Child India

February 2022

Monthly e-Newsletter of Indian Academy of Pediatrics

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CONTENT

Editor's Note

Dear colleagues,

February is the month when we observe World Cancer Day (February 4th) with the theme 'Close the care gap' and International Childhood Cancer Day [ICCD] (February 15th) continuing the three-year campaign for ICCD [2021-2023] under the theme of 'Better Survival'. Therefore, we dedicate the Feb issue of Child India to Pediatric Cancers.

Ongoing advances in the field of pediatric oncology continue to positively impact our approach to the diagnosis and treatment of childhood cancers resulting in overall high cure rates. Nevertheless, there are still difficult-to-treat cancers in children that require ongoing research to identify new therapeutic approaches.

Increasing ability to identify children with hereditary cancer predisposition syndromes also improve survival rates and decrease treatment-related morbidity.

Advances in testing for minimal residual disease (MRD) in the acute leukemias of childhood; risk-based treatment approaches for neuroblastoma; targeted treatment recommendations for pediatric low-grade gliomas (pLGGs); role and benefits of proton radiotherapy in the treatment of pediatric malignancies; and, risk prediction rules for the optimal management of fever and neutropenia in children with cancer and many more have positively impacted the field.

We, our President Dr Remesh Kumar, HSG Dr Vineet Saxena, IAP OB and EB and we in Child India profusely thank our OB and members of IAP PHO Chapter for their contributions on this fast developing field.

Happy reading,

Jai IAP,

Dr Jeeson C Unni
Editor-in-Chief

President's Address

Dear friends,

Greetings!

In the President's Page IP January issue - Under-Five Mortality: IAP Can Make A Difference! – IAP has formulated a new project 'U5MR 25 BY 25' to support the government in implementing strategies to accelerate reduction of under-5 mortality rate in India. As we advance toward the achievement of this goal, initiatives aimed at reducing the burden of noncommunicable diseases, including childhood cancer, need to be developed.

Approximately 200 000 children and adolescents are diagnosed with cancer every year worldwide; of those, 80% live in low-income and middle-income countries (LMICs), which account for 90% of the deaths. Lack of quality population-based cancer registries in LMICs limits our knowledge of the epidemiology of pediatric cancer. Globally, the number of new cancer cases at all ages has increased from 10 million in 2000 to 15 million in 2020 and will increase to 24 million in 2050, and close to 70% of those cases are expected to occur in LMICs. Indian data regarding comprehensive childhood cancer burden in country is lacking due to low reporting and urban predominant coverage of population-based cancer registry programs.

Though the childhood cancer services in India have made significant improvement in last few decades, they are predominantly restricted to few tertiary care centres in major cities. Delayed diagnosis resulting in advanced stage of presentation, poor supportive care during intensive treatment, treatment refusal and abandonment remains major hurdles. Last few

The development of InPOG (Indian Paediatric Oncology group) for conducting collaborative trials should lead to adoption of uniform treatment protocols for our country. Government health insurance schemes and philanthropic organizations have supported treatments financially and this is leading to improved treatment adherence and outcome. We need to strengthen the cancer registries for capturing nationwide data, improve care giver and heath workers childhood cancer awareness and improve accessibility of childhood cancer care services beyond major cities. IAP should work with our IAP PHO Chapter towards these goals.

Hoping to see you a;; at Noida for Pedicon 2022 March 19th to 23rd.

Warm regards,

Yours I IAP,

Dr Remesh Kumar
National President, IAP 2022

Secretary's Message

Dear Friends,

It's a great relief that we have come out the storm of omicron relatively unscathed and life is now moving back on the track. It means reopening of schools, public places like restaurants, cinemas and malls and thus resumption of normal lifestyle and commercial activities. We are using this opportunity to organize NTEP Workshops in physical mode in various cities at a rapid pace. Bhavnagar and Ghaziabad had it on 20th Feb, Kutch, Bareilly, Bhubaneshwar , Raichur and Varanasi are having it on 27th Feb, Kutch and Udaipur are having it on 6th March, while Haldwani & Palakkad are having it on 13th March. By the end of this year we will be conducting NTEP Workshops in majority of Branches in whole country and thus fulfill IAP's commitment to Eradication of Tuberculosis, particularly in Children.

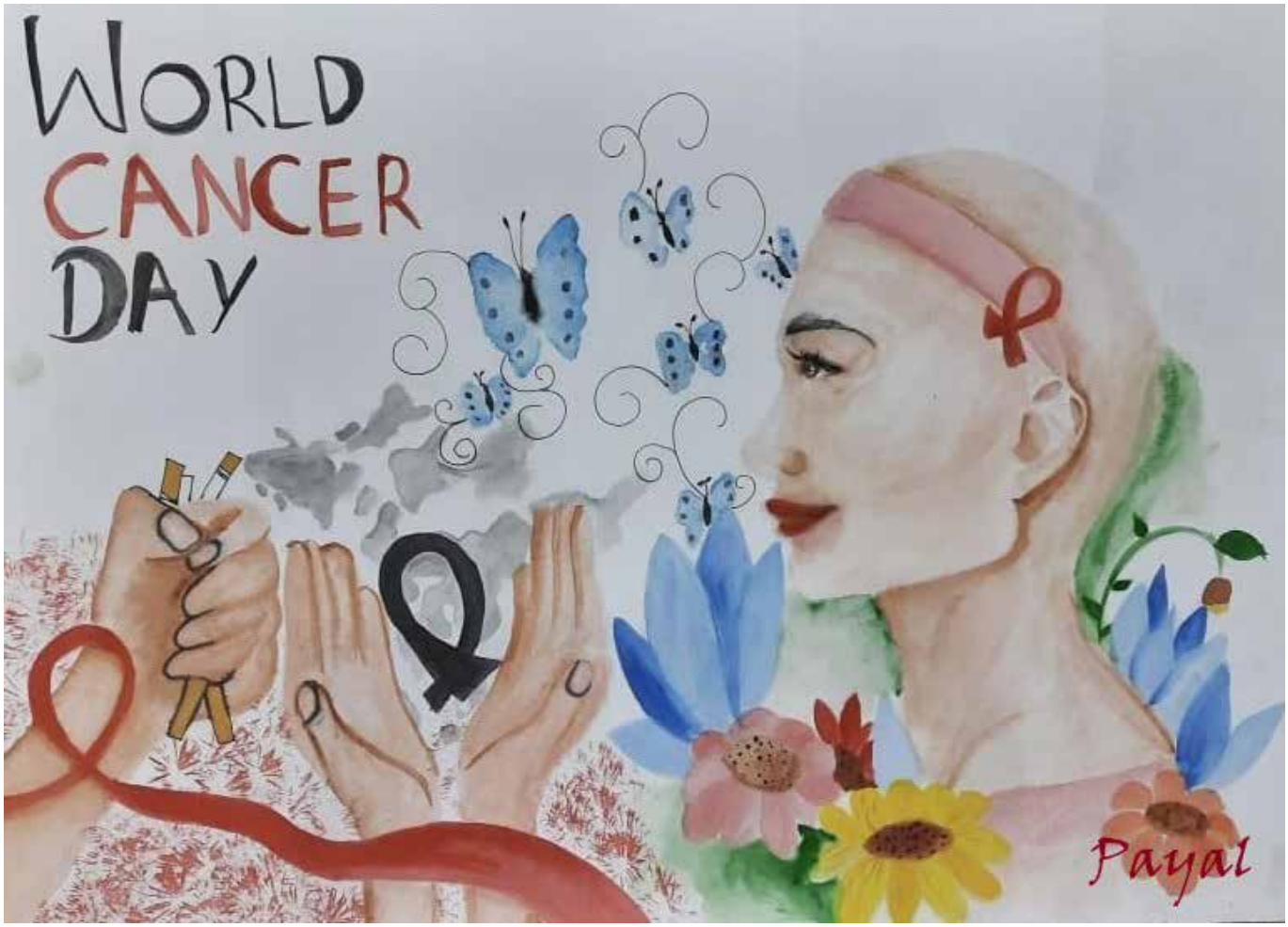
We had a session on Digital mode on the burning topic of Omicron and conducted a meeting of Presidents and Secretaries of all the State Branches. We will try to roll out various IAP Programs with cooperation and collaboration with State Branches and reach out to all the small and big branches of various Districts. Other than NTEP, the National Program which is all set to roll is ECD, the Early Child Development Module, which is again extremely important from Social point of view. IAP will try its level best to make this great organization count for Social causes besides academics.

Friends after a prolonged gestation period of two years, the most awaited event, the Noida Pedicon 2022 is all set to take place on 19th -23rd March. It will be a great opportunity for our members to mingle with each other, shake hands, hug each other, share a cup of coffee or meal or a hearty laugh and indulge in animated discussions. We all are yearning to see meet each other in true sense.

The Organizing Team of Noida has put in a lot of effort and hard work and Indian Expo Mart is the biggest venue in Asia of its kind. So lets meet there in huge numbers, celebrate the spirit of fellowship with a mega academic feast and make our very own National Conference a roaring success.

Long Live IAP! Jai IAP!

Dr Vineet Saxena
Hon. Secretary General 2022 & 23


WORLD
CANCER
DAY
Payal

Childhood Cancer In India : 35 Years Of Progress

DR RASHMI DALVI
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Professor & Head, Dept of Pediatrics
Bombay Hospital Institute of Medical Sciences
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Farther we look back, further we can see to the future
- Lord Winston Churchill

It is estimated that over 60,000 new cases of childhood cancer are incident in India each year, representing 4-5% of the overall cancer burden in the country and 0.5-1 % of pediatric admissions; adolescent and young adult cancers (AYA) account for another 5.7% of all cancers. Global modelling studies have shown that 40% of cases in South Asia, go undiagnosed, with a 5-year net survival estimate of 39.6%. This article outlines the evolution of pediatric oncology in India over three and a half decades and the road map of our progress.

EARLY YEARS

Back in the late 1980s, a diagnosis of cancer provoked societal stigma and a nihilistic attitude among physicians. Pediatric cancers were earlier handled by adult oncologists in cancer centres and self-trained pediatricians in medical college hospitals. In 1987, interested pediatricians under the leadership of Dr MR Lokeshwar formed the Pediatric Hematology Oncology Chapter of the Indian Academy of Pediatrics (PHO-IAP), and focused over the next decade on the conduct of academic programmes to disseminate knowledge and provide a national forum for data presentation. Gradually over the next decade, several Pediatric Hematology Oncology Units developed their services; however, survival outcomes were severely compromised by neutropenic infections, poor nutrition & hygiene, chemotherapy intolerance, blood product shortages, transfusion transmitted diseases, inadequate infection control measures, and lack of dedicated staff. But our major barriers were socio-cultural and economic: access to care, treatment abandonment and financial resources.

OVERCOMING BARRIERS

In 1992, several of us had the opportunity to attend the annual conference of the International Society of Pediatric Oncology (SIOP), and the first symposium on Pediatric Oncology in Developing Countries (PODC) at Hannover. Our participation at this international

forum & SIOP-PODC over the next few years, elicited interest from the SIOP board to invite projects from India to improve childhood cancer care. The by-now expanded PHO group, then led by Dr Bharat Agarwal, brainstormed and based on our own data, outlined a primary problem: that of delayed diagnosis resulting in advanced disease, and treatment refusal or noncompliance. In 1997, with modest funding from SIOP, the National Training Programme in Practical Pediatric Oncology (NTP-PPO) was launched. The NTP-PPO workshops were a 2-day module aimed at increasing awareness among primary care pediatricians, of childhood cancers, demonstrating their clinical presentations to enable early referral, and highlighting potential curability, if treated promptly and completely. It also aimed at developing shared-care in pediatric oncology with interested pediatricians. The target participants also included surgeons, pathologists, general practitioners and post graduate students. Over 1500 physicians across the country were trained in the initial 10 years, and the programme still continues into its 25th year, with further refinements. We have also been invited to conduct these workshops in Nepal, Bangla Desh and Oman.

A major change that eased our relatively dismal outcomes at the turn of the century, was the availability of better anti-infective agents, safer transfusion products, better access to drugs, infection control awareness among health care workers.

ACADEMICS & TRAINING

The year 1997 also marked another milestone with the conduct of the first independent PHO chapter conference, "PHOCON", which will see its 25th meeting this year in 2022. The PHOCON continues to be the much awaited annual meeting of the PHO chapter, with a high quality academic programme, where much of our pediatric oncology data is presented & issues debated upon.

The next step was setting up a formal training programme in PHO to train more specialists, a process initiated by Dr Anupam Sachdeva, with the National Board of Examinations (NBE) New Delhi. A fellowship program with the NBE, was started, to begin with in 3 centres, with the first candidates graduating in 2009. Since then, there are several training centres through the NBE , through the IAP, State university fellowships, and a few centres with degree (DM) courses as well. Several of our young trainees, pediatric residents & fellows have also further trained in state-of-art centres abroad and are now part of the pediatric oncology community here. Fellowship training programs and exposure to other systems of medical practice, automatically improve the academic quality and thus the care in a cancer unit. In 2016, the Pediatric Hematology Oncology Journal (ISSN 2468-1245) was launched as an open access journal, through the PHO Chapter.

CAPACITY BUILDING & SUPPORT

Another game-changer which helped improve childhood cancer care and brought the pediatric oncology community further together, was the India Pediatric Oncology Initiative, benevolently set up by the Jivdaya Foundation and Dr Vinay Jain, an adult oncologist from USA in 2008. This foundation addressed the basic financial resource barrier and helped in work-force capacity building at 44 pediatric cancer units across India, by funding personnel as required: doctors, nurses, social workers, psychologists, data managers, nutritionists etc. They also set up the India Pediatric Oncology database (IndiaPOD) a free online registry with training for data managers. This brought in hospital based registry data and also made us comfortable with data-sharing.

Soon after, many robust non-governmental organisations developed from strength to strength, financing patient treatments, healthcare workforce, nutrition support among many other areas. Several among these are the

CanKidsKidsCan, Impacct foundation and several other local & regional ones. After-Chemotherapy care was led by Dr Purna Kurkure in the early years; now with improved outcomes we are better focused on & disciplined with late effects of cancer treatments & quality of life. Survivorship NGOs such as KidsCan, Ugam (indian Cancer Society) and several others provide valuable support. We also have Nutrition Intervention & Training Workshops & Nurses Training through SIOP-PODC & PHO India.

RESEARCH

There can be no progress without information on the scope of our challenges, audit of our clinical practice, innovations to develop a cost-effective childhood cancer care, as well as looking towards newer therapies for those who need them. To improve survival, answers need to come from our own data. Most research in the early years and even now, has been through individual institutions, both small and large. The earliest multicentric trials for Acute Lymphoblastic Leukemia were conducted in the 1980s in collaboration with the NCI-NIH, USA, using the MCP-841 protocols, in 3 Cancer centres, showing improvement in outcomes from 20% to 60%. Though formed in 2008, it took us several years of discussion and planning to bring structure & function to the Indian Pediatric Oncology Group: InPOG (now INPHOG) in 2015. A vibrant arm of the PHO chapter, the InPOG has 25 Disease subcommittees, has conducted over 20 multicentric trials in over 10,00 patients and has brought out several publications.

ROLE OF PROFESSIONAL SOCIETIES

Professional societies have had a significant role in driving scientific and clinical advancement in pediatric oncology. Childhood cancer needs a continuum of care which is multidisciplinary for which they provide common interactive platforms. Through all these years of progress, the PHO-IAP, has provided a forum bringing us together for education, training, access to opportunities, enabling dialogue between stakeholders and inspiring change. The SIOP and SIOP-PODC that most of us are members of, also has promoted scientific dialogue between the excellence of care in developed countries and the challenges in resource restricted settings; fostering collaborations, and sharing best practices.

Pediatric Oncologists from India have marked their presence on the international academic front as well; several of our members have held leadership positions in SIOP, SIOP-Asia, SIOP-PODC and other activities related to Global Oncology. The PHO-IAP community has played host to major international conferences, including SIOPAsia 2002 (New Delhi), SIOP 2007 (Mumbai) and Virtual SIOPAsia 2020/21 (Mumbai). Several high quality research papers from India are regularly presented and published, and we are looked up to, as an example & leader among the Low Middle Income countries wrt progress in Pediatric Oncology. The InPOG and PHO chapter are also well represented in the Asian Pediatric Hematology Oncology Group (APHOG), a new Collaborative Clinical Trials arm of the SIOP-Asia Continental branch. Pediatric oncologists from India also play an active role in the WHO's Global Initiative for Childhood cancer and WHO-SEARO Childhood Cancer forum.

WHERE WE ARE TODAY

We are in the midst of an exciting and challenging era in Pediatric Oncology. The past decade has brought in novel therapeutics and newer understanding of the cancers that we treat. Precise diagnosis at a molecular level, better treatments and supportive care has translated into cure & improved quality of life. However, for a country like ours, alongside progress, we also maintain a primary focus on early accurate diagnosis & guiding appropriate, affordable therapy. Pediatric Oncology is a team activity and the paediatrician's role remains pivotal, from diagnosis, through to survivorship. Where we

stand today, we have a trained workforce, there are avenues for funding of standard childhood cancer treatments, holistic care for nutrition intervention, palliative care, rehabilitation, support for travel & accommodation among many others. Though far from ideal, as we will still have patients who go undiagnosed or untreated; there is continued progress: We have several centres in India, successfully providing Hemopoietic Stem Cell Transplantation and newer immunotherapy modalities such as CAR-T cell therapy are being developed in the country.

We owe to the visionaries and teachers who believed it possible to cure childhood cancer under challenging circumstances: Dr Zinet Currimbhoy, Dr V Shanta, Dr SH Advani. Acknowledgements to my colleagues and founding stalwarts of PHO-IAP, Drs Lokeshwar, P Kurkure, B Agarwal, A Sachdeva, the late Dr RK Marwaha and late Dr LS Arya. Dedicated colleagues took progress further, many of whom are authors in this issue and lead the PHO chapter & its activities, and the next generation is already here with their bright minds and enthusiasm.

Childhood Cancer is Curable: Say YESS!! To curing childhood cancer.

INTP – PPO, Faculty, 1997

The Burden of Childhood Cancer in India in 2022

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How do we determine the number of children suffering from cancer in India?

A deceptively simple question whose answer is complicated! India has a huge population of 360 million children 0-14 years of age, almost double that of the pediatric populations of North America, Western European and Australia combined, spread across diverse regions and ethnic backgrounds. [1] In addition, childhood cancer is relatively rare (typically 1-2% of all cancers), made up of a wide variety of unique cancers, usually with no obvious cause. Adult-type carcinomas, rely on the ICD-10 coding system to stage by site, but childhood cancers are very different, and are classified based on histology/site using the WHO's International Classification of Diseases for Oncology (ICD-O-3). [2]

This means that population-based cancer registries (PBCR), used across the world for over 70 years to estimate the number and types of cancer that occur in a given region, struggle with childhood cancer. In India, the Bombay Cancer Registry was established in 1963, and the National Cancer Registry Program (NCRP) set up three more PBCRs in 1981; now India has 38. The relatively small population covered, with uneven distribution (mainly metro areas), and the high level of skill needed to obtain accurate data (since cancer is not notifiable, and physicians may not always know the diagnosis), add to the challenges of defining the incidence of childhood cancer. [3] Hospital Based Cancer Registries (HBCRs) overcome some of these issues, and can also provide follow-up and survival data; starting from three in 1981, there are now 165 HBCRs registered with NCRP. They are cost-effective since patients come to them, but bias remains since those who do not seek care will not be counted. Between HBCRs and PBCRs in India approximately 10-15% of the population is covered.[4]

PBCRs in India still form the backbone for determining incidence: their data goes to the International Associations of Cancer Registries (IACR) and the WHO International Agency for Research on Cancer (IARC), who collaborate to produce reports including the Cancer Incidence in Five Continents (http://ci5.iarc.fr) and International Incidence of Childhood Cancer (http://iicc.iarc.fr). The most recent edition of the latter in 2018 was Vol. 3 (IICC-3) with data from over 500 quality assured registries in 82 countries on 770,000 children. In the GLOBOCAN project (http://gco.iarc.fr) IARC uses sophisticated algorithms to extrapolate cancer incidence in various regions worldwide. Mumbai (Tata Memorial Center) became the first IARC regional hub for Asia in 2011.[5] A

study from India published in 2016 used verbal autopsy reports to estimate childhood cancer mortality at 37/million/year, higher than previously estimated by traditional tools. They noted that only 4–5% of children received any form of cancer-directed therapy before death, even though 82.5 % presented to hospital facilities before death. [6]

So how common is childhood cancer in India?

It depends a little on which report you read. Estimates of childhood cancer incidence in India processed by external agencies such as IARC as described above and published in the GLOBOCAN study, in 2018 estimated that 200,166 new children, age 0-14 years, were diagnosed with cancer globally, of whom 28,712 cases of childhood cancer (14.3%) were from India. [7] This yields an age-adjusted annual rate of cancer of 96.9 cases per million children (AARpm), one-third lower than countries like US, Canada, UK and Australia (140.5-166.9 per million) which would translate at current population levels into 36,000 children 0-14 years of age developing cancer in India each year. In diagnosed children, there is also a male to female ratio of 1.56, suggesting there a gender bias in seeking care. [8]

Since registries only cover 10-15% of the population in India, parents or physicians may not recognize the signs of cancer, and/or lack the resources to seek medical care, and even when cancer is recognized, the family may decide to refuse therapy before the patient is registered, such cases will be "invisible" to the cancer registry, so that the childhood cancer incidence in India is lower than predicted. This "incidence gap" is not unique to India and is found in other low-middle income countries (LMIC).[9] Arora and colleagues in 2021 published an elegant analysis showing that there is good reason to think the childhood cancer annual incidence rate as estimated below, may be closer to that in higher income countries, which means an occurrence of over 50,000 cases of childhood cancer per year 0-14 yrs of age across India. [10]

TABLE 1: Estimated Childhood Cancer Incidence Rate in India [10]

Incidence rate (per million children)	0-14 yr M	0-14 yr F	0-19 yr M	0-19 yr F
	151.4	129.4	163.2	143.6

In the long run, establishing linkage among various PBCRs, and PBCRs with HBCRs, as has been done in Tamil Nadu, will improve cancer registration quality, and improved standard of living, and better recognition of childhood cancer, will lead more parents to seek prompt medical care for childhood cancer.[11]

TABLE 2: Childhood Cancer Underdiagnosis in India based on GLOBOCAN report [10]

	0-14 years of age		
	GLOBO-CAN	Esti-mated	% Diagnosed and Registered
TOTAL	28712	52366	54.8
Boys	17468	29425	59.4
Girls	11244	23045	48.8
Leukemia	11056	17281	64
Lymphoma	3591	5661	63.4
Brain tumors	3626	10503	34.5
Kidney tumors	1466	3054	48
Liver tumors	421	857	49.1

What are the different kinds of childhood cancer encountered?

Due to sampling and referral bias there will always be some variation between different children's hospitals and cancer centers. For example, slow growing or visible cancers (e.g. retinoblastoma) are more likely to be encountered, whereas those that spontaneously involute or need special scans to diagnose (e.g. neuroblastoma or brain tumors) are less likely to be recognized. Many differences in the incidence of childhood cancers in India described a decade ago are now recognized to be due to sampling issues. [12] In Figure 1 showing data from a single center in N India, Leukemias (shaded

red) made up a third of all childhood cancers, predominantly ALL, mostly B-cell precursor; with a smaller portion of myeloid leukemias. Lymphomas (shaded purple) make up 15-20%, almost evenly divided between Hodgkin (HL) and non Hodgkin Lymphoma (NHL). Brain tumors (CNS, shaded deep blue) are under-represented, suggesting that many are going undiagnosed, or undergo surgery without further treatment. Remaining solid tumors (shaded brown/green/grey) make up a third of all childhood cancers, with neuroblastoma significantly less than expected.

FIGURE 1: Childhood Cancer Diagnosed at a Single Institution in N. India

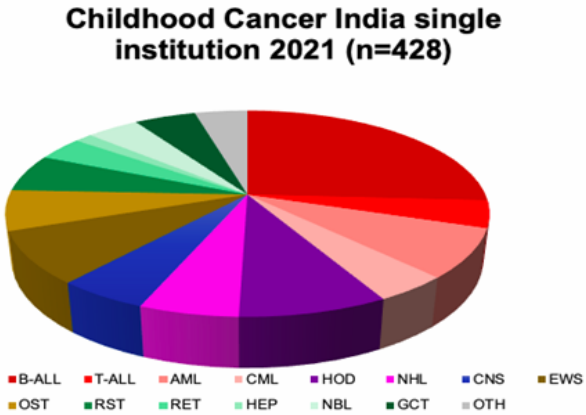

TABLE 2: Pediatric Leukemias/lymphomas incidence per million 0-14 yrs age in India [13]

Type of Cancer	Incidence per million	Comments
Leukemia	46.4	Acute lymphoblastic leukemia (ALL) is the most common, and the incidence of T-cell ALL compared to pre-B ALL is 10-15% (unlike earlier reports). Favorable cytogenetics in pre-B ALL is lower than expected. Acute Myeloid Leukemia (AML) makes up 20% of all leukemias, with a significant proportion having extramedullary presentation; Chronic Myeloid Leukemia (CML) 3-5% of total.
Lymphoma	15.2	Hodgkin (HL) and non-Hodgkin lymphoma (NHL) occur in roughly equal proportions. Mixed cellularity is the most common HL subtype, possibly due to early childhood Epstein Barr virus exposure, with an incidence peak at a younger age, and with advanced stage and B symptoms due to delay in diagnosis (upto half of patients misdiagnosed as Tuberculosis). In NHL, abdominal symptoms, constitutional symptoms and adenopathy are common; a significant proportion of cases presenting in advanced stages. T-cell lymphoblastic lymphoma (30–40 %) and Burkitt's lymphoma (40–60 %) are predominant subtypes followed by anaplastic large cell lymphoma and diffuse large B-cell lymphoma.

TABLE 3: Pediatric Solid tumors incidence per million 0-14 yrs age in India [14]

Type of Cancer	Incidence per million	Comments
Brain tumors	28.2	The lower incidence of CNS tumors could result from a paucity of neurodiagnostic facilities, and missed diagnosis in those presenting with headache, seizures, and altered sensorium. CNS tumours account for 8–12 % of total cases with astrocytoma, medullo-blastoma, craniopharyngioma and ependymoma most common.
Neuroblastoma	10.4	Neuroblastoma, is much less frequently reported in India accounting for 4.2–8.3 % of paediatric cancer incidence. Most present with intra-abdominal primary and INSS Stage 3/4 disease.

Retinoblastoma	4.5	Leukocoria most common presentation followed by strabismus, proptosis, visual loss and red eye, with extraocular disease at presentation in 27–40 % cases in North India with metastatic disease in 10 % cases
Renal tumors	8.2	Wilms tumor is the main entity, and due to rarity and lack of surgical expertise, upfront surgery with suboptimal surgical staging is common, requiring a 3-drug chemotherapy regimen.
Hepatic tumors	2.3	Hepatoblastoma is the main tumor, most present at advanced stage (PRETEXT 3 or 4).
Bone tumors	5.7	10–12 % of total childhood cancers, with Ewing Sarcoma and Osteosarcoma. Ewing's sarcoma may be difficult to recognize in uncommon sites and may be misdiagnosed as tuberculosis of the spine in India. Metastases are seen in around 40 % of patients.
Soft tissue sarcomas	8.9	For rhabdomyosarcoma (including non rhabdomyosarcoma soft tissue sarcoma) data on presentation and outcome are scarce.
Germ cell tumors	4.9	Outcomes with appropriate platinum based regimens are good, but data on presentation and outcome are scarce
Other	5.8	Nasopharyngeal carcinoma, rhabdoid tumor and other rare tumors in childhood are included here, data remains scarce.

Does screening play a meaningful role in preventing childhood cancer?

Preventive strategies play an insignificant role in most childhood cancers. In carcinoma in adults, routine screening (e.g. breast self-exam, prostate exam and colonoscopy in older individuals) plays a role in reducing morbidity and mortality by earlier detection before disease spread. However, there is no equivalent to such screening techniques in the majority of childhood cancers. The frequent occurrence of neuroblastoma in Japanese children led to efforts there from 1985 onwards to screen all children in infancy for elevation in urine vanillylmandellic acid (VMA) which is a marker for this malignancy. Unfortunately, the program ended up detecting a large number of asymptomatic infants with small tumors which would have spontaneously involuted, and the effort was abandoned in 2003, with no detectable impact on mortality. [15]

Some children may rarely have an underlying cancer predisposition syndrome due to inherited DNA repair defects (e.g. Ataxia Telangiectasia, Fanconi Anemia, etc.) and may benefit from targeted screening. An example is head and neck examination in children with Dyskeratosis Congenita where head and neck squamous cell carcinoma is frequent, but the details of individualized screening for these very rare syndromes is outside the scope of this review.[16] What is more important is that the delay in diagnosis of relatively common childhood cancers in the general population be reduced by increased awareness amongst pediatricians about "red flags" for childhood cancer. Some examples are persistent fevers and bony aches and pains in ALL, persistent adenopathy and fevers with sweats in Hodgkin Lymphoma, persistent headaches and effortless vomiting in brain tumors, and absent ocular red reflex in retinoblastoma.

What is the overall survival from childhood cancer in India?

Cancer is among the leading cause of non-communicable disease related deaths worldwide with over a million deaths each year from India,

where the leading causes are carcinoma of the cervix in women and carcinoma of the lung and head and neck in men. Out of total cancer deaths around 2% are in children, so the focus of the National Cancer Control Program of India till now was on primary prevention, e.g. tobacco control and genital hygiene; secondary prevention by screening; and palliative care. However, recognizing the large number of years of useful life which can be achieved by curing children with cancer, the World Health Organization has now thrown its weight behind a global program to improve childhood cancer cure rates.[17]

Childhood cancer is not a single entity, and the various cancers encountered differ in overall likelihood of cure, nevertheless collectively they are much more curable than the carcinomas found in adults, and an estimate of survival for childhood cancer in high income countries (HIC) is around 80%. As mortality from infectious causes in children has declined in India, more patients are now seeking care, but unfortunately a substantial number still go missing or their diagnosis is delayed. As a result, while the overall survival for those who seek treatment is around 50-60%, patients who do not receive treatment will die from their disease so that the overall cure rate in India is estimated at being around 20-30%. [17] There are broadly three reasons for poor outcome of children with cancer in India; non-adherence with treatment, relapses, and toxic deaths. Collaborative efforts to promote treatment of patients on common protocols and increased social support are important. The highest survival in India is seen for Wilms' tumor and Hodgkins' disease where over two-third of children survive for five years or more. [18] The survival for other childhood cancers, especially brain tumors, is lower.

How does cancer epidemiology help achieve better outcomes in childhood cancer?

Cancer registries and epidemiology are only a means to an end. Early diagnosis and referral are the key to improvement of survival outcome, and a better knowledge of our childhood cancer burden and outcomes allows us to increase awareness and leverage more resources to improve outcomes. Pediatric oncology services in India are no longer restricted to major urban centres, but as an "apex" service still need trained staffing and resources. Increased training programs in pediatric oncology, collaborative national clinical trials for common childhood cancers, establishment of the Paediatric Haematology and Oncology (PHO) Chapter under Indian Academy of Paediatrics (IAP) in 1987, and the development of the Indian Paediatric Oncology Group (InPOG) have all contributed to better care. Philanthropic support for nutrition, accommodation and transfusion, introduction of the Ayushman Bharat Program, and improved availability of affordable anti-neoplastic drugs are all areas where work continues. Better public education that childhood cancer is curable, along with tracking to ensure that each child receives complete care, and collaboration with all of our pediatric colleagues will hopefully bring us closer to the WHO goal of 60% survival by 2030.[17]

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Childhood Acute Lymphoblastic Leukaemia (ALL) in India: Journey over the last 4 decades and the way forward....

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Introduction:

ALL remains the most common malignancy of childhood, representing nearly one-thirds of all childhood cancers and 75% of all cases of childhood leukaemia. Childhood ALL is the poster boy for the achievements accrued over the last many decades in the field of paediatric cancer. Long-term cure rates of childhood ALL in the high income countries are approaching 90% with all risk strata (high, intermediate and standard risk strata) taken together. These exciting outcomes have been achieved internationally through multicentric, and often multinational, collaboration which helps in fine tuning risk adapted treatment in successive clinical trials. Increasing accuracy of baseline and response-based risk stratification, tailoring treatment based on risk (improved baseline risk assignment aided by sophisticated cytogenetic and molecular tests including next generation sequencing) and response as assessed by (minimal/measurable residual disease) have significantly contributed to these excellent outcomes. Discovery of new mutations and molecules targeting specific mutations (Ph positive, Ph-like ALL etc.), targeted antibodies/antibody-drug conjugates (blinatumomab/inotozumab) and cellular therapy including engineered anti leukemic T-cells (CAR-T cells) hold promise for a small subset of children harbouring disease difficult to treat with conventional chemotherapy. While so much has been achieved in the highly resourced countries, the outcomes are yet to be replicated in children form the low-middle income countries like India.

Problem statement:

It is estimated that India with its nearly 1.4 billion population, should have approximately 50,000 new cases of childhood cancer each year, and about 20,000 of them are likely to have ALL. Treatment of ALL in India was in its infancy

until mid-1980s. Starting mid-1980s the advent of the multicentre MCP 841 protocol as well increasing use of adapted protocols from various international groups helped in improving the outcome as compared to the pre-1980 era. Thereafter, the outcome has remained rather static over the next 3 decades with the highest EFS reported from few tertiary centres still hovering around 70%. The main reasons behind the inferior outcome are delayed presentation, high proportion of early deaths due to treatment related complications as well as deaths due to lack of salvage options in relapsed/refractory disease. Apart from this it is also certain that a significant proportion of children with ALL do not get a proper diagnosis when they present at peripheral health facilities and eventually die before reaching a cancer hospital.

Treatment modalities

Multi-agent chemotherapy continues to be the mainstay of treatment for childhood ALL. With the exception of mature B-cell leukaemia which is treated with a short term intensive chemotherapy protocol for non-Hodgkin (Burkitt's) lymphoma, the treatment of all other varieties routinely involve a remission induction phase, an intensification/consolidation phase, interim maintenance phase, re-induction/ delayed intensification phase followed by continuation/maintenance phase. Radiation therapy to the brain and spinal cord (neuroaxis) used very commonly in the yesteryears to prevent or treat CNS spread of ALL was associated with long-term neurocognitive toxicities. Due to significant improvement in the chemotherapy backbone with incorporation of agents and doses with better CNS penetration, radiation to the neuroaxis is sparingly used in the current era. Patients with ALL harbouring specific mutations like Philadelphia chromosome/ similar translocations (amenable to targeting) are also treated with targeted agents like tyrosine kinase inhibitors in addition to the chemotherapy backbone. The current treatment scheme for childhood ALL has been shaped as a result of various clinical trials conducted in the affluent countries over the last 5- 6 decades. Due to various reasons and competing priorities multicentric clinical trials have remained a distant reality for paediatric oncology in India until recently.

Though not in the form of a clinical trial, a multicentric protocol to treat childhood ALL was developed in the early 1980s for low-resource settings with the help of the NCI, USA and was used in 3 major cancer centres in India (Tata Memorial, AIIMS and Cancer Institute, Adyar) and in a span of a decade the outcomes in these centres improved from less than 20% (pre-MCP 841) to about 50% with the use of this protocol utilising multi-phasic multi-agent chemotherapy with acceptable toxicity. Two of the 3 major participating centres switched over to different protocols by the close of the last century and the latest survival data available using this protocol varies from 40-60% between centres. Besides this many patients were also treated during this period with protocols adapted from various western groups (most commonly from the BFM group) based on the treating haematologist's preference.

To address the issues regarding suboptimal outcome of treatment in childhood ALL five major paediatric oncology centres in India came together in 2012 to form the Indian Collaborative Childhood Leukaemia (ICiCLe) study group. The first co-operative trial on treating childhood ALL in India was finally launched in the year 2013. After a pre-trial/pilot phase of 3 years the trial ICiCLe-ALL-14 started prospectively recruiting patients in 2016 and is likely to close recruitment later this year. Though the primary objective of this trial is to decrease treatment-related toxicity and mortality and improve survival outcomes using a risk-stratified approach to ALL therapy based on disease genetics and levels of minimal residual disease (MRD), it is also likely to pave the way to successor co-operative clinical trials

in childhood ALL as well as other paediatric cancers alike.

Relapsed and Refractory ALL:

Despite standard treatment about 15-20% of children with ALL will have a relapse during or after the end of their planned treatment. Managing patients with relapse is more resource intense and needs aggressive salvage therapy and supportive care for a favourable outcome. Because of the large numbers of children diagnosed with ALL every year, the group of Relapsed ALL children becomes the second most common cancer in children and needs to be given more importance. More than half of these patients based on the site and timing of relapse as well as response to treatment would also need a bone-marrow transplant to ensure long-term cure. Novel therapies harnessing the immune system in the form of specific antibodies and cellular therapies are emerging as standard treatment for relapsed/refractory disease as they are likely to produce deeper and more sustained remissions as compared to intensive salvage chemotherapy with lesser toxicities. Unfortunately, transplant facilities in India are grossly insufficient to handle the load of patients needing transplant for cure, similarly access to novel agents is also restricted by cost, drug licentiating regulations and lack of domestic production.

Newer developments and targeted therapy

With the fast development in the field of genetic engineering, biotechnology and immunotherapy many ALL specific therapies have come into current use including monoclonal antibodies as well as engineered cellular immunity against cell surface markers of leukemic blasts. Though many of these are being currently tried in the setting of early phase human studies and some in phase 3 clinical trials, anti CD19 antibodies (Blinatumomab), anti CD22 antibodies (Inotuzumab and Epratuzumab) and CD19 specific, CD22 specific as well as CD19/22 bispecific Chimeric Antigen Receptor (CAR) T cells have shown promising efficacy in managing relapsed/refractory disease so much so that they are currently being tested in the setting of phase 3 trials for treatment of relapsed/refractory ALL. Due to superior safety and toxicity profiles these agents are likely to become a part of standard frontline treatment in the near future and have also been included upfront in ongoing phase 3 studies for newly diagnosed cases of childhood ALL.

Late effects of treatment

Based on the reported long-term follow-up of the survivors of childhood ALL, it has been seen that more than half of the survivors are likely to have one or more clinically significant late effects of treatment needing multidisciplinary care. Severe to life threatening late effects can occur in about one-fifth and one-tenth of the survivors respectively. The late effects include premature mortality, second malignancies, organ dysfunction (e.g. heart, lung, gonads), growth impairment, delayed puberty, infertility, impairment of cognitive function and so on so forth. Current treatment protocols are trying to reduce long-term toxicities by limiting exposure to modalities of treatment associated with increased toxicities as well as delivering de-intensified treatment wherever possible based on risk and response. Inclusion of novel/targeted agents onto the frontline therapy in the near future is likely to tame the late-effects further by allowing further de-escalation of chemotherapy. Since most of the children will follow-up with their pediatrician after completion of treatment, the pediatrician can play a major role in looking for and an early referral to the primary oncologist if a diagnosis of any late effect is made (shared care).

Childhood ALL in India .... the way forward:

The first and foremost challenge in caring for children with ALL is to improve access to care, so that all symptomatic children no matter from which corner of the country or what socio-economic background gets an early and proper diagnosis and are started on proper treatment. Providing subsidised/free treatment along with minimising out-of-pocket expenditures during treatment is of prime importance. Ensuring uniform treatment protocol/strategy across the country will be helpful in streamlining care and would minimise long distance patient migration. Strengthening of medical colleges/governmental health facilities as shared care hospitals would reduce the need to travel for routine maintenance and follow-up visits during the later part as well as after end of treatment. This would also streamline referral pathways for children with suspected leukaemia. Inclusion of many more centres in the successor ALL trial planned after the conclusion of the current ICiCLe-ALL-14 trial is likely to improve the overall outlook of ALL in India as has been historically seen when children treated in a clinical trial were found to have better outcomes as compared to those treated outside trials.

Many steps have been taken at various levels in the last few years to circumvent the above mentioned obstacles. The Tata Memorial Centre (TMC) has established 4 outreach tertiary care cancer hospitals with state-of-art facilities in different regions of the country to take cancer care closer to patients' homes, many other super-speciality government hospitals including various peripheral AIIMS are also being commissioned to improve healthcare infrastructure of the country as a whole. Various health related schemes by both union as well as state governments are being rolled out to ensure subsidised/free cancer care to the economically disadvantaged section of population. The National Cancer Grid commissioned under the aegis of Tata Memorial Centre is facilitating uniform treatment guidelines across the country and collaboration as well as capacity building in both governmental and non-governmental health facilities to ensure standard cancer care across the country. Though it is too early to assess the positive impact of the above measures we can just be optimistic that these changes as well as many more in the near future would be instrumental to ensure timely diagnosis and proper care to all children with ALL in India.

Besides these, the importance of improving access to the novel agents for our patients with diseases not amenable to conventional chemotherapy, cannot be overemphasised. Though initially it would serve the need of a small proportion of patients, in the long run it is likely to pave the way for use of these agents for more liberal indications leading to reduction in treatment related toxicity and better long-term outcome. Expansion of bone-marrow transplant facilities is also likely to go a long way in treating children with relapsed/refractory diseases. At least 3 centres in India are in the process of researching and manufacturing CAR-T cells for use in relapsed/refractory ALL and early phase clinical trials are underway, similarly 2 centres in the country are part of an international humanitarian access program of availing blinatumomab (anti- CD19 BiTE) for use in relapsed/refractory setting. Indigenous production of these agents are likely to make these interventions widely available and affordable for routine clinical use.

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Retinoblastoma-Pitfalls in India

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Introduction

Retinoblastoma (RB) is the most common primary intraocular malignancy in childhood with a stark disparity in survival and outcomes amongst developed and developing nations, though 90% of the children affected with RB live in less developed countries.(1) These improved survivals are due to early diagnosis more than the availability of sophisticated treatment modalities. It is a potentially curable malignancy with early diagnosis and appropriate therapy but with increased mortality rates in advanced stages of the disease.

A short summary of the disease

It typically presents in the first 2-3 years of life, most often in infancy with tumor confined to the eyes only in the early stages of the disease. In advanced cases, tumor spreads outside of the eye to involve the orbit, optic nerve, cervical lymph nodes, central nervous system (CNS), bones, bone marrow. Cure rates for intraocular RB can be as high as 95% requiring only focal treatments like laser, cryotherapy, or thermotherapy in early Group eyes to enucleation of the eye in Group E.(2) With extraocular disease, the cure rates decrease to as low as 5-10% in CNS disease and practically no survival in leptomeningeal spread CNS disease.

The International Classification of Intra-ocular Retinoblastoma has developed a grouping system for intraocular disease with Groups A-E of increasing severity which helps to assess the vision prognosis uniformly and plan treatment. There is a staging system for extraocular disease which prognosticates survival. The aim in the treatment of retinoblastoma is first to improve survival, then salvage globe, finally vision.

Incidence

The incidence of RB reported in the Cancer Incidence in Five continents Volume X is lower in the developed nations as compared to the developing countries. Published literature on this rare disease from less developed countries are sparse. National Cancer Registry Programme (NCRP) established in 1982 in India provides data regarding the incidence rates in a defined population though the active collection of data in this registry is far from complete. The pooled crude incidence rate of retinoblastoma across various Population based cancer registries (PBCR) in 0-14 age group was 3.5 and the pooled Age Standardized Incidence Rate (ASIR) was 4.4 per million (data extracted till 2010). The pooled ASIR in the 0-4, 5-9 and 10-14 age group was 9.6, 2.0 and 0.1 respectively. The pooled ASIR in 0-14 age group by sex was 5.2 (males) and 3.5 (females).(3) Though the incidence in this extracted data resembled the rates in developed nations, this must be interpreted carefully as there is a gross active underreporting of cases as evident from the small numbers reported in the analysis. Also, these registries provide data from specific towns and cities only. The database also did not have complete information on laterality, sequence of eye affected, heritability, follow-up,

or survival. Making cancer a notifiable disease would help rectify these shortcomings and help inform policies with better utilization of resources.

In a study published from a tertiary cancer center in India, the median age at diagnosis of 29 months did not differ much from comparable studies though a male preponderance was seen, probably due to referral bias.(4)

Clinical presentation

Clinical presentations of children affected by RB has shown wide variations across different nations. But broadly, developed nations see more of intraocular disease in early phases compared to the advanced intraorbital disease seen in the developing nations. Leukocoria was the most common symptom at presentation, followed by strabismus in developed countries. In a referral center in India strabismus was seen in only 5.5% of cases, and proptosis was the second most common presenting symptom (17%).(4) Extraocular disease also differed widely with a frequency of 28% in the Indian cohort compared to 2-5% in the developed world. Bilateral and unilateral tumors were diagnosed at a relatively earlier age in developed countries like USA (13 months and 23 months) and Australia (5 months and 21 months). In the Indian study cohort, 66% of bilateral cases were diagnosed during the first 2 years of life whereas 68% of unilateral cases were diagnosed after the age of 2 years. Intraocular tumors presented at an advanced stage with 78% cases being Group D or E. Unilateral and bilateral tumors with a diagnosis of Group A-C disease were 5.3% and 38.4% respectively.(4)

Early detection needs to be a priority and requires policy implementation at different tiers of health care. The first steps towards the goal are raising awareness of the medical fraternity (primary care physicians, obstetricians, pediatricians) as well as other frontline health workers to conduct screening examination of the eyes of the newborn and subsequently during a child's health care visits especially the immunization visits. Prompt referral can be facilitated when there are risk factors. This could be integrated into the various existing public health programmes for ease of delivery. Both public and health care professionals need to be educated on this front.

Treatment modalities and outcomes

The various treatment modalities for RB ranges from focal therapies like laser photocoagulation, cryotherapy, transpupillary thermotherapy depending on the size and location of intraocular tumor to enucleation in Group E disease. Chemotherapy is used in various settings for tumor reduction, prophylaxis for preventing metastatic disease post-enucleation in eyes with high-risk pathological features. Radiotherapy also has a role in RB mainly in extraocular disease. A higher rate of enucleation is found in India due to the advanced stage at presentation.

Various newer modalities in the treatment of RB, especially for eyes with diffuse vitreous seeds like intraarterial chemotherapy and intravitreal chemotherapy are commonly employed in the developed world for globe and vision salvage, but these are available only in a few select centers in India. Hence most of the advanced Group D with persistent vitreous seeds also undergo enucleation or receive radiotherapy.

Stark inequalities are palpable in the mortality rates due to RB across developed (3-5%) and developing nations (40-70%) due to delayed presentations. Overall mortality rates of 24% was noted in the Indian cohort reported from a tertiary care hospital. The cumulative 5-year survival probability of 65% was strikingly low when compared to USA (95%), Japan (93%). Stage at presentation, age > 2 years, and a lag period in the diagnosis of > 6months adversely affected outcomes.(4)

The major impediments in the achievement of higher cure rates in RB including lack of

awareness of the disease, inaccessibility to proper medical facilities, poor treatment compliance, absence of a timely referral needs prompt and strategic addressal for any realistic improvement in survival.

Treatment refusal and abandonment

The major reason for abandonment among patients with RB is the reluctance to enucleation which is advised due to the advanced disease at presentation. This stigma associated with enucleation needs to be tackled from various fronts. A better rapport of the treating oncologist and surgeon with the caregivers can provide reassurance regarding the same, especially the cosmetic consequences in a girl child. This can be established with proper counselling at diagnosis with pictorial demonstration of the available prosthesis and survivors post enucleation. A talk with survivors could be arranged for better understanding of the procedure and long-term ocular cosmesis and function. Techniques like oculoplasty, maintaining the movement of prosthesis could really be reassuring. Another group of patients who frequently abandon treatment are those diagnosed with extraocular disease, due to the prolonged duration of treatment and poor survival in these cohorts.

Genetic testing and counselling

The knowledge of genetics of RB helps in tailoring the management. It is the prototype genetic cancer syndrome due to biallelic inactivation of retinoblastoma (Rb) gene. It may be heritable (germline mutations which are present in all somatic cells) as occurs in all bilateral and 15% of unilateral cases or non-heritable due to somatic mutations in the retina only.

Germline mutations are highly penetrant. Over 90% of children carrying the Rb gene defect will develop retinoblastoma. Hence the role of genetic counselling and testing cannot be understated. The differentiation between somatic and germline has major implications for determining the risk to unaffected siblings, relatives, and future siblings. Genetic testing could inform the type of mutation (germline or somatic), risk of unilateral or bilateral disease, choice of treatment protocols and prognosis of the condition and need for surveillance which could go a long way in ocular and patient survival.

At the primary health care level, eliciting a positive family history or any ocular surgeries in the parents could be the initial step forward. Comprehensive genetic counselling and testing could be set up in referral centers or centers of excellence where, in the ideal situation, all cases of retinoblastoma should be referred for screening. In the absence of testing, the 'at risk' siblings and offsprings should be put on surveillance protocols with examination under anesthesia till 4 years of age. In subsequent pregnancies, parents can be offered the choice of amniocentesis and early detection, or where this is not possible, serial surveillance of the baby.

Follow up

The survivors of retinoblastoma need long term follow up, especially in germline cases to detect second malignant neoplasms which occur two to three decades later. The risk is substantially increased in children with germline mutations who have also received radiotherapy. The treatment of patients with RB does not stop with treatment of ocular disease alone in most cases and the patients and health care professionals need to be educated on this. The patients can be provided with surveillance protocols which can be followed up by the local health care professional.

Conclusions

RB is the most common intraocular malignancy in childhood which is potentially curable if detected early and treated on time. There are various pitfalls in the diagnosis and treatment of same in India as detailed above which calls for action from the primary health

care level to implementation of policies by the government aimed at flattening the disparities observed in treatment and outcomes in the country.

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Non-Hodgkins lymphoma in Children: Problems and Progress

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Non-hodgkins lymphoma (NHL) is the 4th commonest group of cancers in children and constitutes about 8% of all pediatric cancers. There are an estimated 56000 new cases of Pediatric NHL annually across the world. In the last few decades (1975-2010) there has been dramatic improvement in survival from 45% to 90%, making it a highly curable group of cancers in children and adolescents. This article will review the clinical presentation, diagnosis and treatment of childhood NHL. The challenges at time of diagnosis, role of supportive care, progress made in treatment protocols and problem areas needing newer strategies will be outlined. The key role of a practicing paediatrician in the diagnosis and treatment is described.

Histopathological sub-types of Pediatric NHL

In adults NHL constitutes a very heterogeneous group of low to high grade tumours of varied histology. In children however, the vast majority of NHL are high grade tumours i.e. they are very rapidly multiplying cells, resulting in often short duration of symptoms and quickly progressive disease, requiring urgent diagnosis and stabilisation of the child. NHL arise from malignant proliferation of lymphoid cells. This lymphoid tissue is seen in lymph nodes or lymphatic tissue elsewhere in the body eg intestine. Lymphoid cells, primarily B cells or T cells at various stages of maturation (immature or mature) can undergo malignant transformation leading to proliferation of a clone of immature or mature B or T cells.

The most common histological groups of NHL seen in childhood NHL are:

1. Mature B cell NHL (Burkitt lymphoma –BL (40%), Diffuse large B cell lymphoma – DLBCL (10%))
2. Lymphoblastic lymphoma – T-LBL - (an immature T cell lymphoma)- 25%
3. Anaplastic large cell lymphoma – ALCL (mature T cell lymphoma)- 10%

Each sub-type has different prognosis and therapy protocols; hence making a complete histological diagnosis is an important step in management.

Clinical presentation

NHL often presents with a rapidly worsening clinical status in a sick child. Often the constellation of clinical symptoms may itself give a clue to the sub-type of NHL and recognition of these patterns are important for early diagnosis. A high index of suspicion, rapid diagnostic tests and recognition and treatment of oncological emergencies can save the child's

life. The paediatrician plays a major role in suspecting and making a timely referral to a Paediatric Oncology Unit

NHL may present with a variety of symptomatology, described in the following case vignettes. .

1. Child with PUO:

Like leukemias, lymphomas may present primarily with a fever that does not have an obvious focus. Lymphadenopathy and hepatosplenomegaly may be present in varying degrees. A normal blood count and a normal bone marrow aspirate do NOT rule out a lymphoma and only in Stage IV NHL is bone marrow or blood count abnormality seen. A chest X-ray with a widened mediastinum or large abdominal lymphnodes picked up on an ultrasound examination may be the only clue to a lymphoproliferative process. Even small generalised lymph nodes may need an excision biopsy to confirm the diagnosis, especially if other common infections have been ruled out.

2. Child with cough and orthopnoea: (Fig 1)

Thoracic lymphnode masses (T- LBL, DLBCL) with or without pleural and pericardial effusions are common clinical presentations of NHL. An unexplained cough / wheeze or a child who tends to have discomfort while lying supine may be the only clue to a rapidly growing mediatinal mass. A sudden onset of wheeze in a child with no past history of asthma should raise a red flag. Facial puffiness / plethora and dilated veins on the neck and chest are subtle clues which are often difficult to pick up especially in dark skinned children. Hasty treatment with oral steroids for possible "asthma" may delay diagnosis as steroids may temporarily decrease symptoms.

3. Lymphnode masses: (Fig 2)

Large painless lymph nodes (sometimes involvement of Waldeyers ring), not resolving with antibiotics or anti-tubercular treatment. Empirical ATT often leads to delayed diagnosis in pediatric lymphoma and all efforts must be made to demonstrate AFB/ granulomas / malignancy by an excision biopsy of a lymph node, before starting ATT as a "possible TB".

4. Bony pains/ back pain:

Like leukemias, lymphomas may present with unexplained bony pains. Lytic bone lesions (characteristic of ALCL) incidentally picked up on xrays may give a clue. Paraspinal masses (seen in BL) may present as a vague back pain and only later in the course of the illness, present with neurological symptoms which prompt a CT or MRI of the spine. A back pain which wakes a child in the night, restricts activity, persists for > 4 weeks and associated with bony tenderness needs imaging with MRI/CT. Blaming a heavy school bag or a low vitamin D level may result is delays in diagnosis.

5. Abdominal mass: (Fig 3)

Progressive abdominal distension due to bowel thickening, right iliac fossa mass, intussusception, progressive ascites are typical presentations of BL. Bilateral uniform renomegaly, bilateral ovarian masses and massive hepatosplenomegaly are all manifestations of NHL. Ascitic fluid may not always reveal malignant cells and careful imaging of the bowel by cross sectional imaging is required.

The above clinical features can mimic a large variety of differential diagnosis like bacterial infections (PUO), tuberculosis (thoracic/ right iliac fossa abdominal mass or ascites), rheumatological / orthopedic conditions (joint pain, back pain) and so a high index of suspicion is required especially if symptoms persist or are rapidly progressive.

Oncological Emergencies in NHL and Diagnostic tests:

The high grade nature (short doubling time of cancer ells) of pediatric NHL, results in many children presenting with potentially life threatening symptoms. The paediatrician/ pediatric intensivist may be faced with the following oncological emergencies in NHL:

1. Mediastinal mass causing Superior vena cava syndrome
2. Acute kidney injury due to Tumor lysis syndrome seen in high grade B lymphomas
3. Acute onset paraperesis in spinal NHL.

Stabilisation using standard protocols with close coordination with a pediatric oncologist is required for management of these oncological emergencies. As majority of NHL respond rapidly to chemotherapy, stabilisation, urgent diagnostic tests and emergent initiation of chemotherapy is essential to improve survival. Histopathological confirmation by cytology from pleural/ ascitic fluid, and tru cut / excision biopsies help confirm NHL. Immunohistochemistry on biopsy tissue or flowcytometry on pleural/ ascitic fluid confirm the sub-type of NHL which is important to decide on treatment protocol. Molecular diagnostics on biopsy help confirm diagnosis.

Making an urgent and complete diagnosis (the histological type) is essential. This can be difficult for the following reasons:

1. Anatomic location (thorax/ abdomen/spine) makes getting a biopsy challenging unless there is pediatric surgical/ intervention radiology/surgical oncology expertise.
2. poor clinical status of patient at presentation
3. Lack of pathology capacity, including tissue processing, staining, and immunohistochemistry (IHC) – to help subtype the NHL.
4. Ability to perform bone marrow aspiration and CSF examination for malignant Cells; incomplete evaluation will lead to the wrong staging and suboptimal treatment.
5. Inability to afford diagnostic procedures

As diagnosis and initiating chemotherapy is urgent, sick children with suspected NHL need to be referred to Pediatric Oncology units with access to all of the above. Often the Pediatric Oncologist will need to work closely with the PICU team to stabilise, make an urgent diagnosis and start treatment as soon as possible. Many of these young children are better served in a Pediatric Oncology Unit rather than an adult oncology unit as supportive care is as important as the chemotherapy expertise in most Pediatric cancers in general, and NHL in particular.

Treatment

The mainstay of treatment of pediatric NHL is chemotherapy. International cooperative groups over the last 3-4 decades have developed protocols where multiple chemotherapeutic agents are used in quick succession to clear tumor growth and prevent progression or relapse. The chemotherapy protocol varies based on the sub-type of NHL and the extent of disease at diagnosis . High grade B NHL is usually treated for 4-6 months while T lymphoblastic lymphoma is treated on leukaemia like protocols i.e. 6 months of intensive therapy followed by two years of maintenance chemotherapy. Most chemotherapy regimens include high doses of alkylating agents (cyclophosphamide), anthracyline (doxorubicin) and antimetabolites (methotrexate and cytarabine) in combination with vincristine and steroids. In developing countries survival of paediatric NHL ranges from less than 30% to over 70%, depending on the capacity to support patients through the intensive regimens. Due to the intensity of the treatment, febrile neutropenia, mucositis and nutrition related concerns are common. Early initiation of antibiotics and assessment for sepsis by the primary care paediatrician for children on chemotherapy with fever, is an integral part of care.

Sub-types of NHL and outcomes

B NHL has an excellent prognosis and the addition of rituximab to certain sub-groups with higher stage disease has improved overall survival to greater than 90%. However B NHL with CNS disease at diagnosis remains a difficult disease to cure requiring a more intensive protocol. Relapsed B NHL and disease progression while on treatment are also subgroups which have a very guarded prognosis with survival of < 25%. Newer agents are being tried and chimeric antigen receptor –T (CAR-T) Cell based immunotherapy is being attempted in DLBCL.

ALCL constitutes about 10 % of childhood NHL. Most patients with systemic ALCL present at advanced stages (stages III-IV) with peripheral intra-abdominal or mediastinal lymph node involvement , frequently associated with B symptoms (fever, weight loss, night sweats) and extra-nodal spread, including skin (ezema like rash), liver, lung, soft tissue and bone (lytic lesions) localization. ALCL sometimes first presents to a dermatologist, with skin involvement alone or part of a systemic disease. Relapsed ALCL has a relatively good outcome compared to other NHL sub-types and recently Brentuximab and crizotinib have been added in clinical trials for ALCL.

T-LBL usually presents with a mediastinal mass and advanced stage disease (stage III or IV in >90% of patients) and may involve bone marrow (25–30%) and, less often, CNS (approximately 5%) at diagnosis. B-LBL is more likely to involve the skin, soft tissue, bone and peripheral lymph nodes and represents most of the localised (stage I or II) stages. Intensive four drug induction and high dose methotrexate are integral parts of treatment. As most protocols are based on extent of disease, molecular markers are being investigated to decide on optimising intensity of chemotherapy. Currently extent of disease at diagnosis and rapidity of response to treatment is both largely assessed by imaging alone. Measurable residual disease (MRD) assessment to quantify response after chemotherapy and Minimal disseminated disease (MDD) to quantify extent of disease at diagnosis are tests by flowcytometry or PCR which are being evaluated. Both may help risk stratify patients at diagnosis and also have a better understanding of which patients are having a sub-optimal response during treatment. Those with a suboptimal response are more likely to relapse and so will potentially be benefitted by intensifying treatment early.

Certain less common subtypes of NHL namely the various mature T cell lymphomas ie peripheral T cell lymphoma (PTCL), angioimunoblastic T-cell lymphoma (AITL) and hepatosplenic gamma/delta T-cell lymphoma and enteropathy-associated T-cell lymphoma (EATL) have a dismal outcome. Patients with advanced and/or refractory PTCL after induction therapy often need to proceed to an autologous or allogeneic stem cell transplant.

Problem areas and Indian scenario

Some areas of are in pediatric NHL remain challenging around the world. Relapsed NHL has a very guarded prognosis with survival of < 25% even in high income countries. Several new strategies employing targeted therapy have emerged, inhibiting different signalling pathways, such as B-cell receptor signalling (the BTK inhibitor, ibrutinib), B-cell lymphoma-2 inhibitors (Venetoclax, Navitoclax), SYK inhibitors (Fostaminib), PI3K (Idelalisib) and Janus kinase-STAT inhibitors (Ruxolitinib, Everolimus and Temsirolimus). None of these agents are used in upfront treatment and data from clinical trials is awaited. Long term survivor health status is also an area where more data is required from all parts of the world. With more children with NHL being cured around the world we also need to focus on potential health concerns in long term survivors. Cohorts of NHL survivors from the developed world have reported a greater incidence of second malignancies, cardiomyopathies, poorer quality of life and social attainment.

In a recent multicentre retrospective

analysis of Pediatric B - NHL (InPOG-NHL-16-01 study) the disease-free-survival (DFS) was 74.4% and event-free-survival (EFS) was 60.7%. Treatment-related mortality (TRM), relapse/ progression and abandonment were 14.3%, 14.5%, and 8.4%, respectively. This is in contrast to high income countries were cure rates are more than 90%. The barriers to cure of NHL in India include need for early diagnosis, stabilisation prior to referral and prompt supportive care of oncological emergencies in PICUs. Social support to families (subsidised treatment, place of stay near the treatment centre) and nutritional support to patients during chemotherapy play a vital role in children completing their treatment. Appropriate treatment is key, as relapsed NHL has a very guarded prognosis around the world, so the first presentation is the best chance to get to cure. The primary paediatrician plays many key roles in contributing to the successful cure of these children in India.

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Fig 1:

8 year old with acute onset of cough – large anterior mediastinal mass with pleural effusion

Presented with orthopnoea, SVC syndrome – diagnosis based on pleural fluid cytology and flowcytometry

Diagnosis : T – lymphoblastic lymphoma; X Ray at diagnosis and after 2 weeks of chemotherapy.

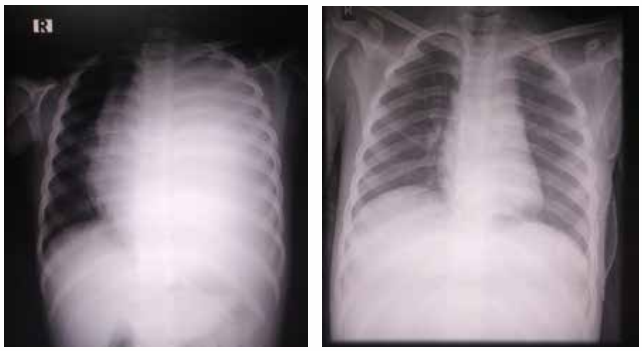
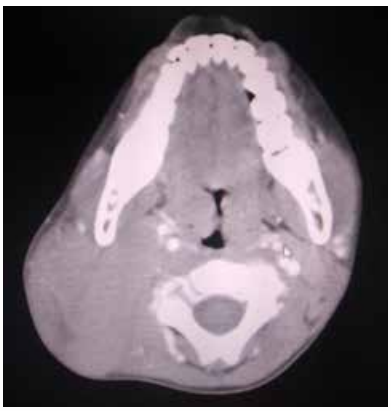


Fig 2:

12 year old with persistent fever and adenotonsillar enlargement

Presented with odynophagia – large adenotonsillar enlargement with cervical lymphadenopathy

Diagnosis: Burkitt lymphoma – rapid resolution in 1 week



Pediatric brain tumors: the need for multidisciplinary management

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Case Vignette

A 4-year-old child presents to a pediatrician with complaints of poor feeding and decreased activity since 10 days. He has low grade fever and vomits once or twice a day. He is given symptomatic treatment for fever and vomiting. Within one week his condition deteriorates, and he develops strabismus. Parents seek a second opinion and the doctor refers them to a neurologist who advises a CT scan of head. The radiologist reports presence of a mass in the posterior fossa and requests for an MRI scan. An MRI is performed which reveals gross hydrocephalus and a large mass with contrast enhancement in the posterior fossa with no spinal metastasis, likely malignant lesion. The child is referred to a neurosurgeon who performs a shunt surgery followed by decompression of the tumor. The child is managed postoperatively by the pediatric intensivists and nursing team. The pathologist performs stains and immunohistochemistry and makes a diagnosis of embryonal tumor, medulloblastoma- classical type. Further molecular testing is done in the lab which confirms it to be a Group 4 tumor. A multidisciplinary team meeting is held in presence of neurosurgeon, radiation oncologist, pediatric oncologist and a social worker and the parents are informed about the diagnosis of cancer, outline of treatment, likely outcome and potential short- and long-term complications. A fund raiser is initiated and support from different Non-Governmental Organizations (NGO) is provided to meet the financial expense of the therapy. After recovery from surgery, radiation oncologist starts radiotherapy to the posterior fossa which lasts for 6 weeks. Anaesthesia team provides daily sedation to the child during the radiotherapy. After 6 weeks, the patient is admitted under the pediatric oncology specialty and is started on chemotherapy. 6 cycles of chemotherapy are given over a period of 6 months with repeated hospitalisation. The social worker meets the family during every visit. A school teacher associated with the NGO provides education during hospitalisation and at home. After completion of therapy, child undergoes regular surveillance scans and check ups by endocrinology and pediatric oncology team. Child is transitioned to after completion of therapy clinic, 5 years post diagnosis of cancer. He is regularly followed up by a pediatric oncologist, endocrinologist, ophthalmologist, audiologist, social worker and special educator.

The case highlights the well-known fact that "it takes a village to treat a child with cancer".

Introduction

Childhood brain tumors are the second most common malignancy after leukemia. They could be classified based on age (congenital, tumors of the infancy and tumors in older children) and based on the location of the lesion (supra and infratentorial tumors). The prognosis of the pediatric brain tumors is reliant on the age at presentation, histological type, biology, extent of resection and degree of metastasis (1,2). An enormous proportion of mortality in childhood cancer is attributable to brain tumors (3).

In spite of the advent of medical technology and knowledge, no direct causes of brain tumors have been recognized. Both the genetic as well as the environmental factors play an indispensable role in the pathogenesis of the brain tumors. A few cancer predisposition syndromes are associated with the brain tumors such as Li-Fraumeni syndrome, neurofibromatosis etc. It has been asserted by some studies that family history, parental age at birth, infectious exposure during childhood and exposure to high dose radiation plausibly play a significant role in the etiology of brain cancer (3).

Supratentorial tumors are more common amongst those younger than 3 years of age whereas infratentorial tumors occur between the ages of 4 to 10 years. However, post puberty both are equally prevalent (4). Amongst young children, tumors of embryonal origin such as medulloblastoma or atypical teratoid/rhabdoid tumor are common. However, tumors of glial origin are highly prevalent in the older children (3,4).

Multidisciplinary approach to pediatric brain tumors

Since the advancement of the diagnosis and treatment of pediatric brain tumors, multidisciplinary approach has become the cornerstone in the management of these patients. Multidisciplinary clinics are the standard of care in high-income countries, however, in Low-to-Middle-income countries (LMIC) such as India, we still have a long way to go.

The survival rate for pediatric brain tumors in the western world is 70-80% and fundamentally is a consequence of improved diagnostic and therapeutic modalities, neurosurgical techniques and the integrated care between specialties. With the escalation of survival rate, more children would be living with the comorbidities associated with the tumor and the treatment. The complexity of management of pediatric brain tumors underscores the crucial role of multidisciplinary approach (5).

A multidisciplinary approach comprises of health care professionals of different expertise, who can together make a colossal impact to patient care and outcome. Research experts proclaim that a multidisciplinary approach leads to comprehensive treatment and holistic decision-making. It paves the path of adherence to evidence based medicine, definitive pathological diagnosis and timely implementation of adjuvant and neoadjuvant chemotherapy and radiotherapy. The added benefits are better patient satisfaction and opportunity for ongoing education of health care providers. Cancer patients managed by multidisciplinary team approach are found to have improved survival in a literature review performed by Hong et al, however, the study was limited due to methodological heterogeneity. Qaddoumi et al affirmed the beneficial effect on patient care via videoconferencing with international experts in pediatric neuro-oncology set up in a developing country (6,7,8).

From the perspective of the parents, it is an exceedingly onerous task to navigate from one hospital to the other, not least when their child is diagnosed with a life-threatening illness.

The multidisciplinary approach can significantly lessen the angst of parents by assuring that the patient's time is judiciously utilized and numerous needs are met with in one visit and in one place. According to a parental survey, social life and independence of children were the two necessary components of quality of life and these are often neglected in an isolated and busy medical or surgical oncology unit (9).

Notwithstanding the innumerable benefits and the dire need of the multidisciplinary approach to childhood brain tumors, we still ought to alleviate variety of technical and logistical challenges in India. For a successful multidisciplinary approach to brain tumors, many departments need to integrate together including pediatric oncology, radiation oncology, radiology, histopathology, neurosurgery, endocrinology, psychiatry, palliative care, physiotherapy, nursing, social workers and dieticians. This would mean more investment from the physicians and other personnel, requirement of adequate meeting space and exam rooms, provision of reading material to families in their own language. Patients and their parents should be provided with enough opportunity to participate in decision-making and to clarify any questions that arise in their mind (10). Because of high patient load per doctor in LMIC, there is a natural resistance for any added responsibilities and coordination with other specialists is generally neglected or procrastinated. Paradoxically, multidisciplinary approach, reduces the workload of primary treating doctor, since it provides a composite effort by different specialists. Appropriate counseling and an integrated approach for management will also curtail the abandonment of treatment.

Histopathological review and molecular work up by experts have revolutionized the therapeutic approach to brain tumors. Their integration in the multidisciplinary team would help in correlating the clinico-radiological-surgical findings, improvise recruitment in clinical trials and guide clinicians in the best feasible and novel strategy for managing brain tumor. In many hospitals, there is a paucity of radiation oncology facility and the patient's family may get exasperated moving from one hospital to the other which may eventually lead to loss of follow up. Often, the fact that chemotherapy is required to treat a particular malignant brain tumor is not revealed to the family up until the completion of radiation and this creates a very disconcerting situation. Sometimes, the patient's family is reluctant for chemotherapy due to the all-pervading myths surrounding its short- and long-term side effects. A multidisciplinary team meeting at the time of diagnosis of cancer helps allay many such doubts and strengthens the faith of family in the entire treatment process. It helps them to plan logistics and finances ahead of time. Endocrinological assessment also plays a salient role in thorough management of pediatric brain tumors albeit it is generally not included in the work up and referrals are delayed until the onset of frank symptoms.

To put it in perspective, although multi-disciplinary approach is certainly critical in management of childhood brain tumors, the variegated barriers need to be addressed efficiently at the earliest. In India, the first step to multidisciplinary approach would be to motivate the diverse specialists to liaise with each other and prioritize the patient's wellbeing above their own convenience. As it is rightly said, "Individually we are one drop. Together we are an ocean". After the instillation of this ideology, different objectives should be elucidated such as mandatory presentation of all new cases to the tumor board and the team should monitor progress of all newly diagnosed and relapse cases. Inputs from dietary, nursing, physiotherapy and social service department should be duly acknowledged and executed. Attendance at the meeting and implementation of the decisions

made by the team should be supervised.

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REVIEW

Emergencies in Oncological care

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Introduction

Advances in diagnostic techniques and increased awareness amongst pediatricians have led to an increase in the estimated childhood cancer incidence in our country (1). Leukemias, brain tumors and lymphomas constitute the commonest childhood malignancies (1). The World Health Organization Global Initiative for childhood cancer envisages a 60% survival in children with cancer across the world by 2030 (2). Children with cancer can present with life-threatening complications. In low- and middle-income countries such as India which face challenges such as late presentation and resource-limitations, it is not uncommon for a child to be critically ill at the time of diagnosis. Timely and appropriate intervention can save the child's life and give the child an opportunity to receive definitive treatment for a potentially curable malignancy.

The review will focus on three oncological emergencies that can be commonly encountered in the day-to-day practice of a pediatrician, namely tumor lysis syndrome, hyperleukocytosis and superior mediastinal syndrome. It is not infrequent to find more than one emergency in the same child. Additionally, there will be a brief description of febrile neutropenia, a treatment related emergency, that can be easily managed with a shared care strategy between the primary oncologist and community pediatrician.

Tumor lysis syndrome

Pathophysiology

Tumor lysis syndrome (TLS) is a bio-chemical syndrome which occurs secondary to the spontaneous or treatment induced breakdown of malignant cells. Intracellular contents such as potassium, phosphates and nucleic acids are released into the circulation in addition to cytokines. Nucleic acids are broken down by xanthine oxidase to uric acid. The metabolic derangement in addition to the inflammatory effects of cytokines predisposes to acute kidney injury. The dyselectrolytemias also affect the central nervous and cardiovascular systems.

Diagnosis

A 'laboratory-TLS' is defined by a ≥ 25% increase from baseline (or an absolute value exceeding the cut-offs mentioned in parentheses) in ≥ 2 of the following serum biochemical parameters: uric acid (> 8 mg/dL),

potassium (> 6 mEq/L) and phosphorous (> 6.5 mg/dL) (3,4). TLS occurs in the time span of 3 days before and 7 days after the initiation of anti-cancer therapy. Hypocalcemia (ionized calcium < 1.12 or a serum calcium corrected for albumin that is < 7 mg/dL) is a secondary consequence of hyperphosphatemia. When these dyselectrolytemias demonstrate manifest consequences such as seizures, arrhythmias and acute kidney injury [oliguria: < 0.5 ml/kg/hour for 6 hours), serum creatinine > 1.5 times the upper limit of normal (ULN) or a rise from baseline by 0.3 mg/dl], then the phenomenon is said to be a 'clinical-TLS (4).' If TLS is diagnosed in the laboratory stage and managed, one can easily prevent the clinical consequences.

Risk stratification

Based on the type of malignancy and disease burden one can classify a patient to have a low risk (<1%), intermediate risk (1-5%) and high risk (> 5%) of developing TLS (3). It is noteworthy that the presence of a pre-existing renal dysfunction or above-mentioned biochemical abnormalities will escalate the risk group irrespective of the diagnosis.

1. High risk: acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML) with a white blood cell count (WBC) of ≥ 1 lakh/cu.mm, Stage III/IV Burkitt lymphoma (BL) or lymphoblastic lymphoma (LBL), ALL/BL/LBL with an elevated serum lactate dehydrogenase (LDH) of ≥ 2 x ULN irrespective of WBC count and stage

2. Intermediate risk: ALL/BL/LBL not satisfying criteria for high risk, AML with WBC 25000-1 lakh/cu.mm or LDH ≥ 2 x ULN

3. Low risk: AML with WBC <25000/cu.mm and LDH < 2 x ULN, other non-Hodgkin lymphomas, Hodgkin lymphoma, solid malignancies such as Wilms tumor, neuroblastoma, germ cell tumor

Management

Prevention

Prevention is key in TLS. The initiation of hydration at the rate of 2-3 litres/m2/day or 1.5 times the maintenance requirement (200 ml/kg/day if weight is ≤ 10 kg) with plain saline-dextrose (N/2-5%dextrose or N/4-5%dextrose) is the most important step in the management of TLS (5). It is important to not add potassium or calcium to the fluids. There should be stringent monitoring of the input and output with a desired target urine output of 80-100 ml/m2/hour (4-6 ml/kg if ≤ 10 kg) (5). Furosemide may be administered at a dose of 0.5 mg/kg/dose 8-12 hourly after ensuring there is no obstructive uropathy, if the urine output remains sub-optimal (5,6). Alkalinization by adding sodium bicarbonate to fluids was a historically popular strategy that is no longer recommended in TLS. It can facilitate phosphate and xanthine product induced renal injury. The second preventive measure is to administer allopurinol which is a xanthine oxidase inhibitor. The dose is 10 mg/kg/day in three divided doses (or 50-100 mg/m2/dose, available as 100 mg tablets) with a maximum daily dose of 300 mg/m2/day or 800 mg/day (5). A 50% dose reduction is recommended in patients with evidence of renal injury and an alternative in such patients is febuxostat at a dose of 10 mg once a day (7).

Treatment

Vigorous hydration with output monitoring is the first line for treatment of TLS and should be ensured before any other intervention. Additional strategies for individual issues are listed below (Figure 1)

1. Hyperuricemia: Rasburicase (recombinant urate oxidase which converts uric acid to soluble allantoin) is administered at a recommended dose of 0.15-0.2 mg/kg/day in 50-100 ml of normal saline intravenously over 30 minutes for 5 days (5). Providentially, a single dose

of the 1.5 mg vial often achieves significant reduction in the serum uric acid levels and the drug is now easily available in most Indian cities at a cost of approx. Rs 8000. Serum glucose-6-phosphate dehydrogenase (G6PD) levels must be sent before administration as the drug can potentially cause life-threatening hemolysis in G6PD deficient individuals. Serum uric acid samples must be transported on ice to the lab after exposure to the drug to prevent its ex-vivo action.

2. Hyperphosphatemia: Aluminium hydroxide (easily available in the form of antacid) can be given at a dose of 50-150 mg/kg/day every 6 hours as a gut phosphate binder. An alternative oral binder for severe cases is sevelamer administered at a dose of 100 mg/kg/day in three divided doses (5,6).

3. Hyperkalemia: This is a life-threatening abnormality and needs immediate attention. Intravenous administration of calcium gluconate 100-200 mg/kg under electrocardiographic monitoring to stabilize the heart followed by insulin-dextrose infusion (0.1 U/kg of regular insulin in 2 ml/kg of 25% dextrose) is indicated (5,6). Adjunctive measures include intravenous sodium bicarbonate (1-2 meq/kg), salbutamol nebulisations (0.15 mg/kg q 4-6 hourly) and gut exchange resins administered preferably by oral route (kayexalate 1 g/kg q 6 hourly) (5,6).

4. Hypocalcemia: Since this is a secondary abnormality, it is not addressed in asymptomatic patients. In children with symptoms such as arrhythmias, tetany or seizures, 50-100 mg/kg of calcium gluconate can be administered intravenously under cardiac monitoring (5).

5. Renal replacement therapy: Dyselectrolytemias that are refractory to the above medical measures, inability to hyperhydrate due to development of pulmonary edema or acute kidney injury with oligo-anuria are indications for renal replacement. Continuous renal replacement is the method of choice followed by hemodialysis in older children (6). Peritoneal dialysis can be used only if the above methods are unavailable.

Based on the above risk stratification, all high risk and intermediate risk patients must receive TLS prophylaxis with hydration and allopurinol. When easily available, rasburicase can be administered upfront in high risk patients (3,4). Also, it is important to monitor for the development of TLS by sending the requisite blood parameters 8-12 hourly in high-risk cases and 12-24 hourly in intermediate risk cases. In low-risk cases, at least a single baseline evaluation is prudent and further monitoring may not be required in an otherwise stable child.

Hyperleukocytosis

Pathophysiology

In children with acute leukemia, 10-20% present with a WBC count of ≥ 1 lakh/cu.mm that is arbitrarily defined as hyperleukocytosis (8). Leukemic blast cells are much larger than the normal circulating blood cells and increase the viscosity of blood, in addition to adhering to endothelium and causing sludging in the microcirculation. Hyperleukocytosis thus results in 'leukostasis' and end organ damage, particularly in the brain and lungs, secondary to ischemia, thrombosis and hemorrhage (9). Early mortality rates can approach 20% in children with this complication (9). Infant leukemia, ALL of the T-cell type, AML of the monocytic type and leukemia with certain adverse genetics such as the MLL rearrangement are associated with this complication.

Diagnosis

For the pediatrician, it is vital to differentiate leukemic hyperleukocytosis from other differentials of high WBC count. These

include the leukemoid reaction of infections such as staphylococcal sepsis and pertussis (WBC count is usually < 1 lakh/cu.mm and the peripheral smear shows mature cells with no atypical cells or blasts). Further, infants and young children with thalassemia major can present with spuriously high WBC count (a peripheral smear will demonstrate nucleated red cells that are falsely counted as WBC). Thus, a complete blood count with a peripheral smear seen by an experienced pathologist is mandatory to confirm the diagnosis. Additionally, the smear can give a clue to the type of leukemia (myeloid or lymphoblastic). Children with chronic myeloid leukemia usually present with prolonged symptoms and hyperleukocytosis with a 'full-house' differential leukocyte count (circulating myeloid precursors, basophilia and eosinophilia) and a normal to elevated platelet count (in comparison to acute leukemia where the differential leukocyte count is predominantly comprised of blasts and platelet count is low). TLS often accompanies hyperleukocytosis and must be tested for.

The airway, breathing and circulation must be stabilized awaiting investigations and evidence of central nervous system or pulmonary involvement must be assessed. A fundus examination for papilledema and retinal hemorrhages and a chest X-ray are desirable. In the absence of facilities to establish a complete diagnosis of leukemia such as immunophenotyping and genetics, it is prudent to stabilize the child and transfer to a higher centre as soon as possible.

Management

The first step is vigorous hydration, following the same principles outlined under TLS. In children with acute leukemia with a low Hb ≤ 6 g/dl, there is a concern of precipitating fluid overload and congestive failure and one may start with a near maintenance volume of fluids. The blood transfusion strategy is vital in this complication and include two aspects:

1. Platelet transfusion targeted at maintaining a platelet count of > 30000-50000/cu.mm to prevent intracranial and pulmonary hemorrhage.
2. Packed red cell transfusion is typically avoided till the WBC count is brought down as it can increase blood viscosity and potentiate leukostasis

Fresh frozen plasma at a dose of 10-15 ml/kg can be given to children with deranged coagulation parameters which may be seen in AML, particularly of the M3 type.

Leukoreduction is vital in hyperleukocytosis. The most effective way is to establish a speedy diagnosis and initiate chemotherapy. Steroids in ALL and cytarabine in AML can bring down the WBC in 48-72 hours of initiation. Leukapheresis is a procedure that removes the circulating WBC through an apheresis machine and often performed in children with very high WBC counts. However, the procedure carries risks such as the need for a central venous access, exposure to anticoagulation a potential risk of bleeding. Systematic reviews and meta-analyses performed in ALL and AML have concluded that leukapheresis has not demonstrated any benefit in reducing early mortality (8,9). A partial exchange transfusion similar to what is done in newborns with hyperbilirubinemia is another procedure that is sometimes practiced, particularly in children with severe anemia and hyperleukocytosis. In the author's experience a guarded packed red cell transfusion administered at a lower dose of 5 ml/kg can be safely given to children with severe anemia. In stable children with Hb ≥ 6 g/dl, the transfusion can be delayed till the reduction in WBC by chemotherapy (Figure 1). The first few days till the WBC count reduces are critical and need close monitoring of vitals, sensorium, intake/output and blood counts and TLS parameters.

Superior mediastinal syndrome

Pathophysiology

Due to a relatively smaller chest volume, mediastinal masses can lead to the compression of the airway and superior vena cava (SVC) in children leading to the superior mediastinal syndrome (SMS) (10). Greater than 30% compromise of the airway lumen can pose a risk for total airway obstruction in children (10). The commonest malignant causes for the syndrome are non-Hodgkin lymphoma (T-lymphoblastic lymphoma, primary mediastinal B-cell lymphoma), ALL (particularly the T cell type) and germ cell tumors. Although Hodgkin lymphoma is well known to cause mediastinal adenopathy, the slow progression of the disease allows compensation and SMS is infrequent. Occasionally tuberculosis and thrombosis secondary to central line/cardiothoracic surgery can present with a syndrome similar to SMS.

Diagnosis

The compression of SVC leads to swelling and venous engorgement in the upper part of the body. Airway obstruction manifests with respiratory distress, stridor, inability to lie supine and cough. A chest X-ray with a posteroanterior and lateral view often reveals the mass and its position in the mediastinum (Figure 2). Lymphomas/leukemias are often associated with concomitant pleural and pericardial effusions. A contrast-enhanced computerized tomography can further confirm the mediastinal mass, particularly when the X-ray is not able to give a clear diagnosis. Less invasive tests which cause minimal discomfort must precede more invasive modalities, as the patients have a compromised airway and are poor candidates for sedation and anesthesia. A complete blood count with a peripheral smear can reliably diagnose acute leukemia. When the peripheral blast count is high, further immunophenotypic characterization and genetic tests can be performed in the peripheral blood, avoiding the need for a bone marrow. Concomitant TLS must be evaluated for and presence indicates a hematological malignancy. Serum alpha-feto-protein and beta-human chorionic gonadotrophin levels when elevated can establish the diagnosis of a malignant germ cell tumor without the need for a biopsy.

If the above tests do not establish the diagnosis, one can plan a bone marrow under local anesthesia if there are blood cytopenias; or a fine needle aspiration (FNA) or an excision biopsy from a peripherally palpable significant lymph node. A radiologically guided FNA or biopsy of the mediastinal mass may be required as the last resort using local anesthesia or minimal sedation under close vital monitoring.

Treatment

Head end elevation will facilitate venous drainage and reduce airway compression. Spontaneous breathing must be encouraged (10). As per the level of respiratory distress, oxygen by face mask, high flow nasal canula or non-invasive ventilation may be initiated. Due to risk of respiratory failure, the use of sedation and neuromuscular blocking agents is discouraged. Prophylactic measures for TLS must be initiated. Due to the life-threatening nature of SMS, steroids can be started upfront while awaiting all the investigations. Dexamethasone 6 mg/m2/day in two divided doses or hydrocortisone 5 mg/kg/dose q6H are effective as most of the causative lymphomas and leukemias are sensitive to steroids and steroids reduce the airway edema too (11). However, the investigations for diagnosis must be expedited as beyond 48 hours of steroid exposure, the histopathological diagnosis may be significantly compromised by the steroid response. In the event of poor response to steroids, the addition of low dose empirical chemotherapy with vincristine and cyclophosphamide may aid tumor reduction and reduction in the distress. Administration of radiotherapy for SMS is historical and has a limited role in the contemporary management of SMS.

Febrile neutropenia

Pathophysiology

Children who are receiving chemotherapy can develop myelosuppression and neutropenia as adverse events. This predisposes them to severe bacterial infection. In the absence of antibiotic administration within the golden hour, a systemic inflammatory response may set it leading to organ dysfunction and death. Often, children with cancer travel far from home to reach centers that offer oncological services. A 'shared-care' approach between the oncologist and the local pediatrician can allow the children to continue treatment while staying at home, particularly in less intensive treatment phases. Febrile neutropenia is defined as a fever > 38 deg C for more than 1 hour or a single fever ≥ 38.3 deg C in a patient with a absolute neutrophil count (ANC) of < 500 cells/mL (or <1000 cells/mL with an anticipated fall due to recent exposure to chemotherapy) (12). The most serious infections are caused by gram negative organisms such as Pseudomonas and Enterobacteriaceae (12).

Diagnosis and treatment

When a child receiving chemotherapy arrives to the outpatient clinic or emergency with fever, the treatment should be empirical without waiting for reports. After checking for vital instability requiring stabilization, an intravenous access must be established. The first dose of intravenous broad-spectrum antibiotics must be administered after sending blood culture and a complete blood count. Third generation cephalosporins such as cefaperoazone-sulbactam and piperacillin-tazobactam are readily available at most centres and can be used as first line. Carbapenems and gram-positive cover with vancomycin may be used when a child presents with vital instability needing resuscitation. Based on the response of the child and available resources the local pediatrician may then decide to continue antibiotics till the blood culture report arrives or refer the child to the primary center for further treatment.

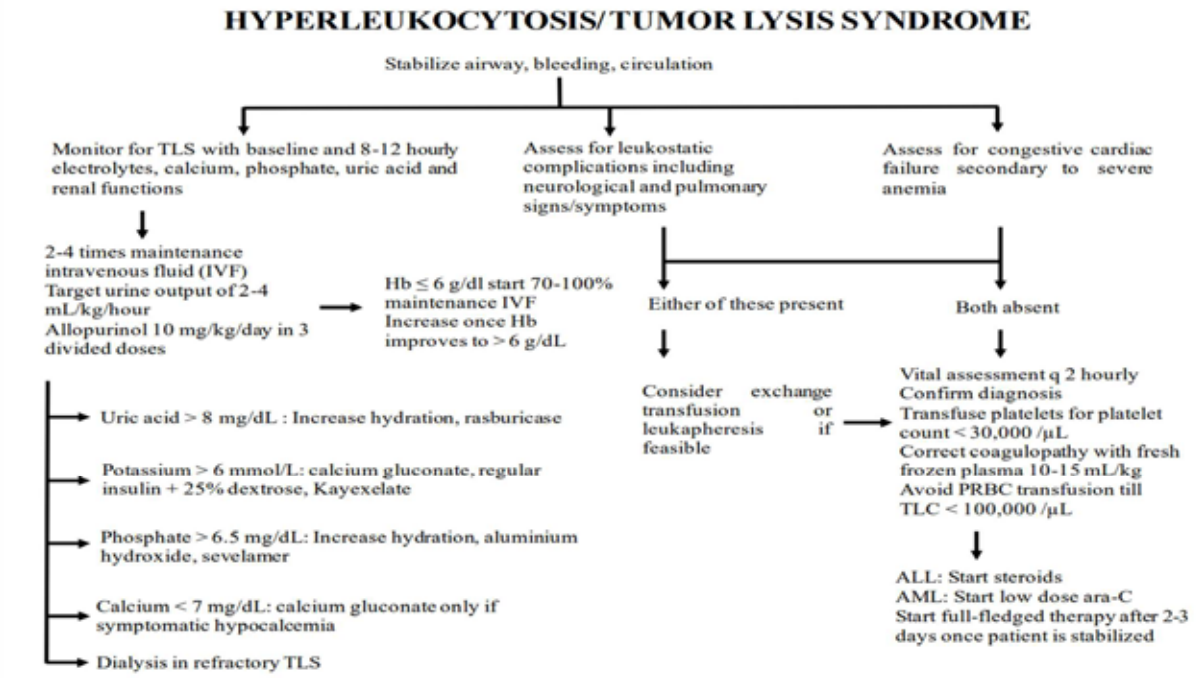

Figure 1. Flowchart demonstrating the treatment of tumor lysis syndrome (TLS) and hyperleukocytosis

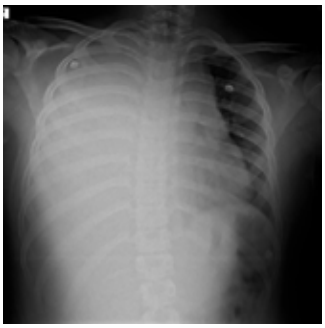

Figure 2. Chest X-ray in a 12-year-old boy presenting with respiratory distress and facial swelling, demonstrating mediastinal widening and an opaque right hemithorax. A right sided pleural tap was subjected to flow cytometry and yielded the diagnosis of T-lymphoblastic lymphoma.

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Hematopoietic Stem Cell Transplantation in children – the coming of age

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Background

The field of Hematopoietic Stem Cell Transplantation (HSCT) has progressed remarkably over the past decade in India. We can now provide access to care to all children at a unit close to their home and deliver international standards of care to children with rare blood disorders and refractory blood cancers. Miracle cures continue to be performed in children by transplant physicians across the country, and they are the gentle giants of our community. Thirty years ago, the first HSCT was conducted in India. We now have rich experience in the field shared through the Indian Society of Blood and Marrow Transplantation with our shared database called ISCTR Indian Stem Cell Transplantation Registry.

Which child would benefit from HSCT?

Hematopoietic stem cell transplantation can be autologous where the child's stem cells are used and allogeneic where the stem cells are from a donor. Autologous HSCT is a procedure performed to deliver high doses of chemotherapy for children with solid tumors such as metastatic neuroblastoma.

The indications for HSCT have been evolving. The standard indications have been stem cell disorders like severe aplastic anemia, red cell disorders like thalassemia major, sickle cell anemia, white cell disorders like primary immune deficiency, and high-risk leukemia. However, expensive enzyme therapy is not available for inborn errors of metabolism, such as Hurler syndrome and Gaucher's disease in India, and HSCT offers a chance of cure. Newer indications include inflammatory bowel disorders like IL10RA defect and autoinflammatory disorders.

Hematological Malignancies

- Acute Myeloid Leukemia – high risk and relapsed
- Acute Lymphoblastic Leukemia – high risk and relapsed
- Chronic Myeloid Leukemia – resistant to tyrosine kinase inhibitors or blast crisis
- Juvenile Myelomonocytic Leukemia
- Non-Hodgkin's Lymphoma – refractory or relapse
- Hodgkin's Lymphoma – refractory or relapse

Solid tumors

- Neuroblastoma- stage 4

- Wilms tumor - relapsed
- Ewing's sarcoma – metastatic in CR1

Non-malignant disorders

- Thalassaemia major
- Sickle cell anemia
- Inherited bone marrow failure syndromes like Fanconi anemia
- Severe aplastic anemia
- Inborn errors of immunity - all primary immune deficiency disorders
- Inborn errors of metabolism – Hurler, Hurler-Scheie, Hunter, Maroteaux-Lamy, Gaucher's, X-linked adrenoleukodystrophy, Metachromatic leukodystrophy.
- Infantile osteopetrosis
- Autoimmune disorders

Who is the ideal donor?

The basis of a successful HSCT has been HLA compatibility. HLA helps the body's immune system to recognize itself from foreign. HLA Class I and Class II determine the chance of rejection and graft versus host disease.

HLA typing – interpretation of reports now done by DNA sequencing method. Class I has HLA A, B, C, and Class II has HLA DRB1 and DQB1. A complete match is where all 10 HLA results are matched with the donor at the antigen and allele level as we inherit one HLA antigen from each parent.

Table 1 - Sample HLA report of potential patient and sibling donor

	HLA *A	HLA* B	HLA *C	H L A * DRB1	H L A * DQB1
PATIENT	02:03 33:03	15:02 15:18	07:04 08:01	04:03 12:02	03:01 03:02
DONOR	02:03 33:03	15:02 15:18	07:04 08:01	04:03 12:02	03:01 03:02

PATIENT AND DONOR - FULLY MATCHED

How would we prepare the child for receiving the new stem cells?

This step of HSCT has been a significant challenge for pediatric transplant physicians as high doses of chemotherapy and radiotherapy used in conditioning cause immediate and late side effects. Newer potentially gonad sparing agents like treosulfan and fludarabine are now available in India to promise reduced mortality and late side effects. The age of molecular diagnosis has also helped us pinpoint children with DNA breakage disorders as they would need far less conditioning chemotherapy than other children and thereby reduce mortality.

The conditioning regimen is typically for seven days, and the use of high doses of chemotherapy and or radiotherapy completely ablates the stem cells and child's lymphocytes.

What are the sources of stem cells?

Bone marrow is the ideal source of stem cells with a good mix of stem cells and lymphocytes, and nutrients required for the growth of stem cells. However, the ease of donation is higher in the case of peripheral blood stem cells with the minimum discomfort to the donor, and the donation is an outpatient procedure in an adult donor. The use of cord blood stem cells in children has declined dramatically over the past five years with the advent of haploidentical stem cell donors. Haploidentical HSCT has been made more accessible to all using techniques called posttransplant cyclophosphamide or TCR alpha beta depletion. The lymphocytes from the donor can potentially cause graft versus host disease. They can be entirely eradicated by administering cyclophosphamide at 50mg/kg/day on day three and day four after the infusion of stem cells. This technique is called PTCY. The lymphocytes from the stem cells can be depleted in vitro in

the lab by using monoclonal antibodies, and this technology is called TCR alpha beta depletion.

Table 2 – Sources of stem cells

Peripheral blood stem cells	Bone marrow stem cells	Cord blood stem cells
Number of stem cells High	Medium	Low
Number of lymphocytes High	Medium	Very low
Time to engraftment 10-14 days	14-21 days	21-28 days

Donor terminology: Now, every child has a donor!

Only 30% of children have a fully matched family donor. For the others, we search for a donor in stem cell registries in India like DATRI and DKMS BMST India. The donor pool has now been expanded to include fully matched sibling or family donors, matched unrelated donors, or haploidentical donors. So now, every child can be offered a chance of cure!

Table 3 -Types of HSCT donors

Syngeneic donor	Twin
Matched Sibling Donor	Brother or sister
Matched Family Donor	Mother or father or grandparents or cousin
Matched Unrelated Donor	HLA matched donors from any registry worldwide
Haploidentical Donor	Half matched sibling or parent donor

Table 4 - Types of haploidentical HSCT

HAPLO HSCT	PTCY	TCR ALPHA BETA DEPLETION
Cost	Low -1200 rupees	High- 12 lakh rupees
Technology	Nil	Needs skilled personnel
Immediate toxicity	High - cardiac and cystitis	Nil

How would we provide optimal supportive care?

Once infused into the child, the stem cells start functioning between 10 to 21 days. The first of the two days when the absolute neutrophil count (ANC) is above 500 is called engraftment. These two weeks pose a significant challenge as the child needs optimal supportive care, especially from bacteria they harbor in their own body and environmental pathogens. Clean air rooms, trained nursing personnel, and access to antibiotics are the key to surviving the phase of zero white blood cells. The advent of newer antibiotics and antifungal agents has helped us overcome even resistant infections. In addition, granulocyte transfusions have now been incorporated into the protocol in most transplant units. Vigilant follow-up for organ dysfunction, including heart, liver, kidneys, and lungs, are now standard of care.

What are the challenges in balancing graft rejection and graft versus host disease?

The profound exchanges between the host and donor T cells determine the outcome of HSCT. If the recipient T lymphocytes are active, they reject the new stem cells. If the donor T lymphocytes are functional, the recipient's body is recognized as foreign and causes a condition called graft versus host disease or GVHD. GVHD can cause significant morbidity and mortality, and all efforts to prevent GVHD must be made while planning HSCT. The children remain on immunosuppression for about 6 to 18 months.

How should we provide long-term follow-up?

Hematopoietic stem cell transplantation is unique in organ transplantation. The need for immunosuppression is only for one year until the new graft is fully functional instead of solid organ transplantation, where the medications need to be continued lifelong.

Children on cyclosporin or tacrolimus need to be monitored with care for infections. Children on immunosuppressive therapy need to be treated with appropriate antibiotics for every febrile illness in the community as there is a possibility of overwhelming sepsis. Vaccination guidelines are available as IAP and International guidelines to help immune reconstitution post-transplantation. Puberty must be supervised carefully to ensure adequate growth and development.

The scenario in India

With increasing awareness and the availability of pediatric physicians leading transplant teams, the number of transplants performed in children each year has increased from less than 500 to over 1000. There is scope for further improvement, and the emphasis is on early referral. Thalassaemia major HSCT is best performed before age seven as there are iron overload-related complications. Children with primary immune deficiency need to be transplanted before serious infections cause organ damage. Metabolic disorders arrive too late to help with HSCT, as seen in children with Hurler syndrome. The procedure needs to be done before the second birthday for optimal neurological outcomes. Insurance schemes from the government and access through NGO schemes like the Coal India project for Thalassaemia major HSCT will help improve access to care.

Gene therapy

Single gene disorders of the hematopoietic system can now be cured using gene therapy and the future is here! Gene therapy is essentially a form of autologous transplantation. The risk of rejection and graft versus host disease are eliminated by the use of the patient's own stem cells.

Step 1

Collect peripheral blood stem cells from the child

Step 2

Incorporate missing gene using a viral vector

Step 3

Conditioning chemotherapy to eradicate defective stem cells from the child

Step 4

Infuse the stem cells with the gene into the child into a central vein

Step 5

Provide supportive care for two weeks until the cells engraft

Conclusion

Early referral is the key to the best outcomes in HSCT for all blood disorders like thalassemia major and inborn errors of immunity. Advances in donor selection have made HSCT available to all children. Newer conditioning, chemotherapy, and supportive care have reduced transplant-related mortality in our country. Government and non-governmental agencies are working hard to ensure that we can close the gap for children who require this life-saving treatment—the guidance and support before and after transplantation results in the best possible outcomes. HSCT offers a cure not just for a child but brings back the most needed harmony for the entire family.

Suggested further reading

- National guidelines for hematopoietic stem cell transplantation – ICMR 2021
- EBMT Handbook

A perspective on childhood cancer survivorship in India

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Advances in modern therapy have led to sustained improvements in cure rates for childhood cancer. This has been responsible for a burgeoning in the number of survivors world over. It is well known that the outcomes are much better in the high-income-countries where nearly 8 out of 10 children are cured.

The annual number of new cases of cancer occurring in low and middle income countries (LMIC) account for 80% of the global incidence with Africa and South East asia constituting 69% of them, and India has 45% of all cases from SE Asia. Despite the fact that only 20% of the world's childhood cancer cases live in HIC, it is estimated that the USA and Europe each have a population of almost half a million childhood cancer survivors (CCS). Hence even though the cure rates are lower in LMIC like India, a large number of survivors are added each year to their population.

Experience with follow-up of CCS has revealed that they are at substantial risk of late and long-term adverse effects of cancer therapy. Long term side effects are those complications of treatment that occur during therapy and persist even after the treatment is over. Late effects appear months or years after the completion of treatment.

Each child getting cancer treatment is unique. The treatments used vary from child to child and from one type of cancer to another. Other things that can affect a child's risk include:

- The type of cancer
- Where the cancer was in the body
- How old the child was when treated
- The child's overall health before the cancer
- The child's genetic make-up (inherited risk for certain health problems)

Late effects are caused by the damage that cancer treatment does to healthy cells in the body. Most late effects are caused by chemotherapy or radiation. Major surgery can also lead to late effects based on its anatomic location and extent.

These are wide-ranging and may impact any of the major organs or systems. Frequently occurring health problems affecting life expectancy and/or quality of survival include second malignancies, organ dysfunctions, endocrine and metabolic disorders, and cognitive and psychosocial impairment. Evidence reveals that by 30 years after diagnosis, almost 40% of all

CCS will experience at least one serious late effect of treatment that will influence their health and quality of life. Hence the need for a systematic follow-up and surveillance plan for them.

Recent concept of a truly "cured child" in pediatric oncology envisages not only a biological cure of the disease but a child on par with peers in growth and development physically and in achievements and aspirations, both mentally and emotionally. Because of the young age of these survivors and their potential for longevity, the delayed consequences of therapy may have a serious impact on their lives and family at large than do the acute complications of the cytotoxic therapies that they had experienced.

Care for survivors in India

In India there are many barriers that impede the provision of evidence-based follow-up screening services to childhood cancer survivors. Furthermore, there is heterogeneity in care for survivors and is most often pediatric oncologist driven with few exceptions wherein few healthcare driven comprehensive models also do exist. Training and resources for survivorship care are lacking. There is no national or state-level policy that addresses medical care, employment, or health insurance barriers for survivors of childhood cancer. Furthermore, most survivors of cancer in India are not eligible for health or life insurance, regardless of time elapsed from treatment.

Until recently, survivors in India were mainly cared for in cancer treatment OPDs. Fortunately in the past five years many large pediatric cancer units have established clinics to serve the CCS, these are termed as after completion of therapy clinics (ACT) or survivorship clinics and are dedicated to screening, counselling and management of late effects. Depending on the individual needs of the survivors, these clinics co-ordinate and provide access to multiple disciplines of care like endocrinology, physiotherapy, dentistry, ophthalmology, psychology, nutrition etc.

Transitioning to care under the Pediatrician

Although primary care physicians lack specific oncologic training, they are well placed to provide holistic care to young and older survivors of pediatric cancers.

Often survivors express reluctance to transition to paediatricians being more familiar and comfortable with the oncology team. Hence, although hospital-based survivorship care is preferred by many survivors, it is not a sustainable long-term option. Primary care physicians are in a better position to deliver more accessible and comprehensive survivorship care, particularly to long-term survivors who are at low risk.

Evidence from surveys indicate that primary care physicians/ pediatricians are somewhat uncomfortable in dealing with survivors of lymphoma and leukemia. They admit to being concerned about their own readiness to assume responsibility for follow-up care of survivors of childhood cancer. This is logical to a large extent, as discussed below.

As we know CCS are treated during childhood when the body is still developing, hence these health problems or late effects may emerge many years, even decades after the end of cancer treatment. Often they are no longer under the care of pediatric oncology specialists.

Some of the important parameters that a pediatrician could well manage after completion of cancer therapy is catch up vaccination (which are with-held owing to down regulated immune system during the course of chemotherapy or stem cell transplant).

Growth retardation due to hormonal imbalance (sex hormones/thyroid hormone/ growth hormone) caused due to either a brain surgery or a gonadal surgery or due to chemotherapy affecting gonadal cells. In this

scenario, the pediatrician would need to work up the child in accordance with general guidelines for underweight or short stature, however awareness of possible treatment related would definitely facilitate and streamline care.

Furthermore, behavioral abnormalities are not uncommon in this cohort, which may range from simple anxiety to pathological depression. Rather as per late effects guidelines, there is a whole spectra of behavioral issues, due to trauma of disease and treatment, these kids encounter during their early years of development. There also occurs a significant impact of certain treatment modalities accounting to the former, like cranial irradiation and brain surgery. These may impact their scholastic performance and general behavior. These issues need to be recognized and addressed promptly, as they may affect the survivor's as well as their family's quality of life. The attending pediatrician or physician would therefore need a one to one interaction and would need to refer the family to a psychologist or psychiatrist depending on their clinical judgment. It would be of vital importance to assess the developmental milestones, in young children (<5years) to look for developmental delay.

It is not just the physical parameters, but the pediatrician will have to inculcate the importance of healthy lifestyle (healthy food, sleep hygiene, avoidance of unsafe sex etc) in young teenage survivors.

Even with contemporary protocols injury to normal tissues and developing organs is often unavoidable. These may occur at different time points and are influenced by various factors making the follow-up plan complex for those who have not treated the child. These include underlying cancer (histology, site) and its specific treatment (chemotherapy, radiation, surgery) and additionally by certain host factors like age, sex, genetics, health behavior (tobacco, diet, exercise, alcohol, safe sex (BRCA, p53 etc.) and other co-morbid health conditions (hypertension, obesity, dyslipidemia, diabetes mellitus, hepatitis etc).

Some illustrations of risk based follow up care are described here:

- Younger patients are more vulnerable to neurocognitive dysfunction after cranial radiation
- Older females are at higher risk for ovarian insufficiency after alkylating chemotherapy or abdominal pelvic radiation or bone marrow transplant
- Boys treated with high cumulative doses of alkylating agents are more likely to have low sperm counts
- Children with brain tumor treated with radiotherapy need regular hormonal evaluation for endocrinopathies
- Children exposed to anthracycline need regular echocardiograms whose frequency is determined by cumulative dose administered
- Cisplatin exposed children should be followed up with hearing tests (Pure tone audiometry or BERA)
- Pulmonary function tests are recommended for those exposed to bleomycin, busulphan or pulmonary radiation

As illustrated above, based on the nature of disease and the treatment exposure (chemotherapy agents, dose and field of radiotherapy, extent of surgery) it is possible to anticipate the late effects which in turn have led to the development of risk-based guidelines for the follow-up care of CCS. Most of us prepare our follow-up care plans based on the – North American, Children's Oncology Group Survivorship Guidelines that are a free web-based resource.

Risk based survivorship care (Figure 1)

1. Host factors: age, sex, ethnicity, genetics (BRCA, p53, polymorphisms)

2. Tumor related factors: site, histology, stage
3. Treatment factors: chemotherapy, radiation, surgery, BMT, immunotherapy, events
4. Health behavior: tobacco, diet, exercise, alcohol, safe sex
5. Co-morbid factors: hypertension, diabetes mellitus, dyslipidemia etc.

Therefore it is imperative that the pediatricians and practitioners caring for them have the knowledge and awareness to monitor and detect these health conditions. Majority of them report not receiving any treatment summary or follow-up plan. It is the responsibility of the Pediatric Oncologists to provide all survivors/ families with end-of-treatment summaries, and to create evidence-based follow-up care plans for all cancer survivors.

Follow-up at survivorship clinic usually includes the following (see Table 1):

1. The clinics are held once or twice a week
2. Patients are monitored for relapse in the initial few years (upto 5 yrs from diagnosis, atleast 2 years after completion of therapy)
3. An end of treatment summary is prepared, that has demographic, disease and treatment related details
4. Risk based follow-up plan that includes

   a. certain routine clinical screening for second malignancies, monitoring growth and development, sexual maturation, neurocognition

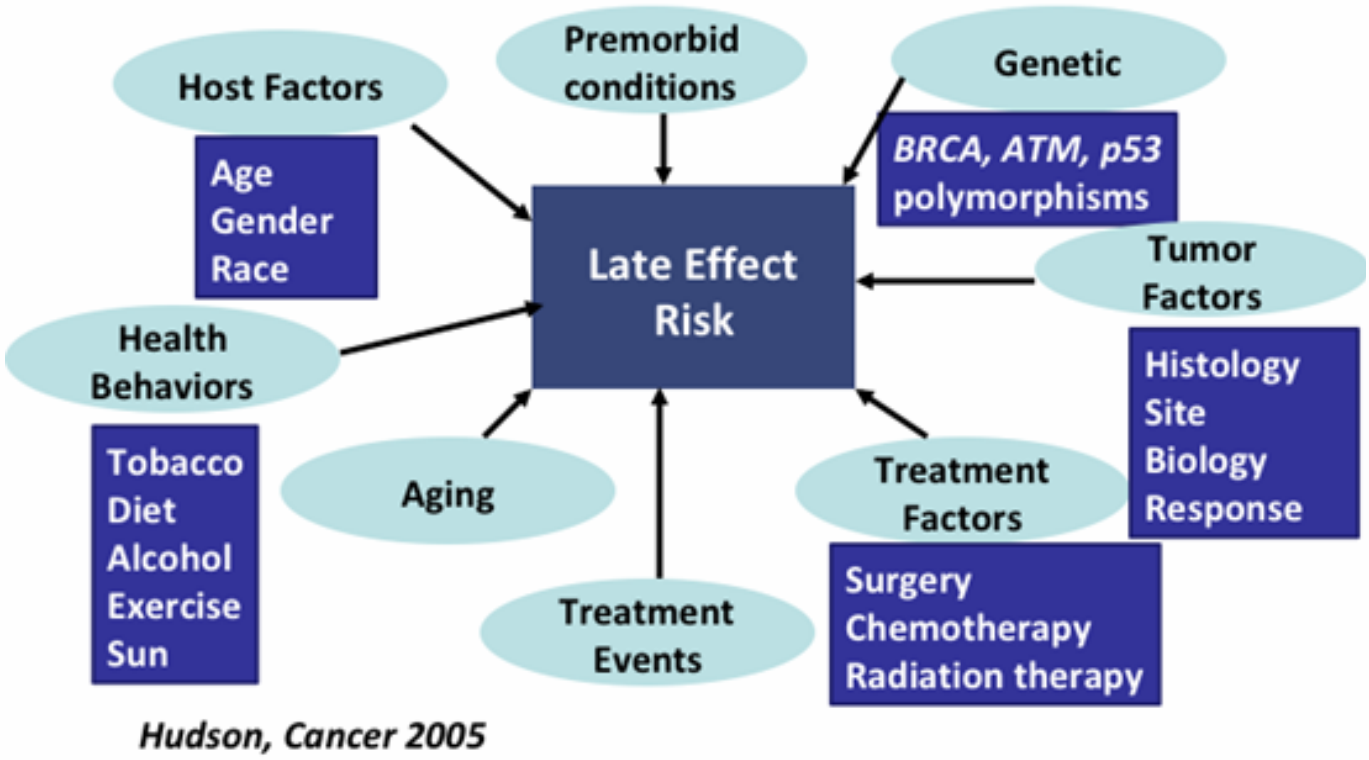
   b. High risk patients undergo specific screening like echocardiogram or PFT or KFT, musculoskeletal evaluation (extremity tumos), etc based on their disease and treatment exposure.
5. Immunization
6. Psychological counselling – is available wherein the psychologist has interviews with the patients and their parents to discuss any fears and anxiety related to the disease or its aftermath. Confidence building, career counselling, educational support are other activities provided.
7. Support groups are formed to provide a forum for and by survivors to dvelop social support networks with each other
8. Intervention and management for any late effect that is identified and the child is referred to the respective specialty.

Conclusion

- Childhood cancer survivors represent a growing and medically vulnerable population.
- Long-term and late effects reduce quality of survival and increase the risk of premature mortality.
- The risk of specific long-term and late effects is directly related to the specific cancer treatments and mediated by a variety of factors like age, genetics, health behavior and other co-morbid health conditions.
- The late effects may be missed by cursory exam
- They can be treated or modified for the benefit of the child with regular monitoring
- Survivors' confidence in general pediatricians may be improved by better involving primary care physicians throughout treatment and early survivorship, and by introducing the concept of eventual transition to primary care services.

Pediatricians have an important role in early diagnosis and intervention to give survivors a good quality of Life.

Fig 1. Risk based survivorship care



Hudson, Cancer 2005

Table:
End of Treatment Summary card and follow-up plan at RGCIRC (ACT card)

1. Demographics: age at diagnosis, sex
2. Disease: site, histology, stage
3. Specific details of cancer treatment/ Exposure
   - Surgical procedures
   - Chemotherapeutic agents, doses
   - Radiation treatment fields and doses
   - Blood product transfusions
   - Hematopoietic cell transplantation
   - Immunotherapy
4. Follow-up plan:
   - Annual visits to the clinic
   - Problem list
   - Clinical examination
   - Monitor growth and development (weight, height, BMI, pubertal development)
   - Scholastic performance, attention – (IQ if required)
   - Immunization: up to date, catch-up as required
   - Life style counseling –watch your weight, regular physical activity/ exercise, healthy diet, avoid tobacco and unsafe sex
   - Specific individualized organ/system work-up based on disease and treatment.

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FROM MY SECRET TO MY STRENGTH

Prakshi Vig.
Survivor of ALL (she is in high school)

It is well said that life is like a Rocky Road;
And if compare to the sea it's like a sailing boat.

Every strong and successful person has a story to tell;
And that story is always like a magical spell.

Here I am presenting a story of mine;
From which I learnt how to shine.

Once in my family function I got to know about my past;
It felt as if my heart exploded like a blast.

An aunt behind me was curious to get her answer;
She asked- a child in your family, suffered from cancer?

I noticed my grandmother respond by pointing at me;
My mind blew away and furiously fought to disagree.

I was disappointed - why didn't my parents disclose to me my past;
Thousands of questions arose and how long did it last?

Suppressing my thoughts I just shared it with my diary;
From a new perspective doctor ma'am seemed like a fairy.

With a heavy heart one day I shared this with my mother;
Seeing me mature, tears rolled from her eyes, one after another.

She made me sit and told me everything;
And inspired me it's the time to fly high with my wings.

My parents told me that- by your past you never have to gain sympathy;
But all those people who think you are weak prove them with your capability.

They inspired me so much that I realised-
My past is no more a secret but my biggest strength;
And it became a story of bravery, from a story of fear and suspense.

VICTORY THROUGH ACCEPTANCE

Pooja Neelkanthan
Survivor of ovarian GCT (she is an Ayurveda doctor)

As a teenager busy shaping my life, Mixed Germ Cell Tumor of the Ovary seemed to be a dead end. My family looked anxious on hearing about cancer and chemotherapy, but I stood blank. The efficient oncology team explained the process and convinced that all changes will be temporary. I was anxious, but my family took it in the right spirit and stood by me as pillars of strength. We stepped into the unknown, with faith.

Anticipating the changes, with a sunken heart I got my tomboy haircut. Post first cycle - a touch and my tresses were in my hands. Soon I resembled my bald childhood photos. As my family and team at the hospital did not treat me differently, I soon came to terms with it and diverted my mind. I had nausea which made me averse to any food. I was also losing weight and my new bony look in the mirror ran a chill down my spine.

As my 6-month treatment came to an end, I grew hopeful yet anxious. It had just dawned upon me that regrowth of hair post therapy was not a miracle. As a solution we were guided to Marchers-the wigmakers. Hoping he would give me my old look, I met him with great enthusiasm. After working on me when he finalized the bob cut hair, my smile vanished. It took a lot for him to convince me with his idea of the new me. The questions from my friends on cutting my long tresses were on my mind. With hope and anxiety, I joined back school. The new look was a hit but my classmates were uncomfortable. Gradually I realized it was due to their lack of awareness.

In this process of settling down socially, I learnt the importance of self-acceptance and the role of feeling good for looking good. It gave me the courage to carry the new look. Also, the importance of encouragement and warmth from people who matter to us – our parents, family, friends, teachers etc. acted as a fertilizer in re-establishing myself and moving ahead in life.

Almost all cancer warriors would have faced similar body image issues. Our acceptance and belief help us to cope with the new normal. This process is also influenced by how people close to us react and support us. This is possible when they also accept and take it in the right spirit. We also understand that all this is indeed a temporary phase in life. Today as a doctor myself I am able to connect to people and help them cope with their challenges because I have also been in their shoes. On looking back at those unpleasant days, I realize that I am stronger. Acceptance and hope helped me tide over challenges. We imbibe gratitude, empathy, spirit of a warrior and learn to celebrate every moment of life.

THROUGH THE LENS OF A SURVIVOR

Saksham Katiyar
Survivor of brain tumor (he is pursuing graduation in engineering)

It takes time and experience to alter a stigma or perspective relating to an understanding. Cancer is a disease that society perceives as a pathway to death due to lack of knowledge. The primary struggle for a Cancer Patient is generally not his treatment but the phase there after. Being an example of getting through the battle myself, I can proudly say that my journey of 1.5 years fighting Cancer was virtually painless. The real war was still to be fought after.

Cancer as a disease has two impacts on an individual's life- Physical and Emotional. We all talk about the complications of Surgeries, reactions to Chemotherapy, allergies from radiation, etc. But what we do not talk about is the emotional burden or the brawl that the survivor must go through. Your identity drastically changes from what you were pre and post this phase. I have a new identity as a Saksham Katiyar who has undergone cancer treatment. The information regarding dropping school was somewhat of a nuclear bomb but dealing with it patiently was the need of the hour. To avoid the pressure and discomfort of friends and classmates going a year ahead, I planned on dropping from school while keeping in contact with my close ones.

The lack of proper knowledge and information is evident in Society. My personal experiences with people have shown me how informing them about my Diagnosis was news of my demise. As a country, we might have failed to generate ample awareness regarding Cancer, the public's equation is still stuck at 'Cancer=Death.' I had all sorts of reactions to my diagnosis. The mindset was very harsh/negative, relating to the result. At the same time, some of them were over-sympathetic. We, as survivors, require a neutral response from Society since we have fought and won our war and are ready to face the world with determination. Our experience has made us capable enough to tackle future barriers efficiently.

Furthermore, standing inch-close to life and death situations took me no time to believe that life is extremely precious. Positivity and willpower played an essential role in getting me through my treatment. The experience of shaking hands with the Devil was fruitful after all, and I learned to choose my company. One good friend is better than a handful of them. From my experience, I can say that building a like-minded community of people and ensuring contact with them has worked in my favour.

Cancer was undeniably a roller-coaster ride with ample twists and turns, but the experience overall was vast learning and a blessing for me. From the day I completed my treatment, I promised not to devote a single moment of my precious life to negativity.

FAQs on Childhood Cancer

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1. How common is cancer in children, worldwide and India?

Worldwide, each year, an estimated 4,00,000 children and adolescents of 0-19 years old develop cancer, out of which nearly 76,805 cases occur in India.1,2 Childhood cancer in India accounts for 0.7-4.4 % of total cancer diagnoses as per population-based cancer registry report (2012-14).3 As per the report of International Incidence of childhood cancer volume-3, the age-standardized rate of childhood cancer incidence in India from records of 7 registries is 97 per million.1 Cancer is the 5th leading cause of death among 5-14 year old children in India.

2. What predisposes a child to cancer?

In contrast to adulthood cancers, childhood cancers have few established predisposing conditions. Exposure to high dose ionizing radiation and chemotherapy are known risk factors. Another associated factor is advanced maternal age: 6-15% increased risk per five years of maternal age is found for certain childhood malignancies. 4 An increased risk of cancer is observed in children with primary immunodeficiency disorders. Presence of EBV infection also contributes to certain cancers like lymphoma and nasopharyngeal carcinoma. Hereditary cancer accounts for only 10% of all cancers. The few well known cancer syndromes in children are listed below.[5]

Syndrome	Known associated cancers
Autosomal recessive	
Fanconi anemia	Myeloid leukemia, squamous cell carcinoma, liver tumors
Xeroderma pigmentosum	non-melanoma skin cancer
Autosomal dominant	
Retinoblastoma	bilateral retinoblastoma, sarcoma, melanoma
Li-Fraumeni Syndrome	
DICER1 syndrome	pleuropulmonary blastoma, cystic nephroma, ovarian germ cell tumor, embryonal rhabdomyosarcoma
Neurofibromatosis type 1	neurofibroma, optic nerve glioma, peripheral nerve sheath tumors
Mosaic	
RASopathies	Embryonic rhabdomyosarcoma, neuroblastoma
Aneuploidy	
Down syndrome	Transient myeloproliferative syndrome, acute myeloid leukemia, acute lymphoblastic leukemia

3. Can cancer be prevented in a child?

Compared to the effectiveness of screening programs in preventing adult malignancies, there are only few situations where cancer can be prevented in a child. Classical situations where surveillance is useful are (i) Li-

Fraumeni syndrome: age-specific breast cancer monitoring, colonoscopy every 2-5 years from 25 years of age, and organ-targeted surveillance, based on cancers diagnosed in the family (ii) neurofibromatosis type 1: annual surveillance for ocular signs of optic nerve glioma until 10 years of age and annual blood pressure (iii) surveillance for retinoblastoma in families with inherited RB1 mutation (iv) chemoprevention with celecoxib and prophylactic surgery in familial adenomatosis polyposis.5

4. What are the clinical conditions in which malignancy needs to be suspected?

Signs and symptoms of childhood cancer often overlap with other diseases and may be vague. The scenarios which are red flag indicators for malignancy are listed.6

a. Blue-berry muffin rash in early infancy

b. Any combination of persistent or unexplained fever, weight loss, anorexia hepatosplenomegaly, lymphadenopathy, or pallor

c. Arthralgia that is persistent, nocturnal, and not responding to NSAIDs

d. White eye reflex in an infant

e. New onset headache that worsens in the morning

f. New-onset persistent back pain in a young child

g. New onset severe mucosal bleeding

h. Palpable mass in abdomen ± hematuria/ hypertension/urine retention or enuresis

i. Palpable new-onset mass, especially that is non-tender, hard and > 2 cm in diameter

j. Persistent lymphadenopathy, not responding to antibiotics

k. Intussusception or gastrointestinal obstruction in an older child

l. New-onset scrotal swelling

5. What laboratory findings can give a clue to childhood cancer?

a. Lymphocytosis and lack of thrombocytosis or presence of thrombocytopenia in a child evaluated for arthritis

b. Single lineage or multi-lineage cytopenia that is persistent ± fever

c. Multiple site lytic bone lesions

d. Hyperuricemia +/- hypocalcemia and hyperphosphatemia

6. What is the average symptom-to-diagnosis/ treatment interval for childhood cancer in India?

The median interval from symptom to diagnosis, observed in multiple studies was about 60 days. 7,8 Delay varies according to the type of cancer, with acute leukemia and abdominal lumps being diagnosed faster while CNS tumors, Hodgkin lymphoma and bone tumors suffering maximum delay up-to months.

7. Which malignancies require urgent referral for specialist services?

Leukemias presenting with hyper-leukocytosis, suspected acute promyelocytic leukemia, superior mediastinal syndrome, non-Hodgkin lymphoma are few conditions that are life-threatening and require immediate specialized services. Complications like tumor lysis syndrome, respiratory failure, intestinal obstruction, intracranial hemorrhage are high in these diseases and require management in centers with advanced diagnostics and multi-disciplinary clinical service facilities.

8. What are the requirements for evaluation of suspected malignancy?

For hematological malignancies, complete hemogram with peripheral smear, bone marrow aspiration and flow cytometry are minimal

requirements for diagnosis. For solid tumors, pediatric surgical services along with biopsy, and histopathology with immunohistochemistry are required. For CNS and paraspinal tumors, neurosurgical services are essential.

9. How can a family with a child suspected to have malignancy be counselled?

Counselling the families regarding the suspicion of malignancy and the need of further evaluation is a must before referral. It is imperative to drive the urgency of the situation without instilling much fear. A realistic hope of treatment and cure can be informed to the families. It is ideal if the referring pediatrician can inform the oncologist regarding the referral.

10. How can a delay in diagnosis be prevented?

It is observed that majority of delay in treatment of childhood cancer happens in the diagnosis: time from first physician contact to the diagnosis. On an average it takes 37-40 days to navigate the primary and secondary care to reach a diagnosis and a specialist center. Majority of the delay can be reduced by having a lower threshold of suspicion and evaluation. If diagnostic services are not accessible, it is better to counsel the families and refer to the nearest specialist center at the earliest.

11. Where can a child with/suspected to have cancer be referred to?

Most pediatric oncology centers are in urban areas. Children with cancer are mainly treated by pediatricians with specialist training and by few adult oncologists. IAP has recently started a national specialist advice program in which pediatric oncology is involved. The link to the same is Pediatric Oncology – Smart Clinic 2.0 (diapindia.org). Similarly, a list of centres with oncology services is available at Cancer Hospital in India | Superficiality Tertiary Cancer Centres | CancerAssist.

12. What is the survival of a child with cancer in India?

Most of the published reports are from individual hospital-based data and are not representative of country. Acute lymphoblastic leukemia accounts for 40-50% childhood cancer burden in India and the overall survival (OS) observed varies between 45-81% in various institutions. 9 In Hodgkin lymphoma, OS of around 94% is observed, while in non-Hodgkin lymphoma OS is 74.4%.10 In CNS tumors, survival varies from 30% in glioblastoma multiforme to 34% in advanced medulloblastoma to 73% in average-risk medulloblastoma to 90% in intracranial germ cell tumors. 11 In other solid tumors, survival varies from 50% in Ewing's sarcoma, rhabdomyosarcoma, osteosarcoma, and neuroblastoma to 85% in nephroblastoma and retinoblastoma.12

13. What roles can pediatrician undertake in shared care of children with cancer?

Primary care pediatricians play a critical role before, during and after treatment for cancer. As the pediatric oncology teams are mostly urban, primary pediatricians can play a big role in shared care of children with cancer. They can assist in outpatient care by monitoring blood counts and nutrition, managing febrile neutropenia, providing transfusion services, or arranging blood donation camps, and even administering un-complicated chemotherapy injections. Pediatricians can also be of great help in directing families for financial support and in mobilizing finances in the community. After treatment, children can be managed effectively by pediatricians in consultation with the concerned oncologist, focusing on cancer recurrence and side-effects of therapy.

14. What is the role of bone marrow transplant in treatment of childhood cancer?

Most of the childhood cancers can be cured without a bone marrow transplant, by chemotherapy alone or by a combination of

chemotherapy, radiotherapy, and surgery. The role of hematopoietic transplant is in leukemias without remission after induction, relapsed leukemias, refractory lymphomas, advanced neuroblastoma, and refractory solid tumors.

15. Is cord blood banking useful in treating childhood cancer?

Cord blood contains stem cells that can be utilized as a piggy bank during bone marrow transplant. However, the cord stem cells of the same individual are not used for the same patient in view of possible inherent genetic defects in the stem cells. Moreover, long-term viability of stem cells in private banks is questionable. Hence, cord blood banking is advised for storage in public banks or in a family where elder sibling needs bone marrow transplant and younger sibling is an HLA match.

16. What are the support programs available currently in managing a child with cancer?

The Central government and various State governments have various health schemes in support. All India Schemes are namely Health Minister's Discretionary Grant (HMDG), Ayushman Bharat - Pradhan Mantri Jan Arogya Yojana (PM-JAY), Cancer Patients Concession for Travel by Air, Health Minister's Cancer Patient Fund (HMCPF) of Rashtriya Arogya Nidhi (RAN), Dr Ambedkar medical aid scheme, and Railways' concession for Passengers who are Cancer Patients. State government schemes are listed below

a. Arogyasri Scheme (Andhra Pradesh and Telangana)

b. Mediclaim under DHS (Goa)

c. Chief Minister's relief fund (Karnataka)

d. Cancer Suraksha Scheme (exclusive for under 18 years), Society for medical assistance, (Kerala)

e. State Illness Assistance Fund (Madhya Pradesh)

f. Free Chemotherapy Program (Odisha)

g. Free Cancer Medicines Scheme (Rajasthan)

h. Free Cancer Treatment (West Bengal)

i. Mukh Mantri Cancer Raahat Kosh Scheme (Punjab)

j. Chief Minister scheme (Tamil Nadu)

Apart from these schemes, many NGOs are working for the cause, namely CanKids KidsCan, Cuddles Foundation, St Jude India Childcare Centers, Indian Cancer Society, Sahayta charitable welfare society, Jiv Daya Foundation, Udhavum Ullangal Public Charitable Trust, Hope foundation , Yuvraj Singh Foundation, and Tiara hemophilia and cancer foundation.

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Access to childhood cancer care in India

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Today, with timely and optimal treatment, eight out of 10 children with cancer can achieve long term cure and go on to lead fulfilling and healthy lives. This is a result of ever-improving cancer-directed treatment which is multidisciplinary in nature, is backed by robust supportive care, and is in the context of early access to high quality healthcare resources and infrastructure. Accessing healthcare (described as the "degree to which individuals are inhibited or facilitated in their ability to gain entry to and to receive care and services from the health care system") can be challenging in low and middle income countries (LMIC) leading to delays in diagnosis and treatment, ultimately resulting in poorer outcomes.

Childhood Cancer Awareness and Recognition

The first key aspect is ensuring that the child is diagnosed as quickly as possible in order to provide the greatest chance for cure and full recovery. This requires the general public and the community/district health service, including the general physician and paediatrician to be highly aware of the potential for children to develop cancer. The Union for International Cancer Control (UICC) has developed material (Figure 1) to assist health workers to recognize suspicious signs of cancer in children and encourage referral to appropriate health facilities for timely testing, diagnosis and treatment. Since 1997, the Pediatric Hematology Oncology Chapter of the Indian Academy of Pediatrics (PHO IAP) has been running the Indian National Training Project – Practical Paediatric Oncology (INTP-PPO) convincing pediatricians about curability of childhood cancer and educating them in practical pediatric oncology so that they become capable for an early diagnosis and referral of children with suspected cancer. (Fig 1)

Childhood Cancer Referral Pathways and Networks

Confirmation of diagnosis and commencement of treatment necessitates that the child is transferred to centres of excellence usually termed principal treatment centres. The teams at these centres should have readily available full diagnostic services, all necessary drugs and supportive care to optimise survival and minimise toxicity. It is also desirable that the patient does not have to travel excessive distances to receive treatment. Research has shown that greatest delays in LMIC are in navigation of the health care system from first healthcare contact to the eventually reaching the centre of excellence.

The National Cancer Control Program (NCCP) in India was launched by the government

Figure 1 Childhood cancer warning symptoms and signs (Acknowledgement UICC)

Figure 2 Centres of excellence for retinoblastoma in India (Acknowledgement Cankids)

in 1975 and revised in 1984. The main focus of NCCP is on primary prevention (through tobacco control) and early detection of cancer (through screening), both of which do not apply to childhood cancers. NCCP also extended and strengthened therapeutic services nationally by creating one regional cancer centers (RCCs) in every state. These are meant to act as centres of excellence which are in turn linked with oncology units in existing medical colleges and the more peripheral health infrastructure (district hospitals, tehsil hospitals and primary health centers). While this three-tier model is supposed to make cancer care accessible across all socioeconomic groups and geographical areas, given the geographic expanse and the vast population, cancer care facilities remain unavailable to the majority of the population from lower socioeconomic strata and those living in remote areas. There is now a National Cancer Grid linking major oncology centers across the country to facilitate the development of a cooperative cancer management network for the transfer of standard treatment guidelines and expertise; facilitation of uniform standards for education, training, and human resource development in cancer care; and creation of a cooperative oncology research network to conduct studies of national importance.

But still the focus is on cancer in adults and relevant surgical and radiation oncology. Whilst all this is important, most children with cancer (of which leukemia is most common) seek and receive treatment at pediatric departments under the care of paediatricians, and this has been missing in many RCCs. Consequently, till recently, there have been no defined childhood cancer referral pathways and network in India.

One of the civil society organisations Can-kids, has worked with health care professionals (pediatric oncologists and ocular oncologists) and institutes to create a network of centres of excellence for retinoblastoma in India.(Figure 2)

Accessing Care Throughout the Cancer Continuum and Preventing Abandonment of Treatment

Achieving diagnosis and commencing treatment in time, while essential and critical, is only the first part of the cancer continuum. The child with cancer should also have timely access to the necessary modality of cancer-directed treatment (chemotherapy, surgery, radiation) and supportive care.(nutrition, blood products, intensive care, etc.) as well as palliation and survivorship (Figure 3).

Figure 3 The cancer continuum and access its components

Abandonment of treatment which is defined as defined as the failure to start or complete curative therapy in pediatric cancer affects outcomes adversely and is often the most common cause of treatment failure in LMIC exceeding toxic mortality as well as disease progression/relapse. The reasons for abandonment of treatment are multifactorial with limitation of financial resources underpinning most of the factors. Several studies in India and internationally have shown that this can be reduced by providing social support to the families, communication and counselling, adapting treatment protocols, reducing treatment intensity, tracking patients, and many other such interventions.

Standards for a Pediatric Cancer Unit

The existence of centres of excellence and expertise in paediatric oncology is essential for providing comprehensive multi-disciplinary facilities and optimum standards of care, reflecting the local population and geography It is with this in mind, that standards for pediatric cancer units in Europe and USA are expected to have the following

Table 1 Recommendations for personnel, facilities and capabilities in a pediatric cancer unit in Europe and North America.

TABLE 1

Personnel	• Pediatric hematologists/oncologists • Pediatric oncology nurses • Radiologists with specific expertise in the diagnostic imaging of infants, children, and adolescents • Pediatric surgeons • Surgical specialists with pediatric expertise in neurosurgery, urology, orthopedics, ophthalmology, otolaryngology • Radiation oncologist trained and experienced in the treatment of infants, children, and adolescents • Pathologist with special training in the pathology of hematologic malignancies and solid tumors of children and adolescents • Pediatric subspecialists available to participate actively in all areas of the care of the child with cancer, including anesthesiology, intensive care, infectious diseases, cardiology, neurology, endocrinology and metabolism, genetics, gastroenterology, child and adolescent psychiatry, nephrology, pulmonology • Pain and palliative care physician and nurse • Pediatric physical and mental rehabilitation services including pediatric physiotherapy and occupational therapy • Pediatric (oncology) social worker(s), pediatric psychologists, child life specialists, teachers and access to family support group services • Pediatric nutrition experts with the capability of preparing, administering, and monitoring total parenteral nutrition

Facilities	• An immediately accessible and fully staffed, onsite pediatric intensive care unit • Up-to-date diagnostic imaging facilities to perform radiography, computed tomography, magnetic resonance imaging, ultrasonography, radionuclide imaging, and angiography; positron-emission tomography scanning and other emerging technologies are desirable with the possibility for anaesthetics • Anaesthetics for diagnostic procedures or therapeutic interventions • Up-to-date radiation-therapy equipment with facilities for treating pediatric patients • A hematopathology laboratory capable of performing cell-phenotype analysis using flow cytometry, immunohistochemistry, molecular diagnosis, and cytogenetics and access to blast colony assays and polymerase chain reaction-based methodology • Access to hemodialysis and/or hemofiltration and apheresis for collection and storage of hematopoietic progenitor cells • Microbiology laboratory • Pathology laboratory (for morphologic, immunohistochemic and genetic tumour diagnostics) • A clinical chemistry laboratory with the capability to monitor antibiotic and antineoplastic drug levels • A blood bank capable of providing a full range of products including irradiated, cytomegalovirus negative, and leucodepleted blood components • A pharmacy capable of accurate, well-monitored preparation and dispensing of antineoplastic agents and investigational agents • Capability of providing sufficient isolation of patients from airborne pathogens, which could include high-efficiency particulate air (HEPA) filtration or laminar flow and positive/negative pressure rooms • Access to stem cell transplant services
Capabilities	• Maintain database of all childhood cancer patients based on the internationally recognised classification – International Classification of Childhood Cancer ver.3 (ICCC-3). • Deliver services in outpatient clinic, ambulatory daycare setting and inpatient ward • Educational and training programs for health care professionals including the primary care physician • A regularly scheduled multidisciplinary pediatric tumor board • An established program designed to provide longterm, multidisciplinary follow-up of successfully treated patients at the original treatment center or by a team of health care professionals who are familiar with the potential adverse effects of treatment for childhood cancer • Membership or affiliation with national collaborative research group to provide access to state-of-the-art clinical trials • Capability of providing parent, caregiver, and patient education • Social support for families including residential facilities for parents and siblings

Centres in India providing care to children with cancer are heterogeneous in size (smaller centers and larger centers), in the financial model (public sector where most are borne by the government, charitable trust sector where the trust subsidises the cost to the patient and the private sector where the patient pays for most of the cost through insurance or out of pocket) and by the nature of the hospital (cancer hospital, pediatric hospital or multi specialty hospital). Till date no authority (government or otherwise) has undertaken a assessment of these services are available in all the centres. The National Center for Disease Informatics and Research (NCDIR) under the Indian Council of Medical Research (ICMR) is currently undertaking a situation analysis of child cancer services in India which would be a first such exercise. This will provide valuable information going forward for patients to decide where to seek treatment and for primary care physicians/pediatricians as to where to refer the child.

Access to Childhood Cancer Clinical Trials in India

All children with cancer should be treated according to the best available treatment protocols. There is general agreement that this is best provided within units that are active in clinical research and cancer registration processes. When available, children should be offered the opportunity to participate in relevant clinical trials that aim to improve the optimal treatment for all children. Where there is uncertainty about the optimal treatment, these trials may be randomised.

While enrolling children with cancer in prospective multi-centre trials has become the norm in high income countries (where upto 90% of children with cancer are enrolled on to trials), it has remained an exception in LMIC. The Indian Pediatric Oncology Group (InPOG) was

Established through the PHO IAP to accelerate the development of prospective multicentre childhood cancer clinical trials in India, with the ultimate mission of improving outcomes of childhood cancer in India through collaborative research. Since 2015, 10 017 children with cancer have been enrolled in 23 clinical trials with 6944 [69·3%] of patientsin observational studies and 3073 [30·7%] of patients in interventional studies in 114 different institutions across the country, implying that only 2% of children with cancer in India are being enrolled onto InPOG studies annually.

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The Need For Dedicated Units And Shared Care For Pediatric Cancers

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As per the WHO 400,000 children are diagnosed with cancer each year. The last few decades have witnessed immense progress and success in the development of successful treatment programs for children and adolescents with cancer with an approximate success rate of 70-80% in pediatric cancers in the high income countries and a dismal 20% in some of the low income countries. The 2030-UN agenda for sustainable development aims to decrease these inequities in care and achieve a 60% survival through capacity building and prioritization of the care of children with cancer across the globe.

Challenges in India

There are numerous challenges faced in India. These are presented in Table 1.

How did the developed nations improve outcome?

In the high income developed nations, these improvements have been possible because of the availability of pediatric cancer treatment centers with collective expertise in the clinical management of children with cancer and the existence of a network of experienced

Patient Related	Hospital/Physician related	Country related
Poor transport facilities	Late presentation	Population
Cost of treatment	Large number of patients (especially in public hospital)	Geographical variation
Accommodation for families during treatment	Inadequate staffing, even in tertiary canter	Lack of universal health coverage
Loss of job (parents)	Lack of multi-disciplinary teams	Rural/urban divide
Lack of awareness	Inadequate laboratory services	
Distance from hospital	Abandonment	
	Less beds for pediatric hematology oncology	

Table 1: Challenges for treatment of cancer at different levels in India

investigators and allied health professionals who recognize the central importance of randomized clinical trials as the best available method for identifying more successful treatment strategies and who have the resources to evaluate new treatment modalities as they become available. The importance of comprehensive, multidisciplinary treatment in improving patient outcome in a cost-effective manner has been well documented for children with acute lymphoblastic leukemia, non–Hodgkin's Lymphoma, brain tumors, rhabdomyosarcoma, Wilms' tumor and Ewing's sarcoma.

In India, though the number of centers with pediatric hematology oncology services has increased, unfortunately there are many areas in the country where services are minimal. A large number of patients present to medical colleges and district hospitals where there are no trained personnel and the facilities are far from adequate. A few private centers would be treating, however, again mostly without trained pediatric personnel.

It has been observed that in places where pediatricians are not available, adult hematology oncology specialists look after the children. Also, we have to bear in mind the costs involved as in India with lack of insurance and not all employees getting reimbursement for medical aid, the financial burden is immense. This burden is extremely high in private set ups and though heavily subsidized in the government institutes; it still takes its toll on the family with a child afflicted with cancer. To compare, in the USA, the incidence of cancer is an estimated 10,270 new cases annually (2017) among children upto 14 years of age, and about 1,190 children are expected to die from the disease. To treat this number, there are 96 dedicated pediatric cancer centers in USA. In UK, around 1,600 new cases are diagnosed every year and there are 21 dedicated hospitals for treating pediatric cancers. In India the estimated incidence of childhood cancer as per ICMR is 18.6-159.6/ million for boys and 11.3-112.4 for girls < 14 years of age. Current childhood mortality from cancer in India is considered to be 39 per million children in comparison. India has developed some pediatric hematology oncology units over the last 2-3 decades. However, these are limited in number and there is a crying need to increase the number of such units in Institutes/medical colleges across the country.

In India, we need to address 2 important issues.

1. What can be done within the existing infrastructure?
2. To develop a comprehensive, multidisciplinary treatment plan focused on improving patient outcome in a cost-effective manner by establishing pediatric Cancer units.

Central points in Childhood cancer

1. Almost 80% of these children can be treated successfully.
2. Early detection, accurate diagnosis, and appropriate treatment depend on a multidisciplinary treatment approach to children and adolescents with cancer
3. Survival for children with cancer is best if they are treated in a pediatric cancer unit on a proper protocol.

Scenario in India

1. A large number of children with cancer in India are treated by cancer specialists who are trained in adult hematology and oncology. Their residency is in Internal Medicine rather than Pediatrics, and their super specialty training emphasizes disorders common in adults. Pediatric cancers and management is vastly different from adults.
2. At present hardly any medical college caters to children with cancer and hematological diseases. In contrast, neonatology, emergency and pediatric ICU's are well developed services at a large number of places.

3. The tertiary care centers which treat pediatric oncology patients are few and far between. Often, a patient has to travel a few hundred kilometers to access care, which includes staying in the city where the center is for a prolonged period of time. This results in a high rate of treatment abandonment in our country.

4. Patients start treatment and complete a reasonable part at the cancer center. They finally need to return to their home towns. Owing to lack of care in the peripheral, remote and rural areas, often patients are unable to get care when they are unwell at home resulting in a greater morbidity and mortality.

Simple steps forward within the existing infrastructure

Every country has a different system of providing health. Despite the shortcomings in our system, we are still able to walk into most tertiary care centers without a prior appointment. There are simple basic things which can be done to improve outcome without heavy investments and create a network of improvement in care.

1. The well established medical colleges need to develop small pediatric hematology oncology units (even 5 dedicated beds) and one consultant should be trained to look after the patients. (a consultant can be deputed to one of the established centers for a short period of 3-6 months to understand the basics of hematology oncology)

2. Establishment of shared care services: What is 'shared care'? Shared care essentially means a facility which is in communication with the main referral/tertiary care center that is able to administer maintenance chemotherapy treatment, has a basic level of diagnostics and is able to conduct follow-up of patients. This facility manages the patient in communication with the referral /main pediatric cancer. We need to evolve a system of care from the tertiary care institutes to the medical colleges in the periphery and in the states. The patient may be diagnosed at a tertiary care center and the initial therapy started there. However, maintenance therapy can be done at the medical college / large hospital near the patient's place of stay and inputs can be provided from the tertiary care team.

3. It is important for everyone to understand that the input from the Government of India towards the management of childhood cancers has increased considerably over the last few years with multiple schemes from the state and the centre which provide the required medications. (in the issue)

4. We need to ensure a system wherein the primary person treating the cancer is a pediatrician.

5. There is a need to nurture other specialties and with the increasing number of childhood cancers, establishing pediatric hematology oncology units is the need of the hour. There should be at least one unit in a radius of 500km, with a shared care facility at every medical college in the country.

6. Interested practitioners can join with the Pediatric Cancer unit in their area. Giving simple chemotherapy, blood transfusions, monitoring of counts and treating uncomplicated febrile neutropenia are a few examples of situations doable by each pediatrician.

7. Promoting telemedicine. The pandemic has taught us the advantages of technology. The country is quite well connected by internet and telecommunication which can strengthen the capacity, accessibility and efficiency of health care delivery.

Enhancing and Augmenting Pediatric cancer units

In India, with a population of over a billion, it is roughly estimated that about 50,000 children develop cancer each year and many either go undiagnosed or without adequate treatment. Of

these, a mere 15 – 20% i.e. 10,000 children are able to reach a cancer unit. This exemplifies how far we are from 'Health for all'.

All children with cancer should be treated according to the best available treatment protocols. This is best provided in a unit dedicated to the care of children with cancer. There are 200 odd units which are treating children with cancer across the country with very few having the required facilities and personnel. Dedicated cancer units should be treating children on a protocol. A cancer unit should have a process of cancer registration. At present the available cancer units are restricted to Institutes of national importance, regional cancer centers and to the large corporate hospitals.

In 2003, the Government of India announced the Pradhan Mantri Swasthya Suraksha Yojana (PMSSY) initiative which aimed at "correcting regional imbalances in the availability of affordable/reliable tertiary healthcare services. This was to be done through two main channels: setting up AIIMS-like institutions and upgrading government medical colleges.

Till date 22 AIIMS like centers have been established/being made, 10 being fully functional. We need to work towards developing pediatric hematology oncology units in these centers in the near future. With the availability of DM and DNB in pediatric hematology oncology as super specialty training, this aim is eminently doable.

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Progress in Pediatric Surgical Oncology

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Introduction

Surgery remains the cornerstone of management of local control and occasionally metastatic excision in all most all children diagnosed with solid tumours. As the surgical, anaesthesia and critical care approaches are refined on a daily basis, it is imperative for the operative team to provide the patient with the safest and the best opportunity for a successful outcome in the resection of a solid tumour.

Even though most protocols like the COG, SIOP and UKCCLG now boast an 84% survival rate in recent SEER statistics,[1] we still seem to live in two different worlds based on where the child with cancer is born. The disparity in the outcomes of patients with Pediatric Solid tumours in high-income countries (HIC) and Low- and Middle-Income countries (LMIC) is alarming. The COG has managed to successfully raise the 5-year survival to more than 90 % in Wilms Tumour (WT) [2,3] and at the same time, children living in LMICs face persistently alarming mortality rates. [4,5,6] The late referrals, giant masses, unavailable expertise are among the main problems faced by Pediatric surgeons in these situations. Poor nutrition status and the low socio-economic status of most patients and their families is an additional burden to be dealt with in LMICs.

Even when the patient is successfully managed, long term follow-up studies mention that approximately 60% of paediatric cancer patients will require management of late effects and issues like body image shaming and infertility. There is a significant role of the surgeon in the prevention and management of these problems.

In this review, we will look at the evolution of Pediatric surgical oncology, the expanding role of surgeons in local control and adjunct therapy. The advances in minimal access surgery and the surgeon's role in managing "late effect" will also be discussed along with the future of this subspeciality of Pediatric Surgery.

Evolution of Pediatric Surgical Oncology

The treatment of most Pediatric solid tumours has quintessentially moved from a surgeon centred approach to that of a multimodal approach. The triumph of the Wilms story [7] has been extrapolated to common

Pediatric malignancies like neuroblastoma, hepatoblastoma, Ewing's and the PNET group of tumours.

In the recent past, the "Surgical" service provider for childhood cancer was essentially a Senior general surgeon who would be "daring" enough to operate a sick child with a large lump in the belly. Even today a large number of these children are operated upon by "Adult and organ specific surgeons" especially in the LMICs. Unfortunately, the number of Pediatric surgeons in most surgical communities is minuscule and further, many of them are not well trained to manage Pediatric surgical oncology.

Despite these local issues, there has been a significant refinement of surgical techniques over the years. The impressive expansion, in the domain of energy devices ranging from the electrocautery to vessel sealants to harmonic and ultrasonic devices. The new kids on the block are the water jet dissector and suction evacuators. These devices aid in easier dissection along with a significant decrease in blood loss. They also aid in simplifying liver and kidney parenchymal dissection allowing a decrease in post-operative complications like bile leak or urinary leaks, which can delay adjuvant therapies.

The use of advanced visual aids from simple loupes to microscopes have been easily available for the past few decades. The recent advances include virtual reality and image-based navigation and guidance systems like the Indo Cyanine Green (IGC) navigation for the excision of liver tumours.[8] Three-dimensional printing and simulation programs are increasingly used for complex surgeries. Modular operating rooms with advanced anaesthesia systems are ever-improving to provide safe and quality assured care to Pediatric Surgical patients.

Complex reconstructions involving multi-disciplinary surgical approach involving plastic surgeons, cardio-thoracic surgeons, orthopaedic and ENT and head and neck surgeons is gaining more and more traction, for improved outcomes in these patients.

Despite the above-discussed advances error traps and protocol deviations are extremely common across surgeons from both HIC and LMICs. For e.g. The commonest protocol deviation in the management of Wilms tumour is inadequate or absence of lymph node sampling which has shown to worsen the outcomes.[9] The same issues of non-adherence of defined protocols are prevalent with other tumours groups.[10] This results in inferior oncological outcomes along with considerable data loss from research protocols.

Local and Metastatic Control

While the surgeon may be involved in diagnostics, achieving vascular access and supporting enteral feeding, and managing metastasis, his/her primary role is defined by the local control of the solid tumour. The timing and role of surgery are essentially defined by tumours biology and stage at presentation. Neoadjuvant therapy may be required as per protocols in several solid tumours. The correct balance between adequate and aggressive chemotherapy is essential as there is increased fibrosis and difficulty in dissection after each cycle of chemotherapy.

The surgical excision of any cancer is essentially a zero-kill approach, which cannot be achieved by both chemotherapy and radiation. In the ideal situation, every tumour should undergo an R0 resection, however, there may be several modifiable and non-modifiable determinants to the completion of resection. During the surgery there may be acceptable complications and morbidities depending on the surgical procedure per se, however, certain intraoperative events may have a bearing on the oncological outcomes. This is best explained by the intraoperative rupture in the case of Wilms, which will not only upstage the tumour but also require intensification of adjuvant chemoradiation.[9]

The surgeons understanding of the exact guidelines (COG or SIOP) is essential for a smooth, complication-free procedure. At the same time, a fine balance should be maintained in conducting the "over-aggressive" or "ultra-safe" procedure. Most protocols discuss non mutilating surgery and try and enhance organ preservation throughout the treatment. This is true, especially for surgery for Rhabdomyosarcoma and some other sarcomas. The extent of the surgical resection of high-risk NBL has been debated for several years with no clear-cut answers. (Table 1) This emphasizes the importance of large collaborative studies with specific research questions in each solid tumour, for the best outcomes for all patients.

Table 1

Study	>90% resection	Impact on EFS	Impact on OS
COG A3973	70%	Improved	Not significant
SIOPEN	76%	Improved	Improved
German NBL	78%	None	None

Table 1: Comparison of NBL excision from different collaborative study groups. [11,12]

Even though the first pulmonary metastasectomy was carried out in the 1950s, there has been no significant consensus in the oncological outcomes across adult and pediatric cancers.[13] There is little benefit claimed in evidence-based studies in the adult population, especially in terms of cure and in the context of advanced malignancies.[14] There is a paucity of Pediatric data, and the largest systematic review has not been able to show any survival benefits in the Pediatric age group.[15]

Minimal Access Surgery

As in adult surgery, MIS has had a great impact on paediatric surgical diseases over the past 2 decades. The main concern of adapting to MIS in Pediatric surgical oncology is the fear of substandard surgery. As the world moves ahead, there is more and more interest in joining the bandwagon of MIS including Robotic Surgery. The da Vinci system and its newer models are exciting for surgeons, as it is better than laparoscopy in terms of ergonomics and "degrees of freedom". This increases the precision of the procedure manyfold. The downsides of robotic surgery are the high cost, limited availability and the poor support from the industry in innovating smaller instrumentation to be used in Pediatric surgery. As the learning curve and economic considerations improve both laparoscopy and robotic surgery will be used more frequently to manage Pediatric patients with solid tumours.

Does the surgeon, critically adhere to the principles of surgical oncology (safe resection/ upstaging/lymph-node dissection) is the question to be asked. MIS has been used for tissue biopsies and excision of smaller lesions like the adrenals, ovary and renal masses comfortably. [16]

There are clear cut advantages of early discharge, less pain medication and early return to normalcy, with MIS. This may theoretically translate to earlier adjuvant therapy as the return of bowel function and mobility are enhanced. The added advantage of decreased body shaming in long term survivors is something, which possibly would be achieved by the application of MIS in children.

A word of caution arises as, the oncological outcomes, are yet to be assessed in most Pediatric solid tumours being dealt by MIS. As an increasing number of surgeons demonstrate the feasibility of MIS for tumour excision, there are some studies from the adult surgical world to suggest inferior oncological outcomes in patients undergoing MIS.[17] The way forward is in conducting high-quality RCTs comparing open vs MIS in large volume centres.[18]

Fertility preservation

Infertility and primary gonadal insufficiency are a significant chunk of late effects, in the survivors of childhood cancer. Both genders in

the survivor groups have considerable chances of being infertile as compared to their peers. [19] Pediatric surgeons are central to several procedures in these children ranging from initial biopsies to central line insertions and various surgeries for local and metastatic control. This gives them an important opportunity to liaison with fertility experts and use the same anaesthesia for planning out relevant procedures. Pediatric Surgeons also have the skill set of MIS even on the smallest of babies and can play an important role in fertility preservation. Oocyte and spermatogonia preservation along with simpler procedures like oophoropexy to shield ovaries from future radiations are being performed in anecdotal settings. The Pediatric Surgeon can help in establishing a fertility preservation program along with specialists from reproductive medicine, gynaecology, Pediatric oncology and allied laboratory services.

Training and sub-specialization

The Indian and the LMIC context to sub-specialization in Pediatric surgical oncology is still in its nascent stages as compared to the west. Several centres of excellence like Sloan Kettering and St Jude's have structured programmes to enhance the subspeciality. The surgeons from India and LMICs have a huge volume of clinical data which can be used for establishing "local" and effective protocols. The sheer number of advanced cases manages in these countries speaks volumes of the two different worlds of healthcare as mentioned earlier.

Few large teaching centres in India have robust training programmes for both Pediatric Surgery and Pediatric Oncology. These institutes must focus on establishing advanced fellowships and specialized training modules for all components of solid tumour management like vascular access and surgical procedures (both open and MIS). Proper treatment roadmaps can be drawn for at least common tumours. This would help in producing future leaders in this extremely challenging sub-specialty of Pediatric Surgery.

Conclusions

Despite the brilliant advances in understanding the biology and physiology of solid tumours, the "Pediatric Onco-Surgeon" continues to play a pivotal role in the management of these patients. Refinement in surgical techniques and the armamentarium is steadily increasing the world over. A better understanding of tumour biology and the increased understanding of the multimodality approach is improving every day. The Cooperative study model has over the decades has shown fantastic results in most solid tumours of childhood. However, many unfortunate children slip through the loopholes of these proactive interventions especially due to the socio-economic reasons in the LMICs. We should ensure all efforts to salvage even the last child struck by this unfortunate malady.

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A government policy for childhood cancer - the final push towards a better outcome

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Background

Childhood cancer is one of the most difficult and feared diagnoses in the pediatric age group. At present, among developed countries, more than 80% of children diagnosed with cancer get cured of the illness and will become long-term survivors. However, in low- and middle-income countries (LMIC) which include India, only about 20% are expected to survive1. As LMICs account for more than 90% of cases of childhood cancer in the world, improvement in child health in these countries, with a special focus on childhood cancer can help us achieve better outcomes. We are currently less than a decade away from the WHO's goal of achieving survival rates of at least 60% by 2030 in pediatric cancer as per the Global Initiative for Childhood Cancer. Although the outcome reported from individual centres treating cancer in our country is much better than 20%, this is out of patients reporting to us rather than the actual number of children diagnosed with cancer.

The reason for such poor outcomes of children with cancer in LMICs includes poor access to healthcare, lack of trained manpower, abandonment of treatment among many others. Thus, many children with cancer are "lost in diagnoses" and never reach a tertiary centre for treatment. Since childhood cancer does not have any preventive or screening strategy, early diagnosis is the only solution to improve outcomes. Once diagnosed, patients need to be channelled quickly to reach a treatment centre without the usual hurdles of disease stigma, monetary constraints and delayed diagnoses.

The under-reported burden of childhood cancer in India

Cancer is the second most common cause of death globally. In India, there have been different attempts to describe the pattern of cancer burden and epidemiology. We still lack a national cancer registry, where cancer of all ages can be made notifiable. The National Cancer Registry Program was established in 1981 to generate data on the magnitude and patterns of cancer through population-based registries. However, it is often criticized that the population-based registries cover only around 10% of the entire Indian population. Further, they are focused more on the urban population and has a significant underrepresentation of rural areas, regions and

few states in the country. The India State-Level Disease Burden initiative was also launched to produce sub-national disease burden estimates. As per this, the incident cancer cases in India was 10,96,000 in 2016. Among children aged 0-14 years, leukaemia was responsible for the highest disability-adjusted life years, followed by brain and nervous system cancer. As per the ICMR Population-based cancer registry report, childhood cancer accounted for <5% of the total cancer diagnoses in the country in 2012-2014. India still ranks low in age-standardized childhood cancer incidence compared to high-income economies such as USA and Canada. The GLOBOCAN 2018 data estimates around 38640 patients in India between 0-19 years of age although as per global incidence rates, we should be diagnosing close to 80,000 per year. In this scenario, due to underreporting, childhood cancers still remain under the radar and are never considered a public health concern.

The vital role of government in improving childhood cancer survival

1. Cancer to be made notifiable: India comprises almost 20% of the world population and is estimated to have more than 1/4th of the childhood cancers in the world. Making childhood cancer or cancer in all ages notifiable helps in generating accurate denominators to create data on treatment response, abscondment and outcome. So also, once notifiable, it comes under the purview of national programs and policies with a standard of care of both diagnosis and treatment similar to tuberculosis and HIV.

2. Childhood cancer network: The development of a cancer network linking treating centres to primary care providers will help reduce the delays in diagnosis and initiation of treatment. Over the years, awareness workshops and the inclusion of haematology-oncology in the pediatric post-graduate curriculum has helped improve the situation immensely. The PHO chapter of IAP regularly conducts National Training Program – Practical Pediatric Oncology and Hematology workshops which address early recognition and management of pediatric cancers.

3. Improvement in facilities for childhood cancer: At present, cancer care is available only in a few tertiary care institutes, medical colleges and regional cancer centers in the

How to overcome barriers in childhood cancer care?

BARRIERS	WHY	WHAT CAN BE DONE
Late presentation to a healthcare facility	Lack of awareness among parents, physicians, paediatricians Inaccessibility of nearby healthcare facilities Absent of health care network Poverty Gender bias Stigma of cancer	EDUCATION UNIVERSAL HEALTH CARE CHILDHOOD CANCER NET-WORK
Delay in diagnosis and treatment	Lack of diagnostic facilities Lack of treatment facilities	STENGTHENING OF EXISTING FACILTIIES
Abandonment	Stigma Fear of chemo/ radiotherapy Opting for alternative medicines	Counseling Survivor stories
Treatment toxicity	Infections, lack of antibiotics and antifungals Lack of transfusion support	Improving nursing care Education and training of doctors

country. Instead of developing new cancer centers, strengthening of existing pediatric departments in government and private medical college can help improve the situation immensely. In order to achieve this, dedicated faculty in pediatric haematology-oncology or pediatric oncology would be needed for this intensive branch of paediatric super speciality.

4. Treatment at affordable cost: The treatment of pediatric cancers including supportive care, surgery, radiotherapy and bone marrow transplant if needed is costly. Treatment facilitation is available through various programs of the government such as Prime Minister Relief Fund, Chief Minister Relief Find, Health Minister's Discretionary Grant, Rashtriya Arogya Nidhi and Ayushman Bharat Yojna. Only a fraction of the utilization of many of these schemes is for pediatric patients. Also, at times, due to the non-availability of appropriate documents and delays in approvals, there may be significant delays in sanctioning of funds. The provision of universal health care for childhood cancer patients can help in preventing such delays. Development of a national policy for childhood cancer care, similar to that for thalassemia and haemophilia could also help in appropriate resource allocation and defining basic standards of care.

The outcome of childhood cancer has seen significant improvement in the past few decades in our country. This improvement has come not necessarily from new drugs or diagnostic facilities. It has come from a better understanding of the disease and multidisciplinary care, risk stratification with an early escalation of treatment where necessary, collaborative trials to develop indigenous solutions to vexing problems and better-trained nursing and support staff. So far, in view of the few numbers of patients, cancer in children has not received the government attention that it deserves like neonatal care or infections. With the engagement of all stakeholders and better focus, we hope to get the final push to improve pediatric cancer outcome in our country.

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Childhood Cancer Day

I know one thing about cancer, its scary but why is it scary?Is it scary because you have to take a lot of medicines? Is it scary because you get a lot of injections? .Why are you scared When you have doctors that will help you get healthy again. I know doctors can be scary sometimes especially when they take a lot of blood samples or give you injections but always remember they are doing it to make you healthy again. You have your family and friends with you that are supporting you so much and will stay by your side no matter what. I know that you can do this, you WILL beat cancer like I did, and when you are feeling low get a paper and a pen and write down things you are grateful for example, I am grateful for my family and friends, I am grateful for the doctors that helped me get through it and the list goes on.

I am a 11 year old kid and when I was under maintenance I would still go to birthday parties and I would see people eating loads of junk food. It made me feel sad that I could not eat any of it my mother would send me homecooked meals at parties. I stared at the food and my brother who was with me at party saw that, so he refused to eat any of the food too.

The point is that you have to be strong for yourself and family. You can get through this like I did. Believe in yourself like your family believes in you. If u ever feel negative, listen to motivating songs or read motivating books. You have doctors, family and even god with u to get through this JJ…

"I don't want my pain and struggle to make me a victim,
I want my battle to make me someone else's hero "
- Sukhnaaz Dhillon

From Darkness to Life

Optimism holds you firm and steady in your darkest times. This is what I have learnt as a cancer survivor. This is 10 years after being successfully treated from a deadly disease Hodgkin's lymphoma which you all know as CANCER .

I was being treated at a hospital for cancer in 2010. That was a period of depression and melancholy. All I felt was despair . Life is very precious gift and unfortunately, you don't truly realize it until you are fighting to stay alive .

Persistence and determination of my parents to get me my life back truly helped me to fight back my biggest enemy . The consistent efforts of my Doctors gave me hope . I followed each and every step of my treatment and medication.

It is okay to be scared but the belief that you can fight back takes you halfway towards your goal .

Finally after a period of time,I was declared free from cancer. Although my journey was bumpy and was full of ups and downs but I am thankful for the lessons I learnt throughout.

I started a new phase of my life .....a life where I value my health the most. CANCER can be cured and life led by survivors is as NORMAL as others.

For any of you finding hope ,believe me, YOU CAN and YOU WILL. I know times are difficult but your optimism is your strength. Fight back and you will definitely WIN.

A college student

IAP Ghaziabad

On 20th February 2022, IAP Trans Hindon Ghaziabad Branch (Academy of Pediatrics Ghaziabad) successfully conducted National Tuberculosis Elimination Program NTEP in IMA Bhawan which was attended by Dist. CMO Dr. Bhavtosh Shankhdhar, ACMO Dr. Vishram Singh, Dist. Tuberculosis Officer DTO Dr. R K Yadav, Dr. GV Bhasavraja, former Honorary Secretary IAP central and other members.

Around 70 members participated in program.

IAP Maharashtra

- CaP TB (Catalysing Pediatric TB Innovations - Dissemination) program

Activity was organised by the SAATHII (Solidarity and Action Against The HIV Infections in India).

Date: 30/12/2021 at 10 AM to 12 PM

Venue: Four Seasons, Viman Nagari, Pune

IAP Maharashtra

Parental awareness & Hesitancy to administer the vaccines in this Pandemic has increased the eagerness among pediatricians.

Pediatric Practitioners have to answer a lot of queries put forward by the caretakers.

MAHAIAP & IAP Raigad celebrated the New Year Eve of 2022 with an academic fiesta of JOURNAL JOURNEY solving the queries of COVID-19 vaccine & Rotavirus vaccine

Date: 01/01/2022 at 9 PM

Speakers: 1. Dr. Pankhuri Kothari (NH SRCC Hospital, Mumbai) &

2. Dr. Rajendra Chandorkar (Past President, IAP Raigad, Alibag)

Expert: Dr Raju Shah (CIAP President, 2005)

Chief Guest: Dr Chetan Shah (CIAP WZ VP 2022)

Topics: 1) Changing Serotypes of Rotavirus in Western India & Clinical Severity of Diarrhoea.

2) Understanding COVID-19 Vaccine Hesitancy

On MAHAIAP Zoom as well as Live streaming on MAHAIAP YouTube Channel:

https://youtu.be/0OPSIn-9KA8

IAP Maharashtra

Maharashtra State Branch of Indian Academy of Pediatrics (MAHAIAP) came up with a fantastic chat show on

Date: 07/01/2022 at 3.00 PM

Topic: The Covid Chat Show- From Variants To Vaccines.

On MAHAIAP Zoom as well as Live streaming on MAHAIAP YouTube Channel:

https://youtu.be/vt4w0RzZC-0

Chief Guest: • Dr. Upendra Kinjawadekar (President Elect. 2022)

Speakers: • Dr. Suhas Prabhu (Chairperson, Maharashtra Ped. Covid Task Force)

• Dr. Vijay Yewale (HOD Pediatrics, Apollo Hospital Navi Mumbai)

Moderator: • Dr. Jeetendra Gavhane (President, IAP Navi Mumbai)

IAP Maharashtra

Maharashtra State Branch of Indian Academy of Pediatrics (MAHAIAP) arranged an exclusive academic session on

Date: 21.01.2022 at 9.00 PM

Topic: "CHAMPIONS FOR CHILDREN - END PEDIATRIC TB BY 2025"

Chief Guests:

1. Dr. Bela Verma (EB Member CIAP)
2. Dr. Jayant Upadhye (VC West Zone 2021)

Speakers:

1. Dr Sushant Mane (Incharge State Pediatric Centre of Excellence for TB & Pediatric Asthma Division.)
2. Dr Satish Kumar (Country Director at SAATHII, India)
3. Dr Ramji Adkikar (Joint Director (TB-Leprosy), Maharashtra)

On MAHAIAP Zoom as well as Live streaming on MAHAIAP YouTube Channel:

https://youtu.be/RC0caPm_G1Y

IAP Maharashtra

Women Committee of MAHA Academy of Pediatrics celebrated National Girl Child

Date: 23/01/2022 at 5 PM

Topic: On MAHAIAP Facebook Live and later uploaded on MAHAIAP Youtube Channel: https://youtu.be/pPhTd1HEZNo

Chief Guest: • Dr Swati Bhave (Patron, MAHAIAP Women Committee)

• Dr Hemant Gangolia (President, MAHAIAP)

• Dr Amol Pawar (Secretary General, MAHAIAP)

Panelist: • Dr Deepa Phirke (Asso. Prof., Govt Medical College, Kolhapur)

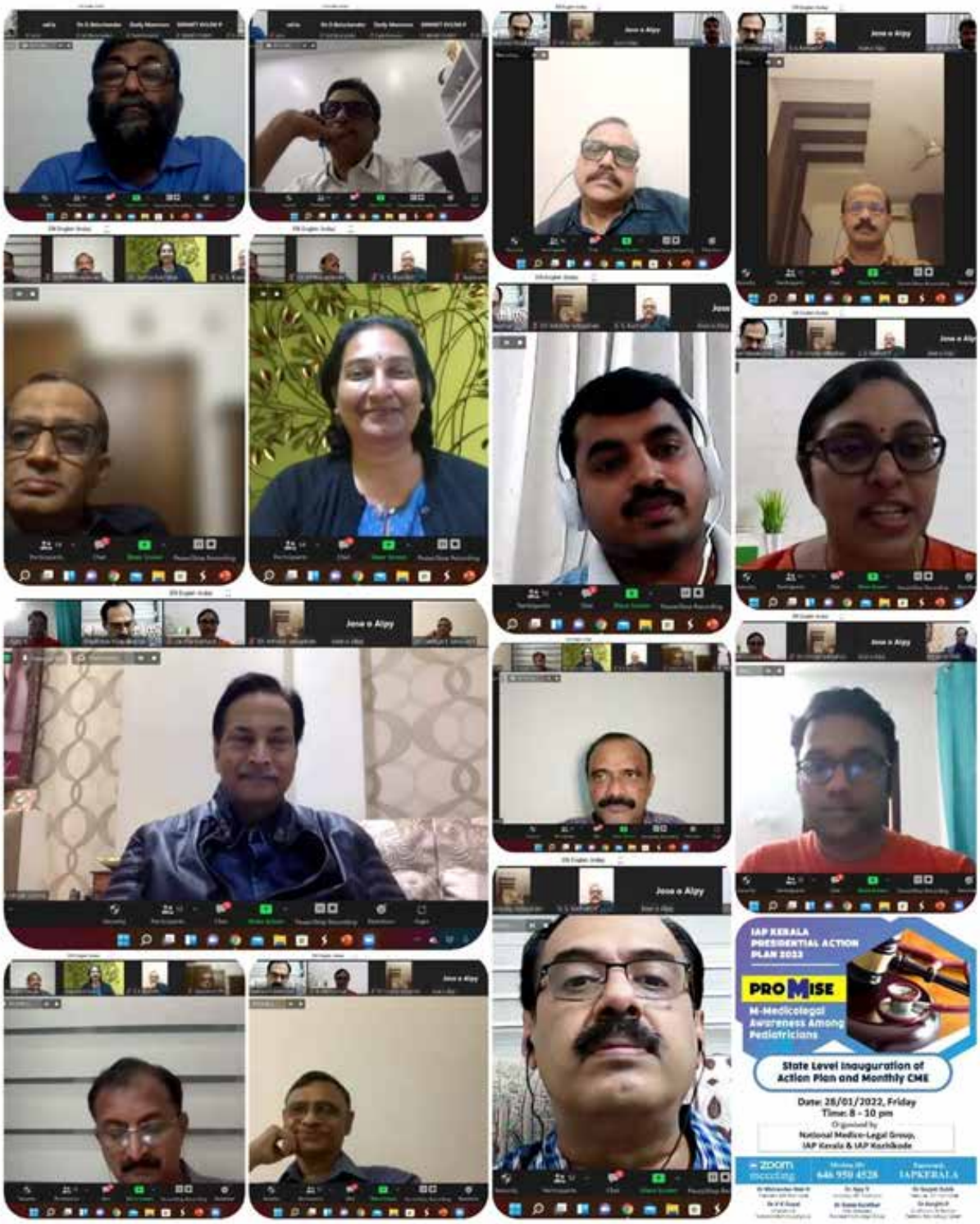
• Dr Renu Boralkar (EBM MAHAIAP 2022, Aurangabad)

• Dr Abhilasha Behere (Secretary, IAP Chandrapur)

Moderator: • Dr Sonali Shirbhate (EBM MAHAIAP 2022, Amravati)

• Dr Jayashree Shiwalkar (Developmental Pediatrician, Child/Adolescent Counsellor, Nagpur)

IAP Kerala



PROMISE 22- M - Medicolegal awareness Presidential action plan inaugration - IAP Kozhikode & IAP Kerala

IAP Kerala

Medical camp IAP Kasargode

IAP Kerala

National girl child child day - IAP Kozhikode

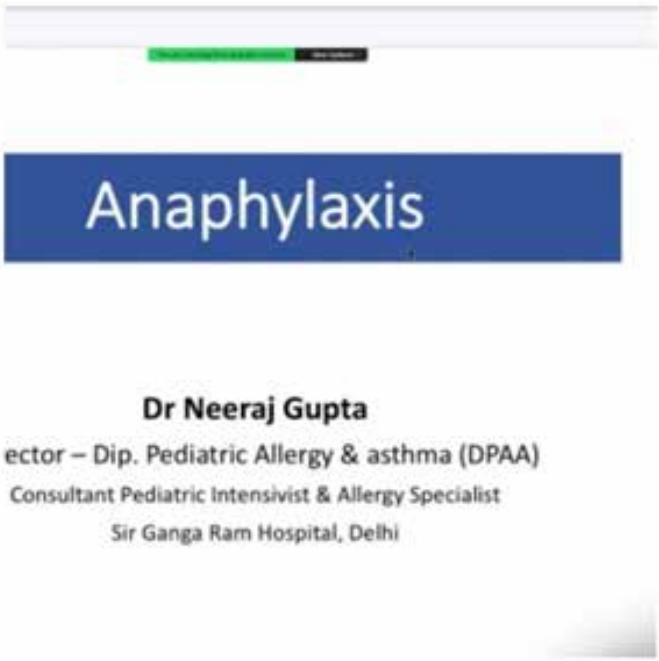
IAP Kerala

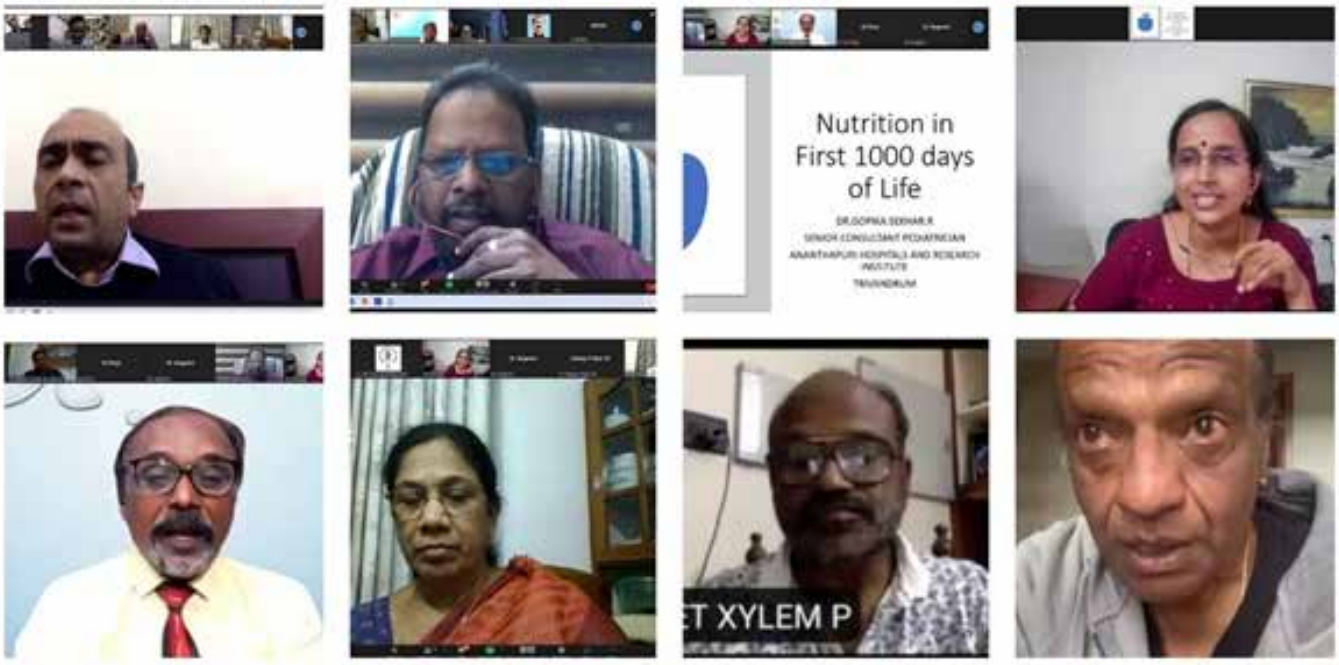
National girl child child day - IAP Trivandrum

IAP Kerala

-Installation IAP Vadakara OB

IAP Kerala





Tuesday series - IAP Trivandrum