



SPECIAL DELIVERY

NEWS FROM SINGAPORE'S ACADEMIC TERTIARY HOSPITAL FOR WOMEN AND CHILDREN

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PROFESSORSHIP LAUNCHED TO BATTLE CHILDREN'S CANCERS

Children's cancer research fund named after paediatrician and pioneer Professor Tan Cheng Lim.

Report by Rebecca Tse



(R to L): Prof Tan Cheng Lim, Emeritus Consultant, KKH; Ms Grace Fu, Minister, Prime Minister's Office, Second Minister for the Environment and Water Resources and Second Minister for Foreign Affairs; Assoc Prof Ng Kee Chong, Academic Chair for SingHealth Duke-NUS Paediatrics Academic Clinical Programme; Assoc Prof Ho Peng Kee, CCF Patron; Prof Kenneth Kwek, Chief Executive Officer, KKH; and Mr Ho Cheng Huat, CCF Chairperson.

Aiding the fight against childhood cancers, SingHealth Duke-NUS Academic Medical Centre's Paediatrics Academic Clinical Programme (Paeds ACP) and Children's Cancer Foundation (CCF) have jointly established the Tan Cheng Lim-CCF Professorship in Paediatric Oncology, named after one of Singapore's pioneers in paediatric oncology, Professor Tan Cheng Lim.

Currently Emeritus Consultant with the Department of Paediatric Subspecialties at KK Women's and Children's Hospital (KKH), Prof Tan is one of the longest-serving paediatricians in public healthcare. Throughout a career spanning five decades, Prof Tan has trained and mentored generations of healthcare professionals and helped to shape the practice and landscape of paediatric medicine in Singapore.

"Building on the expertise and resources of SingHealth, Duke-NUS Academic Medical Centre and KKH, the Tan Cheng Lim-CCF professorship will enable long term medical advances

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benefiting Singaporeans and the global community," says Associate Professor Ng Kee Chong, Academic Chair, SingHealth Duke-NUS Paediatrics Academic Clinical Programme.

This endowed Professorship, established under the Paeds ACP, will be awarded to an outstanding individual who has demonstrated extraordinary achievements in advancing medical

science with positive outcomes in healthcare delivery and a keen interest in advancing research and education in paediatric oncology.

"The appointed chair of this Professorship in Paediatric Oncology will be a role model for Asia's next generation of doctors, pursuing advances in clinical research primarily in paediatric oncology, while mentoring medical students

and serving paediatric patients in the community," adds Assoc Prof Ng, who is also Chairman, Division of Medicine; and Head and Senior Consultant, Department of Emergency Medicine, KKH.

The professorship was made possible through a \$2.5 million gift from CCF, with dollar-for-dollar matching from the Singapore government doubling the benefit to patients to \$5 million.

TO WATCH OUR PATIENTS GROW OLD

One of Singapore's longest-serving paediatricians in public healthcare, Professor Tan Cheng Lim shares his views on challenges, research and children's cancers.



"My greatest wish is to see my patients grow old," says Professor Tan Cheng Lim.

"I am a paediatric oncologist, but my oldest patient is 42 years old. He insists on coming to see me for a yearly check-up, even though his cancer has been in remission for many years. This is what I wish for every child with cancer – a full and healthy life."

One of the longest-serving paediatricians in public healthcare, Emeritus Consultant with the Department of Paediatric Subspecialties at KKH, Prof Tan has been an influential pioneer in paediatric medicine in Singapore, throughout a career spanning 50 years.

"Children's cancers have a direct link to infant mortality. If the patient is not cured, they will almost certainly die. The challenge we face is to cure our patients," says Prof Tan.

Prof Tan was President of the Singapore Paediatric Society in 1973, and subsequently

helmed the paediatrics department at Alexandra Hospital (1974 – 1977), Singapore General Hospital (1977-1997) and KK Women's and Children's Hospital (1997-1999), firmly laying the foundations for paediatric medicine in Singapore.

For Prof Tan, the only difference between a challenge and an obstacle is perception. In the 1960s, about to begin his first appendectomy as a House Officer, he realised that work processes and standing positions in the operating theatre were organised for a right-handed doctor.

"I am left-handed. After the initial surprise, the medical staff and I calmly made the necessary adjustments, and proceeded with the surgery," says Prof Tan.

Through the years, the percentage of survival and cure for childhood cancers in Singapore has steadily risen as national infant mortality rates have plummeted to rank amongst the lowest in the world. Where some might see achievement, for Prof Tan, this poses another challenge which he eagerly embraces – to continue driving these trends.

"Research, particularly in the area of genetics, is of crucial importance in the pursuit of management and cures for cancer. It is well-established that cancers can be genetically inherited, or result from spontaneous genetic mutation. We must press on in this area, as it is the next frontier of cancer treatment," says Prof Tan.

Prof Tan also advises an eponymous research and education fund administered by the SingHealth Duke-NUS Academic Medical Centre's Paediatrics Academic Clinical Programme, which supports

"WHERE THE END GOAL IS TO CURE EVERY CHILD WITH CANCER, THERE SHOULD BE NO END TO THE PURSUIT OF KNOWLEDGE."

Professor Tan Cheng Lim

research in paediatric cancers and blood disorders, and disburses public healthcare scholarships.

Over the years, Prof Tan has trained, nurtured and inspired many generations of healthcare professionals. He continues to contribute to medical education as a member of the SingHealth Institutional Review Board, and Adjunct Professor, Duke-NUS Graduate Medical School and Yong Loo Lin School of Medicine, National University of Singapore.

"Since the advent of medicine, its practice has and will continue to evolve. We must learn to be humble, eagerly embrace new evidence, and allow ourselves to be the shoulders upon which others reach new heights of medical discovery," says Prof Tan.

Where the end goal is to cure every child with cancer, there should be no end to the pursuit of knowledge."



MANAGEMENT OF ADVANCED HEART FAILURE IN CHILDREN

Dr Chen Ching Kit, Consultant, Cardiology Service, KK Women's and Children's Hospital

Dr Loh Yee Jim, Head and Consultant, Cardiothoracic Surgery Service, KK Women's and Children's Hospital

A HEART-BREAKING CASE OF FEVER AND RASH

A seven month-old boy diagnosed with Kawasaki disease (KD) was treated with intravenous immunoglobulin (IVIg) and high-dose aspirin. He showed defervescence initially, only to mount fever again within 48 hours of treatment. He was then transferred to KK Women's and Children's Hospital (KKH) for further management.

Owing to the recrudescence of fever, he was treated with steroid with good response. Although initial echocardiograms demonstrated normal coronary arteries, formation of giant aneurysms was diagnosed one month after the onset of KD.

There were giant coronary artery aneurysms of the left main coronary artery (LCA) and left anterior descending artery (LAD), and multiple giant coronary aneurysms of the right coronary artery (RCA).



Figure 1. The first infant in Singapore to receive a left ventricular assist device (LVAD).

The patient was commenced on anticoagulation with subcutaneous enoxaparin in combination with oral aspirin. Seven weeks after the onset of KD, he presented to the KKH Children's Emergency with cardiogenic shock; urgent echocardiography revealed complete thrombotic occlusion of the LAD and intraluminal non-occlusive thrombus within the RCA, and severely depressed biventricular systolic function. Electrocardiogram revealed findings consistent with myocardial infarction, and cardiac enzymes were markedly elevated.

The patient required extracorporeal cardiopulmonary resuscitation (eCPR) with institution of extracorporeal membrane oxygenation (ECMO) in the Children's Intensive Care Unit. Systemic thrombolysis was administered successfully.

In view of persistent poor myocardial recovery, the patient was converted to a temporary left ventricular assist device (LVAD) after two weeks of ECMO support. At the time of this article, he has been on six weeks of support with the LVAD (Figure 1), and is currently making good progress in his clinical recovery.

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MANAGEMENT OF ADVANCED HEART FAILURE IN CHILDREN (Continued)

Heart failure (HF) in children can be defined broadly as failure of the heart to supply blood at an appropriate rate of flow, or to receive venous return at an appropriate filling pressure, resulting in adverse effects on the heart, blood circulation, and the patient. HF is associated with high morbidity and mortality; less than 50 percent of children who present with symptomatic HF survive beyond five years without heart transplantation.

EPIDEMIOLOGY AND AETIOLOGY

HF has multiple causes: predominant among these in developed countries are the primary cardiomyopathies (accounting for 60% of children requiring heart transplant), and the congenital heart diseases. In addition, systemic processes such as inflammatory diseases (including myocarditis), metabolic disorders, endocrine derangements, and kidney disease are also known causes.

Although ischaemic cardiomyopathy is very rare in children, KD with giant coronary aneurysm (Figure 2), as exemplified by our patient, constitutes a small but important group. There is a paucity of data addressing the prevalence or incidence of HF in children, both in Singapore and internationally. Some authors have indicated a prevalence of 164–480 per million children. Singapore currently has about 607,955 children under 15 years old¹; this translates to a prevalence of 100–250 children in Singapore with HF.

MEDICAL THERAPY

Multiple large prospective randomised controlled trials in adult HF patients have demonstrated the survival advantage of treatment with angiotensin-converting enzyme inhibitor (ACEi), β -blocker, angiotensin receptor blocker (ARB), and aldosterone antagonist. The KKH Cardiomyopathy and Heart Function (KKH CHF) programme has been established since August 2014, providing inpatient and outpatient care to children with cardiomyopathy and HF.

The multidisciplinary programme caters to the specific needs of these patients, providing them with individualised care ranging from advanced echocardiographic imaging to uptitration of their heart failure medications. The KKH CHF programme also provides patients access to the various allied health specialists (such as the physiotherapist, dietitian, pharmacist, and social worker) to optimise their rehabilitation, nutrition, medication counselling as well as psychosocial support.

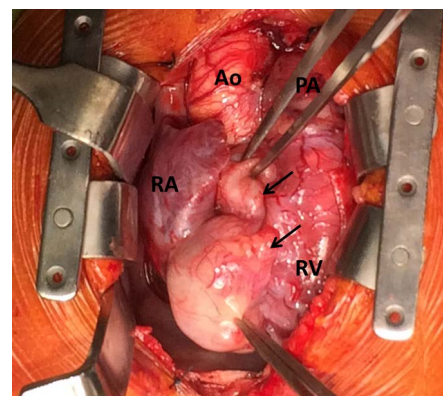
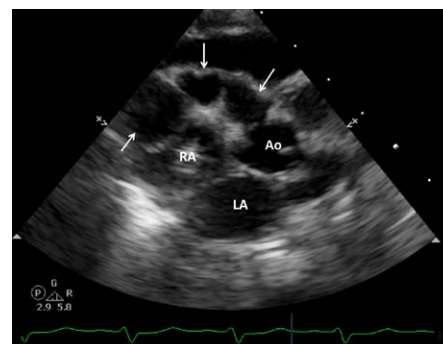


Figure 2. Echocardiographic (top) and intra-operative (bottom) images showing multiple giant coronary artery aneurysms (arrows) of the right coronary artery.

(Ao = aorta; LA = left atrium; PA = pulmonary artery; RA = right atrium; RV = right ventricle)

MECHANICAL CIRCULATORY SUPPORT

HF is a progressive disease; it may reach a level at which medical therapy alone is inadequate to preserve end-organ function, in which case mechanical circulatory support (MCS) becomes necessary to sustain life.

Until relatively recently, the only modality available for children in Singapore with profound and refractory heart failure was ECMO. ECMO is indicated and effective in an acute setting, since it can be deployed rapidly at an intensive care unit when required. The KKH ECMO programme has been providing life-sustaining support to young patients requiring emergency care throughout Singapore.

This modality, however, is not ideal for long-term support for HF. The 2004 Extracorporeal Life Support Organization (ELSO) registry data showed that ECMO deployment for cardiac failure of any aetiology across all age groups remains a very high-risk therapy, with survival to discharge rates of 38 percent, and 43 percent in neonates, and children, respectively².

Thus, patients with ongoing need for circulatory support are converted to a ventricular assist device (VAD), permitting extubation, aggressive physiotherapy, ambulation, and oral intake. Our patient is the first infant in Singapore to have a VAD implantation.



Figure 3. Child with a Berlin Heart EXCOR ventricular assist device (VAD).

One of the greatest advances in paediatric HF management over the last decade has been the increased utilisation and success of VADs for children with end-stage HF. One such device, the Berlin Heart EXCOR (Figure 3) was first implanted in 1990 in Germany, and has now been utilised in more than 1,500 paediatric patients worldwide. Following European regulatory approval in 1999 and North American approval in 2011, the Berlin Heart EXCOR is currently the only long-term VAD available for infants and smaller children, and is the most commonly used paediatric VAD throughout the world.

However, this device is currently not available for use in Singapore. With the first implantation of a temporary VAD in an infant, the process is in place for the Berlin Heart EXCOR to be made available in Singapore. The KKH CHF programme has moved forward to expand the paediatric MCS service to include VAD in order to provide the best possible care to our children with end-stage HF who hitherto have had limited options for survival.

Some patients on VADs have meaningful recovery of ventricular function while on support, and some patients have undergone VAD explant and have remained free from heart failure. Given the limitations of heart transplantation, understanding and expansion of VAD utilisation for myocardial recovery is of paramount importance in the management of paediatric heart failure.

HEART TRANSPLANTATION

Historically, most VAD support in children has been as a bridge to heart transplantation. In developed nations, paediatric heart transplantation has been established as the standard of care for infants and children with end-stage heart disease. The National Heart Transplant Programme has been established more than a decade ago, performing heart transplantation for adults with HF in Singapore. However, heart transplantation is currently not available for infants and children in Singapore.

Children undergoing transplantation are not “just small adults”; they show specific differences regarding their underlying diseases leading to transplant, growth and development, the effects of immunosuppressive therapies, and the impact of infections on the developing immune system.

Since its inception, the KKH CHF programme has had close collaboration with the heart failure and heart transplant programme in National Heart Centre Singapore. The multidisciplinary KKH CHF programme, on the heels of the adult heart transplantation programme, is equipped to expand and augment the National Heart Transplant Programme to include infants and children, to build a heart transplantation programme across all age groups in Singapore.

CONCLUSION

Many children with HF can be successfully managed on medications and remain symptom-free for a period of time. A significant proportion of these patients, however, will progress to advanced HF, and many will require MCS and eventually heart transplantation. Singapore, with its well-equipped health infrastructure, is poised to develop a paediatric heart transplantation programme.

As donor organs and organ utilisation remain limited in most parts of the world, especially in Asia, public education would be an initial step in increasing awareness of organ donation. These organs are the proverbial gift of life for many of these children who are fragile, and have few options for a better quality of life.



Dr Chen Ching Kit graduated from National University of Singapore and pursued post-graduate training in paediatrics and paediatric cardiology at KKH. He further underwent subspecialty training in paediatric heart failure and transplantation at The Hospital for Sick Children in Toronto, Canada. Dr Chen's current research interests include dilated cardiomyopathy, exercise echocardiography in cardiomyopathy, and the impact of de novo anti-HLA antibodies in paediatric heart transplantation.



Dr Loh Yee Jim graduated from National University of Singapore and obtained his Fellowship of the Royal College of Surgeons (Edinburgh) in cardiothoracic surgery. He further underwent a fellowship in congenital cardiac surgery at Boston Children's Hospital, USA, during which he was awarded the position of Chief Resident. Dr Loh is also a visiting consultant with National Heart Centre Singapore. His interests include adult and paediatric congenital heart surgery.

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JOINING FORCES AGAINST ENDOMETRIOSIS

KKH leads multi-institutional research into leading cause of menstrual pain and infertility.

Report by Dr Erin Teo (PhD) and Dr Lee Yie Hou (PhD), KK Research Centre, KK Women's and Children's Hospital

The Singapore Endometriosis Research Network (SERN) for clinical and translational research has one of the leading causes of menstrual pain and infertility under scrutiny.

Launched by KK Women's and Children's Hospital (KKH), SERN seeks to establish the first biorepository matched to clinical outcomes in an Asian population, to facilitate the study of a larger population of patients with endometriosis, and a broader spectrum of cases.

Endometriosis is characterised by the presence of cells from the womb lining, or the endometrium, in areas outside the womb cavity. The gynaecological condition can result in significant morbidity of pain and infertility, and affects up to 10 percent of all women during their reproductive and most economically significant years.

However, as the pathophysiology of the condition remains unknown, both diagnosis and treatment for endometriosis are largely empirical.

“The Singapore Endometriosis Research Network facilitates a multidisciplinary approach as we seek to define the epidemiology of endometriosis, develop an understanding of its pathophysiology, and to derive biomarkers that can indicate a patient’s risk to facilitate diagnosis and monitoring,” says Associate Professor Bernard Chern, who is Head of the Executive Committee for SERN.



FIRST ASIAN CLINICAL OUTCOME-LINKED BIOREPOSITORY

“At KKH, we treat approximately 1,200 women with endometriosis-related problems every year.

By joining forces, we can create an effective clinical outcome-linked biorepository of endometriosis cases,” adds Assoc Prof Chern, who is also Head and Senior Consultant, Division of Obstetrics and Gynaecology, KKH, and Academic Chair, SingHealth Duke-NUS Academic Medical Centre, Obstetrics and Gynaecology Academic Clinical Programme.

“Given the observation that women with endometriosis in Singapore tend to be more florid and severe with relatively less pain, the larger combined caseload and wider spectrum of patients presenting with both infertility and/or pain, will allow multiple questions in the clinical and translational realm to be probed in tandem, in partnership with fellow researchers from other parts of the world,” says Assoc Prof Jerry Chan, who leads the translational research arm of SERN, and is also Director, KK Research Centre; and Senior Consultant, Department of Reproductive Medicine, KKH.

“With this integrated network, researchers are uniquely juxtaposed to capitalise on

the opportunity to approach endometriosis across many disciplines – encompassing immunology, genetics, imaging, biomarker discovery, functional MRI pain studies, and advanced lipidomic/proteomic analyses combined with stem cell biology – in parsing out its pathobiology.”

SERN consists of clinician investigators and researchers across SingHealth institutions; Agency for Science, Technology and Research (A*STAR); Massachusetts Institute of Technology (MIT); Duke University; and University of Warwick, and is supported by the SingHealth Duke-NUS Academic Medical Centre, Obstetrics and Gynaecology Academic Clinical Programme.

SERN STUDY: INVESTIGATING LINKS BETWEEN ENDOMETRIAL STROMAL DYSFUNCTION AND ENDOMETRIOSIS

To better understand the links between endometrial stromal dysfunction and endometriosis, SERN researchers from KKH, National University Hospital Singapore and MIT have collaborated on a study¹ to investigate the impact of low oxygen content in the peritoneum of women with endometriosis on cell movement. In addition, they have discovered a set of sphingolipids which are upregulated in endometriosis patients which has biological activity in enhancing growth and reduced cell death².



Research findings:

Endometrial stromal cells (ESC) from women with endometriosis showed significantly higher migration and invasion through collagen gels under hypoxia, compared with ESC from women without endometriosis.

This was due to the lower expression of the antigen CD26 in ESC from women with endometriosis, and increased expression of cytokines that enhances new vessel formation which is essential for establishment of the lesions.

There are numerous long acyl-chain sphingolipids which were found to be in elevated concentrations in women with endometriosis as a result in induction of key enzymes found in the endometrium driving its metabolism.

These lipids can be found to be elevated in the peritoneum where most of the abnormal tissues reside and also the peripheral circulation, making them an attractive candidate to serve as biomarkers, and to be used for either diagnostic or disease-monitoring purposes¹.



Conclusion:

Identifying the loss of CD26 is the first step to understanding the molecule responsible for increase in migratory and angiogenic factors in endometriotic endometrial stromal cells and in part explain lesion development in endometriosis. Such a pathway may be targeted for drug development against lesion invasiveness in endometriosis.

Understanding the role of deranged sphingolipids found in women with endometriosis may open up new avenues of biomarker discovery, and shed light on their role in lesion formation and maintenance in endometriosis. In addition, some of these lipids may be involved in infertility, and be attractive targets for pharmacological targeting².

These studies were supported by National Research Foundation Singapore; SingHealth Foundation Grant; National Medical Research Council, Singapore; and Singapore-MIT Alliance for Research and Technology (SMART) Centre.

JOIN THE SINGAPORE ENDOMETRIOSIS RESEARCH NETWORK

Clinicians and researchers who wish to participate in clinical and translational research into endometriosis can contact Dr Lee Yie Hou at Lee.Yie.Hou@kkh.com.sg.



Dr Erin Teo obtained her Doctor of Philosophy from National University of Singapore, where she specialised in biomaterials and bioengineering. As Assistant Manager, KK Research Centre (KKRC), KKH, Dr Teo manages the centre's scientific arm and assists with growing the scientific aspect of KKRC's research activities. Dr Teo is also an adjunct research fellow with the Duke-NUS Graduate Medicine School, with particular interests in bone tissue engineering, stem cell therapy and regenerative medicine.



Dr Lee Yie Hou obtained his Doctor of Philosophy in Biochemistry from National University of Singapore, and has worked with Prof Steven Tannenbaum at MIT on dissecting the mechanisms of inflammatory diseases, and pioneering non-invasive biomarkers for their diagnosis and prognosis. Dr Lee is currently Principal Scientist, KK Research Centre, KKH, with particular interests in endometriosis, dengue, and uterine receptivity in in vitro fertilisation. Dr Lee is also affiliated with SMART.

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PAEDIATRIC RHEUMATOLOGY: WHERE TO NEXT?

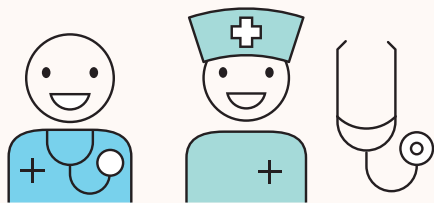
Associate Professor Thaschawee Arkachaisri, Head and Senior Consultant; and Dr Justin Tan, Consultant; Rheumatology & Immunology Service, KK Women's and Children's Hospital

HOLISTIC CLINICAL CARE

Early recognition of rheumatic diseases is paramount as late diagnosis often poses a long-term risk of disability and high mortality. Primary care physicians need to be cognizant of rheumatic disease manifestations so that early referral can be initiated.

A study by the paediatric Rheumatology and Immunology Service at KK Women's and Children's Hospital (KKH) showed that 58 percent of the referrals made to our paediatric rheumatology clinics between January 2009 and March 2012 were rheumatic diseases¹.

Of these, systemic vasculitides, juvenile idiopathic arthritis (JIA) and



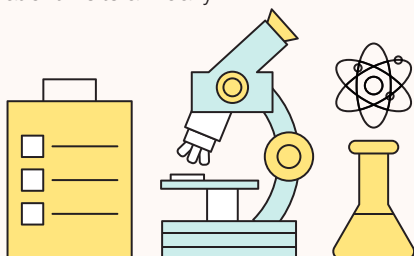
systemic lupus erythematosus (SLE) were the most common rheumatic diseases encountered. Through a better understanding our local disease burden, the awareness in our community – especially amongst primary care physicians – can be increased, leading to earlier diagnosis and treatment.

Treatment of childhood-onset autoimmune diseases has advanced over the last decade, with the advent of new biologics treatment – which targets specific components of the immune system instead of the broad effects of traditional medicine. This gives hope to those who have been refractory to conventional therapy.

RESEARCH AND TRAINING

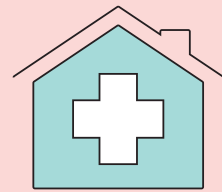
The KKH Paediatric Rheumatology Clinical Program (PRCP) was established in 2009 to spearhead the adaptation of more holistic, patient-centered clinical care along with high-quality, impactful research and a pragmatic academic approach.

Despite the sub-specific area and rarity of rheumatic diseases by nature, we continue to evaluate more than 5,000 patient visits annually.



The Paediatric Rheumatology Fellowship Training programme was also established to train regional paediatricians in order to improve our regional overall disease outcomes.

The advent of musculoskeletal ultrasound and biologics use in paediatric rheumatology over the last decade has improved diagnostic and therapeutic outcomes for children with rheumatic diseases. Through local and international collaboration networks, we engage in burgeoning autoimmune disease research with the aim of improving our prognostication ability and answering some of the unmet medical and therapeutic needs in the clinical care of children with rheumatic diseases.



PAEDIATRIC RHEUMATOLOGY AND IMMUNOLOGY AT KKH

This subspecialty focuses on the evaluation, diagnosis and treatment of disorders involving joints, soft tissues, connective tissues and the immune system in children.

Such conditions include JIA; connective tissue diseases, e.g. SLE, scleroderma, Sjogren's syndrome and juvenile dermatomyositis (JDM); systemic vasculitides, e.g. Kawasaki disease (KD) and Henoch Schonlein purpura (HSP); auto-inflammatory syndromes; and secondary rheumatic disorders, e.g. autoimmune organ disorders.

Through comprehensive and patient-targeted evaluation, the diagnosis of rheumatic diseases is made before initiation of treatment, which is often multidisciplinary involving the physiotherapist, occupational therapist, ophthalmologist, orthopaedic surgeon and other subspecialists.

DISEASE MAPPING

Regional registry for childhood-onset rheumatic diseases

Since the inception of PRCP, the Registry for Childhood Onset Rheumatic Diseases (RECORD), an internet-based registry, was developed with the aim to study the disease epidemiology, efficacy of treatment and outcomes of childhood diseases in Singapore and Southeast Asia longitudinally. RECORD is supported by the National Arthritis Foundation of Singapore (NAF) and International League of Associations for Rheumatology (ILAR).

The registry also serves as a platform for other observational research to be conducted locally and regionally through collaboration with paediatric rheumatologists from Malaysia, Thailand and Philippines. This registry is an invaluable resource for researchers not only in clinical but also translational research.

Precision approach to disease management

In close collaboration with SingHealth Translational Immunology & Inflammation Centre (STIIC), we have also embarked on a "Precision Medicine Research Strategy". A medical model that has emerged as an individualised approach for disease treatment and prevention, precision medicine proposes customisation of healthcare, which includes medical decisions and practices being tailored to each individual patient after taking into consideration his or her variability and capacity in terms of genetic constitution, genetic potentials, environment and lifestyle factors.

Precision medicine aims to identify predictors and surrogates of efficacy and toxicity even prior to treatment. This approach has been the key for immunomics (high-throughput molecular immunologic and functional genomics platforms) studies in JIA in children and rheumatoid arthritis (RA) in adults. Since the advent of biologics a decade ago, high therapeutic outcome expectation has risen and disease remission has become a reality in children with JIA. Prolonged "zero-disease activity" may not be a mere dream any longer.

Juvenile idiopathic arthritis

We are currently collaborating with STIIC on research into the prediction of JIA patient response to certain biologics – especially TNF (main arthritis inflammatory cytokines) inhibitors – and enabling continuous disease remission after treatment stops.

As anti-TNF responders and non-responders are phenotypically indistinguishable, we aim to validate the immunomics signatures and the epipolymorphisms predictive of responsiveness in patients with JIA. However, as polyarthritis JIA is the least common subtype of JIA seen in Singapore, patient recruitment for this study remains our biggest obstacle.

Expanding on this research, our outcome and therapeutic research targets also include other high-morbid rheumatic diseases: SLE, systemic vasculitides with KD and HSP – which are among the most common rheumatic diseases encountered locally and regionally.

Systemic lupus erythematosus

The prevalence of childhood-onset SLE in Singapore is estimated to be at least 14.2 per 100,000 children, and it constitutes the third most common rheumatic diseases with five-year survival in KKH's SLE cohort at 98.4 percent^{2,3}.

Vitamin D has been proven to have immunomodulatory properties which are crucial in maintaining the homeostasis of the immune system. Vitamin D deficiency is not only associated with development of autoimmune diseases, but also correlated with disease activity in adult-onset SLE.

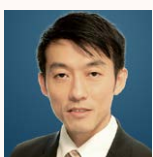
With support from the SingHealth Duke-NUS Academic Medical Centre Paediatrics Academic Clinical Programme Young Researcher Pilot Grant, a study into the prevalence of vitamin D deficiency in childhood-onset SLE and its correlation with disease activity is underway. Biomarkers implicated in the pathogenesis of SLE are actively studied and validated in our patients with SLE, to determine their potential diagnostic and prognostic roles.

Kawasaki disease

As Kawasaki disease is the second most common vasculitis encountered in our population after HSP, we are investigating prognostic factors which may be helpful in predicting intravenous immunoglobulin resistance in our local patient cohort, and coronary artery outcomes due to different treatment strategies, seeking to improve overall outcomes.



A passionate advocate of clinical research in paediatric rheumatology and immunology, Associate Professor Thaschawee Arkachaisri's research interests include outcome measures in childhood rheumatic diseases including scleroderma, systemic lupus erythematosus and vasculitides. Active in medical education, Assoc Prof Arkachaisri is also Core Faculty, ACGME Paediatric Residency Training Program, SingHealth; and Faculty Coordinator, Duke-NUS Graduate Medical School Paediatric Elective Clerkship.



Dr Justin Tan was awarded the Academic Clinical Programme Young Researcher Investigator Grant in 2014 for his research in Vitamin D deficiency in Systemic Lupus Erythematosus. His research interests include outcome measures in Systemic Lupus Erythematosus and musculoskeletal ultrasound in rheumatology. Dr Tan is also a clinical lecturer and adjunct instructor with Yong Loo Lin School of Medicine, National University of Singapore and DUKE-NUS Graduate Medical School, Singapore; as well as physician faculty member with ACGME, Pediatrics Residency Programme, SingHealth.

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WHEN A CHILD IS TOO VOCAL

Diagnosis and management of vocal cord nodules in children

Dr Lynn Koh, Associate Consultant, Department of Otolaryngology, KK Women's and Children's Hospital
Heng Qiwen, Speech Therapist, Department of Rehabilitation, KK Women's and Children's Hospital

Vocal cord nodules are the most common cause of paediatric voice disorders in Singapore and worldwide, and can occur in both adults and children.

These small, benign lesions that arise between the anterior and middle third of the vocal cords are widely thought to be caused by voice abuse – which refers to any behaviour that overuses or misuses the vocal cords.

An isolated instance of vocal abuse might result in temporary swelling of the child's vocal cords, affecting the sound quality of the voice.

For example, a child might have a hoarse voice after an afternoon of screaming at an amusement park. However, excessive and repeated instances of voice abuse can cause the swelling to become callus-like growths called nodules.

Other risk factors for the development of vocal cord nodules include allergies,

prolonged upper respiratory tract infection and gastroesophageal reflux disease (GERD).

From August to December 2014, we reviewed 20 paediatric patients who presented to the KKH ENT outpatient clinic with hoarseness as their primary complaint. Of these patients, 16 (80%) were diagnosed with vocal cord nodules. The children's ages ranged from three to 16 years and the duration of hoarseness ranged from one month to seven years. The ratio of boys to girls was 4:1.



EXAMPLES OF VOICE ABUSE IN CHILDREN INCLUDE:



Frequent emotional outbursts such as laughing, shouting, screaming, or crying

Using an excessively loud voice for daily communication



Poor fluid intake leading to dehydration

Prolonged coughing or throat clearing



EVALUATION OF A CHILD WITH VOCAL CORD NODULES

CHILDREN WITH VOCAL CORD NODULES MAY PRESENT WITH THE FOLLOWING SIGNS AND SYMPTOMS:

Hoarseness - voice may sound lower, rougher or more strained

Difficulty sustaining notes when singing

Straining neck and shoulder muscles during speech

Neck or throat pain after prolonged vocalising

As there are many different causes of hoarseness in children, hoarseness in a child lasting for more than two weeks duration should be evaluated by an otolaryngologist.

During consultation with the otolaryngologist, a detailed history will be taken including the duration and severity of symptoms. Vocal cord nodules tend to present with hoarseness that is worse at the end of the day and better with rest.

A full ear, nose and throat (ENT) examination will be carried out to evaluate the child for allergies and any other contributing factors that may cause hoarseness. Direct visualisation of the vocal cords is necessary to make a definitive diagnosis and rule out other causes of hoarseness, including intra-cordal cysts, benign and malignant neoplasms, recurrent respiratory papillomatosis (RRP) and neurologic causes such as vocal cord paralysis.

In an older and more cooperative child, direct visualisation of the vocal cords may be carried out via flexible nasoendoscopy performed in the clinic. In a younger or uncooperative child, microlaryngobronchoscopy under anaesthesia may be necessary to form an accurate diagnosis.



Vocal cord nodules in a child; note the swollen growths on either side of the vocal cords.

TREATMENT OF VOCAL CORD NODULES

Having chronic hoarseness and difficulty with vocalising can be detrimental to a child both psychosocially and academically, and accurate diagnosis is essential to treatment.



The treatment of vocal cord nodules in children is usually conservative. Risk factors for vocal nodules, such as allergy and GERD, may be controlled with medications and the patient is often referred to a speech therapist for voice therapy. Surgery may be considered in select cases that do not respond to voice therapy or persist into puberty.

Voice therapy for vocal cord nodules - what does it involve?

During voice therapy, the speech therapist works closely with the child and caregiver to improve the child's use of voice and reduce the occurrence of voice abuse. The child will be taught voice exercises and voice

production techniques that are tailored to their needs.

These exercises and techniques are intended to help the child learn to use their vocal cords more effectively, and in turn, develop a better voice quality. In some cases, voice therapy may also involve teaching the child to shout in a safe and effective way.

In the paediatric population, parental involvement and home practice are pivotal for successful voice therapy and long-term improvement in voice quality. Parents are often encouraged to take part in therapy sessions with young children and are expected to supervise their child in completing voice practice at home.



Dr Lynn Koh obtained her Bachelor of Medicine and Bachelor of Surgery, as well as Master Of Medicine in Otolaryngology from Yong Loo Lin School of Medicine, National University Singapore, and subsequently completed specialty training in otolaryngology in Singapore. Dr Koh has a special interest in paediatric airway disease and voice disorders.



Heng Qiwen graduated from University of Sydney with First Class Honours in 2012. She has a strong interest in the areas of paediatric voice and feeding. Qiwen provides assessment and intervention for preschool- and school-aged children, as well as adolescents, for a range of voice disorders such as muscle tension dysphonia and puberphonia.

ADVANCED CARE FOR BABIES AND WOMEN



ONE-STOP SUITE FOR COMPLEX FETAL TREATMENTS

KK Women's and Children's Hospital (KKH) has opened Singapore's first Fetal Surgery Suite, dedicated to providing complex fetal treatments. A one-stop facility for fetal surgeries, the suite offers a comprehensive range of key procedures, including:

Fetoscopic laser photocoagulation	to treat monochorionic twin complications
Biopolar cord coagulation	to treat monochorionic twin complications
Pleural amnionic shunt insertions	to drain excessive fluid in the fetal lung cavity
Amnioreduction	to reduce excessive amounts of amniotic fluid
Amniocentesis and chorionic villus sampling	for the prenatal diagnosis of genetic abnormalities and fetal infections
Fetal blood transfusion	to treat anaemic fetuses
Fetal blood sampling	to detect chromosomal disorders, genetic diseases and fetal infections

Among the procedures offered at the Fetal Surgery Suite is fetal laser surgery for the treatment of Twin to Twin Transfusion Syndrome (TTTS) – a rare syndrome which only occurs in identical twins that share the same placenta. TTTS affects one in 1,600 pregnancies.

For more information about the KKH Fetal Surgery Suite, please contact **+65 6394 2245**.

PRECONCEPTION HEALTH CLINIC FOR WOMEN

The KKH Preconception Health Clinic aims to help women assess their preconception health, and prepare for a healthy pregnancy. Preconception health looks at health conditions and risk factors affecting a woman which may impact an unborn child.

The clinic offers a preconception screening package comprising comprehensive tests that can help detect abnormalities that may impact pregnancy. The package includes the following tests:

- Physical examination
- Body Mass Index
- Body weight & height
- Blood pressure
- Pap smear
- Imaging of the womb and ovaries
- Blood tests to establish ovarian health, determine immunity to rubella, and screen for infectious diseases such as HIV and Hepatitis B

Women attending the preconception clinic who agree to participate in preconception research will receive a revised rate for the screening package.

The KKH Preconception Health Clinic is open on Saturday mornings, by appointment only. For more information or to make an appointment, please contact **1800-7773786**.

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