- high-risk leukaemia where induction treatment has failed the patient.
STEP 7: End-of-life care
Step 7 is concerned with maintaining the child or adolescent’s quality of life and addressing their health and supportive care needs, as well as the needs of the family, at the end-of-life.

Discussion should be held within a paediatric leukaemia MDM to determine patients for whom no further disease-modifying therapy is warranted, to identify those approaching end-of-life, ensuring palliative services are in place.

Referral to palliative care should occur at this time, if not already engaged.

Interventions and responsibilities at the end-of-life are discussed in the ‘fundamentals of care’ section.

Issues at the end-of-life that are specific to children and adolescents with leukaemia include the following:

- **Blood products.** Children with advanced leukaemia often experience pancytopenia and require frequent transfusions. However, transfusion of blood products can have associated burdens, including travel time and inpatient time, as well as the risks of fluid overload and transfusion reactions. The provision of ongoing transfusions should be based on a case-by-case assessment of the child and their experience, rather than just the blood count.

- **Antibiotic use.** Children with advanced leukaemia are often profoundly neutropenic and at risk of severe infection. As a child’s functional status deteriorates, some families prefer to avoid the burden of prolonged inpatient admissions for infection by limiting antibiotic intervention to those able to be administered in the home, or to simply reduce the symptoms of infection. Discussing the different options for infection intervention, and the likely impact on the child, is crucial in supporting patient and family preferences.

Ongoing commitment to continuous improvement
Due to its prevalence in childhood cancer (despite excellent overall survival), leukaemia remains one of the largest causes of cancer deaths in children. Key strategies for paediatric health services to prioritise include:

- continued work in establishing the cause of childhood leukaemia
- improving risk stratification through establishing biologically-defined subgroups
- improving technologies in measuring minimal residual disease and other high risk sub-groups
- reducing the incidence of long-term toxicities from therapy
- improved development of molecularly-targeted therapies
- improved technologies in cellular therapies in treating leukaemia
- improving compliance to therapy, particularly adherence to maintenance therapy
- identifying best-evidence practices for minimising physical and psychosocial suffering and optimising quality of life for children with leukaemia in both curative and palliative treatment phases.
Advance care planning
A process of discussing future medical treatment and care based on an individual’s preferences, goals, beliefs and values, which can guide future decisions should the person become unable to communicate.

Child/adolescent
The Children, Youth and Families Act 2005 defines childhood (including adolescence) as the period from 0 to 17 years. The World Health Organization defines adolescents as individuals aged 10–19 years. The paediatric oncology care pathway is intended as a resource in managing children and adolescents diagnosed with cancer from birth to 18 years of age.

Consumer
A term that can refer to people affected by cancer, patients and potential patients, carers, organisations representing cancer consumer interests, members of the public who are targets of cancer promotion programs and groups affected in a specific way as a result of cancer policy, treatment or services.

Cultural and linguistic diversity
Refers to the range of different cultures and language groups represented in the population who identify as having particular cultural or linguistic affiliations by virtue of their place of birth, ancestry or ethnic origin, religion, preferred language or language spoken at home.

End-of-life care
A distinct phase of palliative care, appropriate when a patient’s symptoms are increasing and functional status is declining despite anti-cancer therapy.

Family
The patient, their carers and relatives. Family may include parents, siblings, other relatives, guardians and friends.

Level five paediatric cancer service
A level five service will provide comprehensive care for the majority of paediatric oncology presentations within its catchment area, with direct links to a level six service. A level five service is recognised as a primary treatment centre and will provide diagnostic services and/or management of at least 30 new patients per year.

Level six paediatric cancer service
A level six service is a state-wide referral centre for paediatric oncology. A level six service is recognised as a primary treatment centre and will provide diagnostic services and/or management of at least 100 diagnoses per year from the local catchment as well as referrals from other geographical regions. A level six service provides state-wide, national and international leadership in paediatric oncology, including research, clinical guidance, education and policy development. A level six service will also assess and manage risk in new therapies and supportive care interventions, providing leadership and planning for other service levels.

Multidisciplinary meeting (MDM)
A regularly scheduled meeting of core and invited team members of the health service for the purpose of prospective treatment and care planning of newly diagnosed cancer patients as well as those requiring a review of their treatment plan or palliative care.

Multidisciplinary team (MDT)
Comprises the core disciplines integral to providing good care. The team is flexible in approach, reflects the patient’s clinical and psychosocial needs and has processes to facilitate good communication.

Oncology care pathway
The key principles and practices required at each stage of the care pathway to guide the delivery of consistent, safe, high-quality and evidence-based care.
**Palliative care**
Any form of medical care or treatment that concentrates on reducing the severity of disease symptoms.

**Primary oncologist**
The clinician who has lead responsibility for managing the patient’s cancer care. The lead clinician may change over time depending on the stage of the care pathway and where care is being provided.

**Rehabilitation**
Comprises multidisciplinary efforts to allow the patient to achieve optimal physical, social, physiological and vocational functioning within the limits imposed by the disease and its treatment.

**Shared care**
The establishment of pathways through which clients and health professionals in hospital and community settings can collaborate in developing a therapeutic plan that meets the clinical and functional needs of the client.

**Surveillance**
Period of time the healthcare team is looking for signs of relapse and monitoring side effects of treatment for cancer.

**Survivorship**
Period beyond surveillance where the healthcare team is looking at the potential late effects of treatment for cancer.

**Telehealth**
Healthcare delivery or related activities (such as education) when some of the participants are separated by distance and information and communications technologies are used to overcome that distance.
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