

MEDICAL DIGEST



Tan Tock Seng
HOSPITAL

11 Jalan Tan Tock Seng
Singapore 308433

Tel: 6256 6011
Fax: 6252 7282

www.ttsh.com.sg

Medical Digest is a quarterly publication of Tan Tock Seng Hospital written by healthcare providers for healthcare providers, as a service to the medical community.

CONTENTS

TTSH RESEARCH NEWS

CLINICALLY-ASSISTED NUTRITION & HYDRATION IN PATIENTS LACKING MENTAL CAPACITY

CANCER REHABILITATION — ARE WE DOING ENOUGH?

FLOWING ALONG THE RIVER OF LIFE IN CENTRAL HEALTH

MANAGEMENT OF UREMIC PRURITUS

RADIOLOGY QUIZ

EKG QUIZ

FROM THE EDITOR

EDITOR

Leong Khai Pang

ASSOCIATE EDITORS:

Charmaine Manauis
Raymond Ng
Melissa Tien
Mohd Fadil Muhammad Farhan

MEMBERS:

Tang Yee Lin
Rafael Saclolo
Ivan Huang Kuang Hsin
Noorhazlina bte Ali
Deshan Kumar
Tan Choon Chieh
Chong Yaw Khian
Kalaiyarasi Kaliyaperumal
Adeline Teh
Yew Min Sen
Shirlene Ho Shu Min
Binedell Trevor Brian

COPY EDITOR

Sheena Nishanti Ramasamy

DESIGNER

Clinton Low

We value your feedback. Please email your questions, comments or suggestions to:
ttsh_ccs@ttsh.com.sg

Please also contact us for notification of change of postal address or requests for additional copies.

While every endeavour is made to ensure that information herein is accurate at the time of publication, Tan Tock Seng Hospital shall not be held liable for any inaccuracies. The opinions expressed in this publication do not necessarily reflect those of Tan Tock Seng Hospital. The contents of this publication may not be reproduced without written permission from the publisher.

I want to give a shout-out to the spouses of doctors out there, because you deserve to be recognised.

Medscape's *Physician Lifestyle & Happiness Report 2020: The Generational Divide*, a survey of 15,000 American physicians in 29 disciplines, gives us an impression of the matrimonial patterns of doctors (<https://www.medscape.com/slideshow/2020-lifestyle-generational-6012424#1>). 80% of the respondents are married: 25% of female doctors are married to another doctor, while 16% of male doctors are. Overall, 55% of the doctors are not married to or living with a partner who works in health care. Incidentally, the same survey showed that Toyota and Honda are the favourite car brands.

The travails of the doctor's spouse are well known. In the 3 Dec 2015 issue of *The New York Times*, Anya Groner wrote about the perennial tiredness of her husband, the huge student school debt he has to pay off, and the envy of her friends. On reflection, she knew that ultimately, he is a kind and humorous man who loves to cook, and an airborne medical emergency reminded her of his competence and humility. The media frequently portrays doctors living lifestyles of luxury and ease. Well, it takes decades to get there, if ever.

It is useful for a doctor to have a spouse who is also one. Think of the interesting conversation, the tacit understanding of the frequent absence from family events and the acceptance of the tired partner who just wants to be left alone. I've once excitedly told my wife about diagnosing hyperthyroidism in a patient taking Slim 10, hypothesizing that it has TSH-like properties. My better-informed partner said, "Don't you know that it's adulterated with thyroxine? It's in the news."

Among the many times I've flown with my wife, the service of a doctor was only required once. Three people put up their hands: my wife (a family physician), me and a surgeon. The patient was a boy who had fever. The surgeon and I were helpless - only my wife knew what to do.

So if you've married a doctor, regardless if you're one yourself, be ready for a long, rough ride. The Toyota and Honda can ease the bumps.

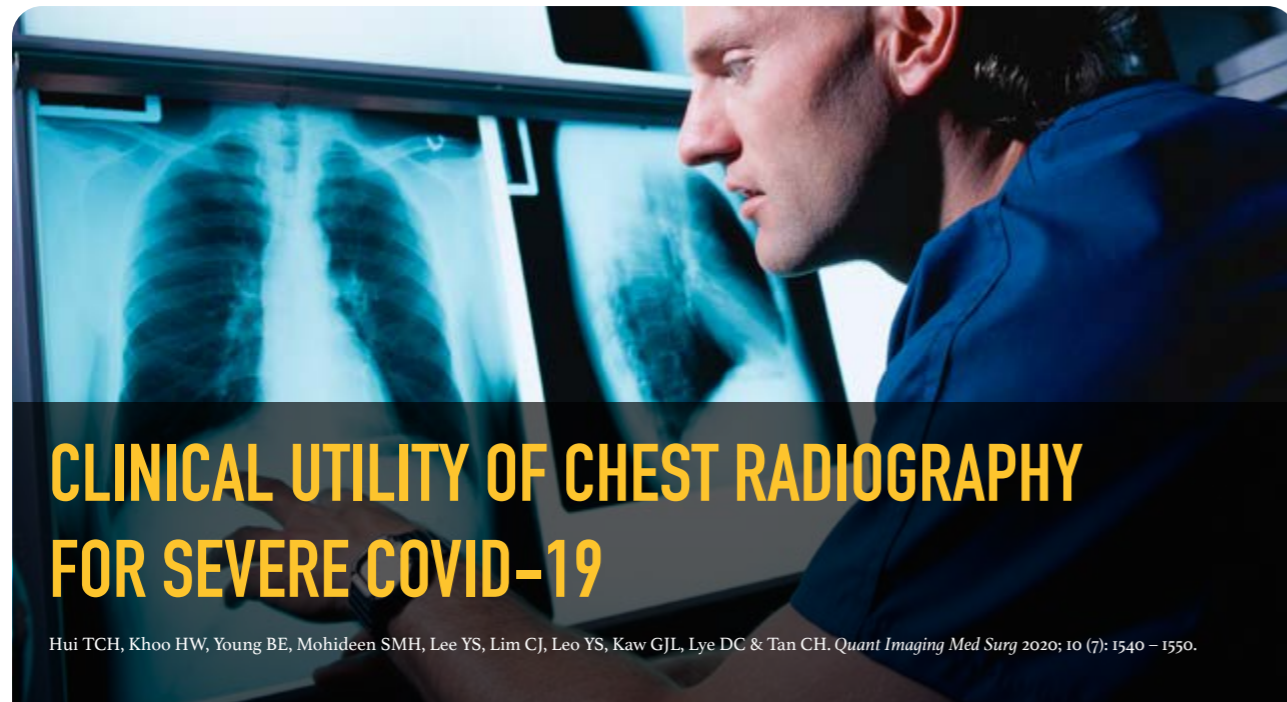
Dr Leong Khai Pang
EDITOR
Medical Digest



RESEARCH EXCERPTS

TTSH RESEARCH NEWS

Every year, TTSH clinicians publish about 300 scientific papers. In this section, we selected a few reports and asked one of the authors of each to summarise and discuss the clinical relevance of their research.



CLINICAL UTILITY OF CHEST RADIOGRAPHY FOR SEVERE COVID-19

Hui TCH, Khoo HW, Young BE, Mohideen SMH, Lee YS, Lim CJ, Leo YS, Kaw GJL, Lye DC & Tan CH. *Quant Imaging Med Surg* 2020; 10 (7): 1540 – 1550.

Imaging in the diagnosis and management of COVID-19 is essential in settings where real-time polymerase chain reaction (RT-PCR) test kits are limited or have high false-positive rates. Chest radiography (CXR) is widely utilised to discriminate between COVID-19 associated pneumonia and common upper respiratory tract infections. Despite a lower sensitivity for pulmonary diseases (compared to a chest computed tomography), wide inter-observer variability as a diagnostic modality and, little published data validating its role in the clinical management of COVID-19, CXR is being used extensively during the current pandemic. Thus, the authors sought to assess the diagnostic performance of CXR, in particular its predictive value, in severe COVID-19 disease.

This was a retrospective cohort study of 109 patients with COVID-19 infection (confirmed by RT-PCR) who were admitted to the National Centre of Infectious Diseases (NCID) from 22 January to 15 March 2020, and followed up for at least 21 days. Blood investigations, demographics and clinical features were retrieved from electronic medical records. A total of 358 anonymized, randomized CXR images (mean of 3 CXR per patient;

IMPORTANCE IN CLINICAL PRACTICE

The degree of CXR abnormalities (based on CRS) correlated with, and reflected, COVID-19 disease severity. This suggests that CRS may be as useful as, if not more than, laboratory markers in determining the severity of COVID-19 associated pneumonia, making it a reasonable diagnostic tool in the community setting.

This summary was prepared by the editorial team of Medical Digest.

range: 1 – 32) were reviewed and graded in consensus by 3 subspecialty-trained radiologists who were blinded to subjects' clinical outcomes. A COVID-19 Radiographic Score (CRS), modified from the Radiographic Assessment of Lung Edema (RALE) score to account for extent and density of airspace opacification, was calculated for each CXR. Need for supplemental oxygen and mechanical ventilation with intensive care unit (ICU) admission was the primary study endpoint.

Patients who needed supplemental oxygen (N=19, 17.4%) were significantly older ($P<0.001$) and had (i) comorbidities ($P=0.011$), (ii) higher C-reactive protein (CRP) ($P<0.001$), (iii) higher lactate dehydrogenase (LDH) ($P<0.001$), (iv) lower lymphocyte count ($P<0.001$) and, (v) lower haemoglobin ($P=0.001$). These patients also had significantly higher initial CRS ($CRS_{initial}$) [median (IQR): 9 (2,17) vs. 0 (0,1); $P<0.001$] and maximal CRS (CRS_{max}) [median (IQR): 26 (20,39) vs. 4 (2,5); $P<0.001$] scores than patients who did not require supplemental oxygen. Adjusting for age and baseline haemoglobin, the authors found that CRS_{max} had a diagnostic performance [area under receiver operating characteristic curve (AUROC) = 0.983] as high as, if not more, than laboratory markers (CRP_{max} AUROC = 0.987, LDH_{max} AUROC = 0.900, lymphocyte count_{min} AUROC = 0.897) in determining the need for supplemental oxygen. Based on a CRS cut-off ≥ 5 (to eliminate false positives and preserve sensitivity, while increasing true positives and specificity), it was found that CXR done between days 6 and 10 of symptom onset (CRS_{D6-10}) had higher sensitivity and specificity in predicting the need for supplemental oxygen (sensitivity 89%, specificity 95%) and ICU admission (sensitivity 100%, specificity 86%) than $CRS_{initial}$ (sensitivity 63%, specificity 91% in predicting need for supplemental oxygen; sensitivity 73%, specificity 88% in predicting need for ICU admission).

EFFECTS OF A MAJOR DELETION IN THE SARS-COV-2 GENOME ON THE SEVERITY OF INFECTION AND THE INFLAMMATORY RESPONSE: AN OBSERVATIONAL STUDY

Young BE, Fong S, Chan Y, Mak T, Ang LW, Anderson DE, Lee CY, Amrun SN, Lee B, Goh YS, Su YCF, Wei WE, Kalimuddin S, Chai LYA, Pada S, Tan SY, Sun L, Parthasarathy P, Chen YYC, Barkham T, Lin RTP, Maurer-Stroh S, Leo Y, Wang L, Renia L, Lee VJ, Smith GJD, Lye DC & Ng LFP. *Lancet* 2020; 396: 603 – 611.



Efforts to map the genetic diversity of the SARS-CoV-2 virus which is responsible for coronavirus disease 2019 (COVID-19), and identify variants which affect the fitness of the virus, are ongoing. A SARS-CoV-2 variant with a 382-nucleotide deletion ($\Delta 382$) in the open reading frame 8 (ORF8) region of the genome has been detected in several countries, including Singapore. This deletion eliminates transcription of the ORF8 protein, whose biological function in SARS-CoV-2 is currently unknown. The authors of this study thus set out to investigate the clinical effects of the $\Delta 382$ deletion in the SARS-CoV-2 virus.

131 patients with confirmed SARS-CoV-2 infection who had been screened for the $\Delta 382$ variant were retrospectively identified from the PROTECT study (prospective observational cohort study of all individuals hospitalised at one of the 7 public hospitals in Singapore with confirmed SARS-CoV-2 infection for the purpose of clinical characterisation of COVID-19). Clinical, laboratory, and radiological data were retrieved from patients' medical records. Serial blood and respiratory samples collected during hospitalisation and post-discharge were analysed. Patients infected with $\Delta 382$ variant were compared to those infected with wild-type SARS-CoV-2. Development of severe COVID-19 (defined as hypoxia requiring supplemental oxygen) was the primary study endpoint; secondary outcomes included concentrations of immune mediators in plasma samples.

92 (70.23%) of the 131 patients were infected with wild-type only; 29 (22.14%) with $\Delta 382$ variant only; and,

IMPORTANCE IN CLINICAL PRACTICE

The clinical effect of deletions in the ORF8 region appears to be a milder infection, with less systemic release of pro-inflammatory cytokines and a more effective immune response to SARS-CoV-2. Given the important role of ORF8 in mediating SARS-CoV-2 immune evasion, inhibition of its function could be investigated as a potential therapeutic strategy.

the remaining 10 (7.63%) had $\Delta 382$ and wild-type co-infection. While rates of pneumonia were similar across the 3 groups, none of the patients with $\Delta 382$ variant only developed hypoxia; this was in contrast to 28% of patients with wild-type only, and 30% of patients with $\Delta 382$ and wild-type co-infection, who required supplemental oxygen (absolute difference 28%; 95% CI 14 – 28, $P=0.005$). Adjusting for age and presence of comorbidities, the authors found that patients with $\Delta 382$ variant only had lower odds of developing hypoxia (adjusted OR 0.07; 95% CI: 0.0 – 4.8, $P=0.0035$) compared to patients with wild-type only. Furthermore, patients with $\Delta 382$ variant only had (i) lower concentrations of pro-inflammatory cytokines and chemokines; (ii) lower concentrations of growth factors associated with lung injury and regeneration; and, (iii) up-regulated T-cell responses and platelet activations (responsible for rapid and effective antibody response), compared to patients with wild-type only.

This summary was prepared by the editorial team of Medical Digest.

BURNOUT AND RESILIENCE AFTER A DECADE IN PALLIATIVE CARE: WHAT SURVIVORS HAVE TO TEACH US. A QUALITATIVE STUDY OF PALLIATIVE CARE CLINICIANS WITH MORE THAN 10 YEARS OF EXPERIENCE

Koh YHM, Hum YMA, Khoo HS, Ho HYA, Chong PH, Ong WY, Ong J, Neo SHP & Yong WC. J Pain Symptom Manage 2020; 59: 105 – 115.

Burnout, defined as a state of mental and/or physical exhaustion caused by prolonged exposure to chronic and excessive stress, can lead to emotional exhaustion, cynicism, detachment, decreased effectiveness and a diminished sense of accomplishment. Burnout is common in palliative care, with a global prevalence rate of 17.3%. Resilience, which involves fostering positive attitudes and effective strategies to combat stress, is associated with lower burnout, increased compassion and longevity. Studies on longevity and resilience in palliative care clinicians are scarce. Thus, the aim of the qualitative study was to deepen the understanding of burnout and resilience in palliative care through the sharing of views on burnout, resilience and coping strategies by palliative care clinicians who have been in the field for ≥ 10 years.

Semi-structured interviews with 18 palliative care clinicians comprising 5 doctors, 10 nurses and 3 medical social workers in various palliative care settings (home hospice, inpatient hospice, hospital palliative care team) were carried out over 4 months. Interviews were digitally recorded, anonymized, transcribed verbatim and analysed using a grounded theory approach. Mean (range) age of the interviewees was 52 (40 – 65) years, with 15.7 (10 – 25) years of palliative care practice. Four major themes were identified, forming a model – SCAR: Struggling, Changing mindset, Adapting, and Resilience. Self-awareness, reflection and evolution were identified as factors that linked and impacted

causality between themes. Transformational growth was the core category that conceptually bridged the themes (Figure 1). The study found that exposure to stress in the form of personal and professional struggles, drawing boundaries, finding meaning and purpose and, the use of coping strategies (such as seeking support and finding solutions), were necessary to build resilience. Respondents described resilience metaphorically as “a tree which bends but does not break” and as “the ability to be stretched beyond yourself”. They also emphasized the importance of building a resilient organizational culture which focuses on both individual resilience and collective (team) resilience.

IMPORTANCE IN CLINICAL PRACTICE

Burnout and lack of resilience are impending crises in the field of palliative care. Insights from this study may inform future strategies necessary to maintain an emotionally healthy and resilient palliative care workforce. Leaders and administrators of palliative care teams should lead by example and emphasize team resilience through programs on (i) building mental fortitude, (ii) forging stronger team relationships, (iii) mindfulness, and (iv) stress management training. They also have to nurture a culture of openness and mentorship.

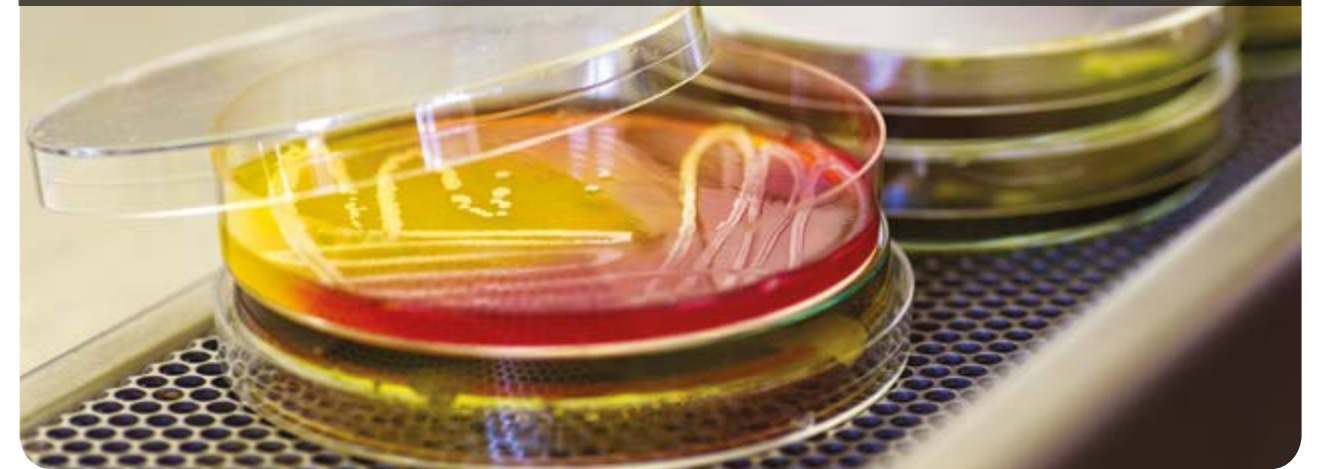
This summary was prepared by the editorial team of Medical Digest.



Figure 1. SCAR (Struggling, Changing Mindset, Adapting, and Resilience) model.

MYCOPLASMA GENITALIUM IN SINGAPORE IS ASSOCIATED WITH CHLAMYDIA TRACHOMATIS INFECTION AND DISPLAYS HIGH MACROLIDE AND FLUOROQUINOLONE RESISTANCE RATES

Hart T, Tang WY, Mansoor SA, Chio TWM & Barkham T. BMC Infectious Diseases 2020; 20: 314.



Mycoplasma genitalium is a sexually transmitted infection (STI) associated with cervicitis, pelvic inflammatory disease and infertility in women, and urethritis in both men and women. Conventional treatment of *M. genitalium* involves single-dose azithromycin (drug class: macrolide), with moxifloxacin (drug class: fluoroquinolone) as a second line agent. *Chlamydia trachomatis*, another (more common) cause of urethritis, is also treated with single-dose azithromycin. *M. genitalium* co-infection with *C. trachomatis* is common, and treatment of the latter has been shown to impact macrolide resistance in the former. Despite this, *M. genitalium* testing is not part of routine STI screening in many countries. Given the increasing number of cases of urethritis caused by *M. genitalium*, as well as growing resistance of *M. genitalium* to both macrolides and fluoroquinolones, the authors of the study sought to establish the prevalence and pattern of *M. genitalium* infection in Singapore, the degree of co-infection with *C. trachomatis*, and the levels of antibiotic resistance.

358 urine samples and 114 urethral swabs left over from routine, clinically directed testing for *C. trachomatis* and *Neisseria gonorrhoeae* were collected from the DSC (Department of Sexually Transmitted Infections Control) Clinic. These were tested for *M. genitalium* using PCR, and sequenced to detect genomic mutations associated with macrolide and fluoroquinolone resistance. 131 urine samples and 54 urethral swabs (185 samples in total) were PCR +ve for either *C. trachomatis*, *N. gonorrhoeae* or both; the remaining 287 swabs and samples were negative. Rate of *M. genitalium* infection in patients +ve for *C. trachomatis* (with or without

N. gonorrhoeae co-infection) was 8.1% (10/123), while that in patients -ve for *C. trachomatis* (with or without *N. gonorrhoeae* co-infection) was 2.4% (6/246). Furthermore, *M. genitalium* was not detected in any patient +ve for *N. gonorrhoeae* only. The study also found high rates of mutations conferring resistance to macrolides (25%) and fluoroquinolones (37.5%), with two-thirds of the resistant isolates demonstrating dual resistance. Resistance mutations were only in samples +ve for *C. trachomatis*.

IMPORTANCE IN CLINICAL PRACTICE

M. genitalium is infrequently diagnosed in Singapore and thus, very rarely specifically treated, whereas treatment (with single-dose azithromycin) of *C. trachomatis* is common. However, given (i) growing evidence that a 5-day course of macrolides is necessary for *M. genitalium* eradication; (ii) the high rate of macrolide resistance mutation in the local population; and, (iii) prevalence of *C. trachomatis* co-infection with *M. genitalium*, the conventional treatment of single-dose azithromycin may be non-curative with respect to *M. genitalium*, and could in fact be driving its resistance. The common association of *M. genitalium* with *C. trachomatis* also suggests that patients with the latter should be screened for the former, and that treatment of *C. trachomatis* should be undertaken with due consideration of the high antibiotic resistance rates of *M. genitalium*.

This summary was prepared by the editorial team of Medical Digest.



FEATURE

CLINICALLY-ASSISTED NUTRITION & HYDRATION IN PATIENTS LACKING MENTAL CAPACITY

“The body’s basic needs are food and water. If you don’t feed her, you are killing her – you are sinning.” In one fell swoop, my grandmother’s primary physician passed a statement directed at my aunt that altered the course of my grandmother’s illness trajectory.

The topic of Clinically-Assisted Nutrition and Hydration (CANH) often evokes strong emotions among clinicians, patients and their caregivers as there are often symbolic and ethical paradigms which we may find difficult to navigate. This article aims to provide a basic outline of different aspects clinicians should consider when

faced with the challenging scenario of deciding whether to initiate, maintain, withdraw or withhold CANH in patients with no Decision-Making Capacity (DMC).

DEFINITION

Clinically-Assisted Nutrition (CAN) can be delivered via enteral or parenteral routes (Figure 1). Clinically-Assisted Hydration (CAH) may be delivered via the enteral or parenteral (intra-venous or subcutaneous) routes (Figure 1). CAN and CAH carry unique risks and benefits that should be separately discussed for each individual.

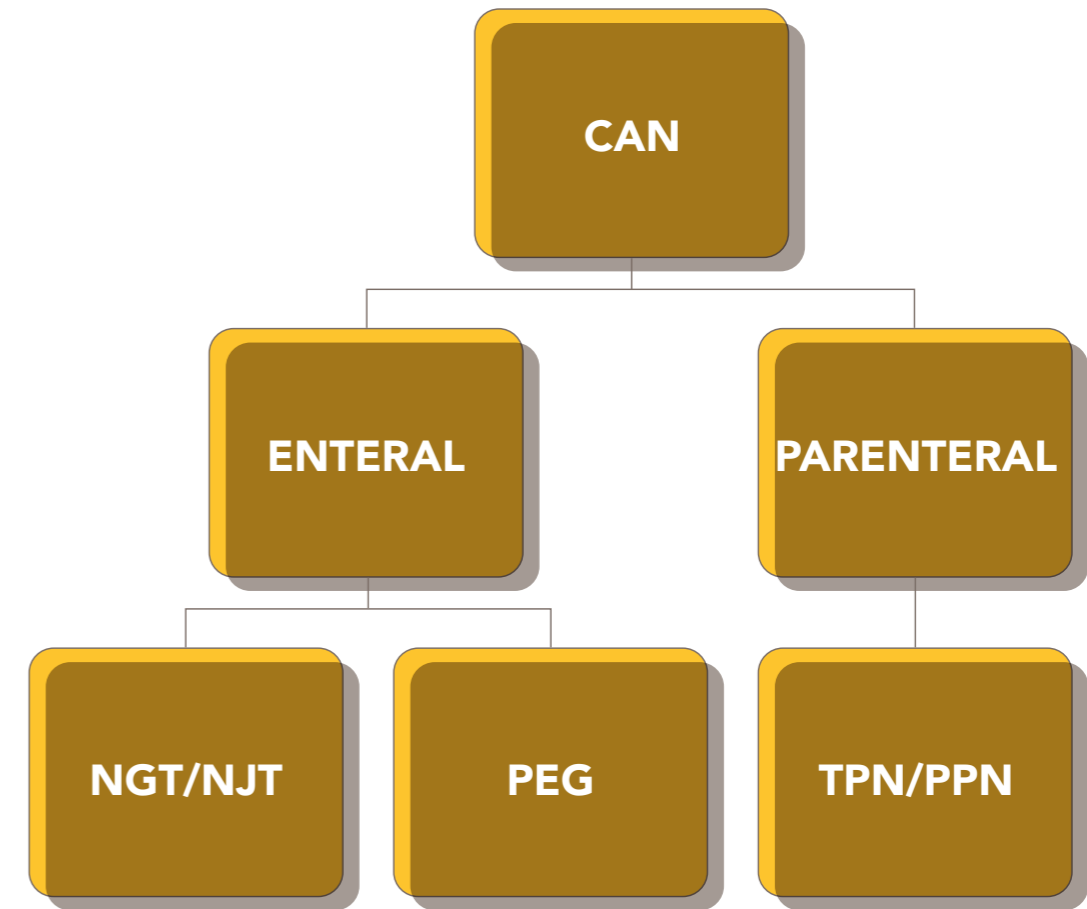


Figure 1. Overview of Clinically-Assisted Nutrition. Clinically-Assisted Nutrition, CAN; Nasogastric Tube, NGT; Nasojejunal Tube, NJT; Percutaneous Endoscopic Gastrostomy, PEG; Total Parenteral Nutrition, TPN; Peripheral Parenteral Nutrition, PPN.

WHEN THERE IS ANY CLINICAL DOUBT OR UNCERTAINTY, THE OPINION OF A SECOND CLINICIAN WHO HAS THE RELEVANT DOMAIN KNOWLEDGE AND EXPERIENCE IN MAKING BEST-INTEREST DECISIONS SHOULD BE CONSULTED ACCORDINGLY. A PERTINENT POINT TO HIGHLIGHT IS THAT ARTIFICIAL NUTRITION BY MEANS OF TUBE FEEDING SHOULD ONLY BE CONSIDERED WHEN THE OPTION OF NATURAL FOOD INTAKE HAS BEEN EXHAUSTED; IT SHOULD NEVER BE CONSIDERED AS A MEANS OF REDUCING ALLOCATION OF NURSING RESOURCES.

A. MEDICAL ASPECTS

Multiple medical conditions may lead to an individual being unable to eat or drink normally to fulfil his or her nutritional requirements. As a result, CANH may need to be instituted. Prior to this, the attending clinician has a responsibility to have a clear indication for medical treatment and to set realistic therapeutic goals. The decision to withhold or withdraw CANH should never be taken lightly, as the deprivation of CANH may drastically shorten the lifespan of an individual. However, unnecessarily continuing CANH can also lead to prolonged suffering in the terminal phase of a patient's journey. Given the consequences of these decisions, the multi-disciplinary clinical team should always make a scrupulous and meticulous assessment of every patient's unique circumstances (Figure 2).

When there is any clinical doubt or uncertainty, the opinion of a second clinician who has the relevant domain knowledge and experience in making best-interest decisions should be consulted accordingly. A pertinent point to highlight is that artificial nutrition by

means of tube feeding should only be considered when the option of natural food intake has been exhausted; it should never be considered as a means of reducing allocation of nursing resources.

Specific Clinical Situations

• **Neuro-degenerative Conditions (including Dementia)**

Ideally, once a patient is diagnosed with a neuro-degenerative condition, the relevant physician should begin engaging the patient in Advance Care Planning (ACP) which includes the discussion of whether he/she would want CANH to be initiated, maintained, withheld or withdrawn. In the early stage of diagnosis, while these conversations are often unsettling and challenging, it will provide much more clarity down the road for both the patient and his/her loved ones. For patients with advanced dementia, a Cochrane review found no conclusive evidence that enteral tube nutrition is effective in terms of prolonging survival, improving quality of life, or leading to better nourishment or decreasing the risk of pressure sores.¹ Current NICE (National Institute for Health and Care Excellence)

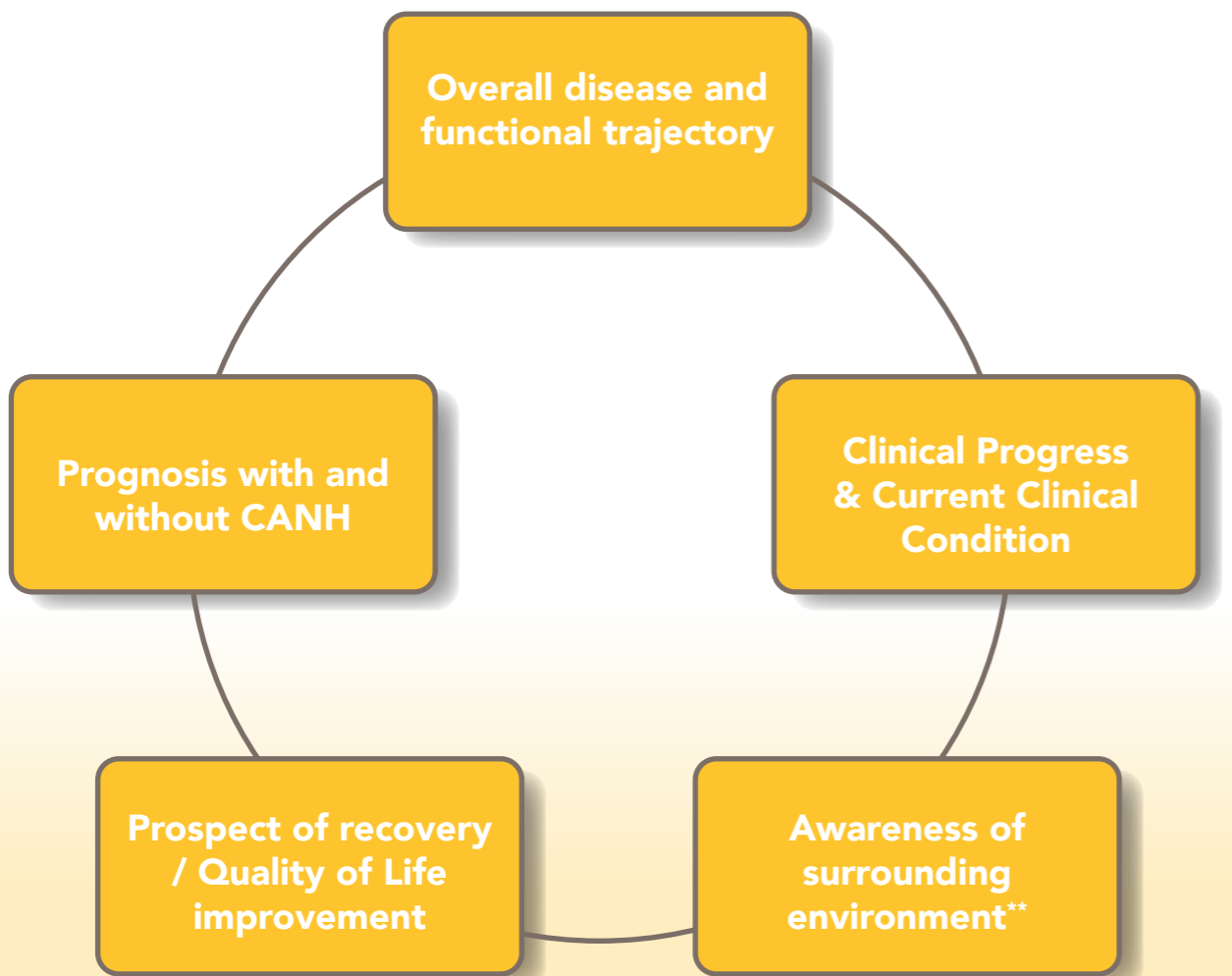


Figure 2. Clinical assessment of a patient's circumstances.

** This includes the patient's ability to experience pain (which should be appropriately managed) or pleasure.

Guidelines also do not advocate the routine use of feeding tubes in patient with advanced dementia; careful comfort feeding by hand is encouraged.² Feeding tubes are not without their adverse effects - their presence can cause discomfort, result in unnecessary use of restraints and, potentially worsen episodes of aspiration.³

• **Prolonged Disorder of Consciousness (PDOC) following sudden onset brain injury**

PDOC refers to a state of wakefulness where patients have absent or reduced awareness for more than 4 weeks. The spectrum of PDOC includes Minimally Conscious State (MCS) and Vegetative State (VS). The main distinction is that in MCS, the patient has awareness of his/her surroundings and may display some purposeful motor behaviour, whereas in VS, the patient only has a state of wakefulness without awareness.⁴ While recovery is often rare in patients with Chronic VS (no neurological recovery at least 3/12 post-insult), CANH should be provided until robust and repeated assessments have adequately established what the patient would have wanted, or prognosis has been acutely shortened from an acute event. BMA (British Medical Association) guidelines on CANH also recommend taking into account the patient's pre-existing co-morbidities which may render a patient frailer, and thus reduce their life expectancy.

• **Terminal Phase of a Life-Limiting Illness**

Death is a clearly defined event, but the end of life is

more appropriately seen as a journey. The terminal phase can loosely be defined as when death is clearly imminent, often occurring within short hours to days. Often, fluid and energy are not needed at this time, and there is no true hunger or thirst. Perceived thirst is usually caused by dryness of the oral cavity exacerbated by medications and oxygen therapy. This may be alleviated with good oral care (moistening lips and oral cavity) and provision of judicious amounts of fluids.³ When true dehydration contributes to delirium, anti-psychotics, anxiolytics and sedatives may be considered instead as the utility of artificial hydration in the dying phase has not been proven to provide clear benefits in the general population. In a large RCT involving hospice patients with advanced cancer, enteral hydration was shown to have no benefit in terms of improving survival or delirium, and instead worsened symptoms such as secretions and oedema at the end of life.⁵

B. ETHICAL ASPECTS

Figure 3 illustrates Jonsen's Four Box Model to guide ethical medical decision making.⁶

The model crystallises the four pillars of autonomy (A), beneficence (B), non-maleficence (NM) and justice (J) into an approach that can be easily applied to nearly all clinical ethical conundrums. This model can also be applied to patients who have DMC, or decisions not relating to CANH.

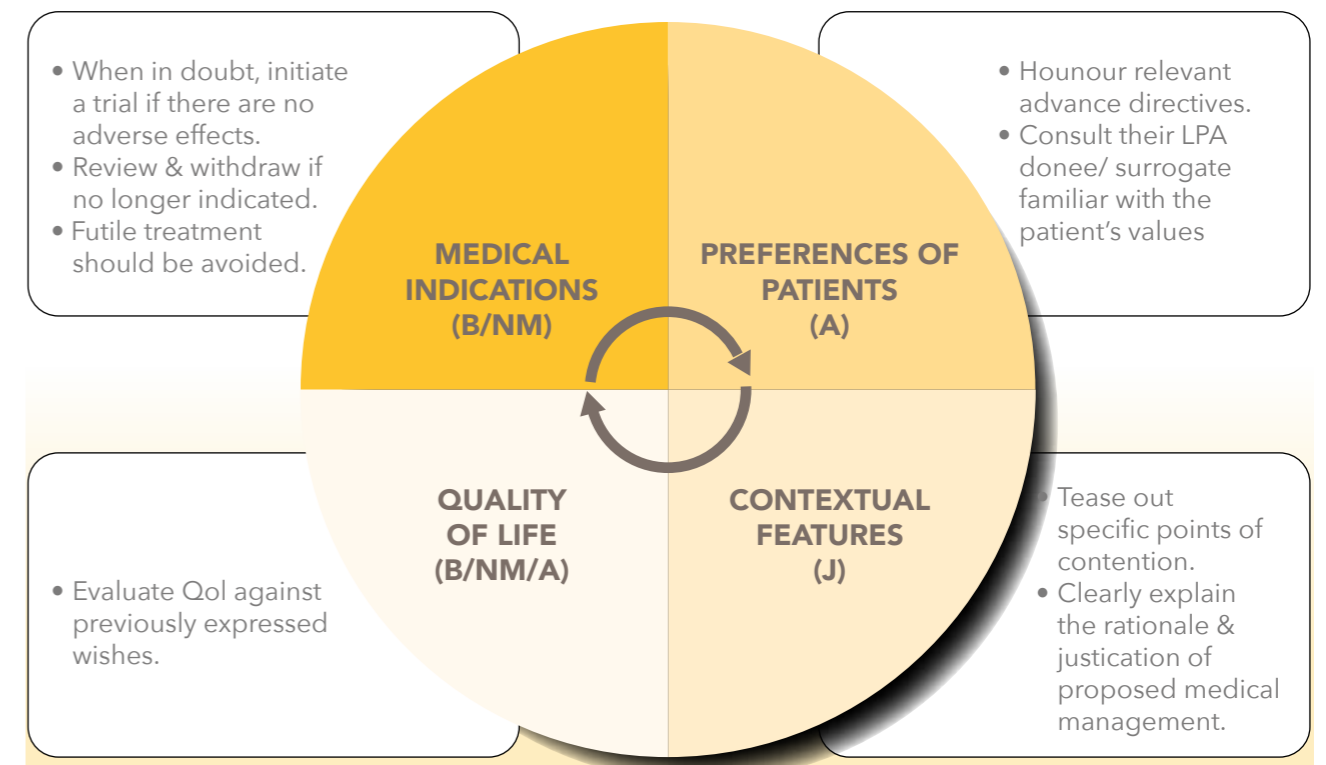


Figure 3. Jonsen's Four Box Model approach.

Autonomy, A; Beneficence, B; Non-maleficence, NM; Justice, J; LPA, Legal Power of Attorney.

Patient's Preferences (Autonomy)

When a patient has no DMC, a decision should be made on behalf of the patient based on the principle of what would be in the patient's best interests. To make a best-interests decision, it is imperative to review any previous advance directives. In the event of a lack of an advance directive, a surrogate can be consulted to better elucidate the patient's values and previously expressed preferences. If a patient has signed an advance directive such as an Advance Care Plan (ACP) to refuse CANH, the clinician should respect the patient's right to refuse treatment/ self-determination. However, there must be a critical assessment of documentation to ensure that the patient made an *informed decision* i.e. patient was adequately counselled with respect to the nature, indications, alternatives, associated risks and benefits of treatment options. The attending clinician must also ascertain that the *specific clinical scenario* which the patient is in is similar to the one discussed during the ACP discussion. The clinician should also ensure that there was no undue external coercion to make particular decisions. Conversely, if a patient had previously stated his/her preference for as much life-sustaining treatment as possible in an ACP or via his/her donee of a Lasting Power of Attorney (LPA), the team is only obliged to follow the patient's wishes within reasonable limits – if there are significant detrimental effects of CANH, it should be reduced or withdrawn.

Medical Interventions and Quality of Life (Beneficence and Non-maleficence)

As with any medical intervention, CANH has its risks and complications. Consequently, it should be instituted in accordance with the patient's wishes and a strong consideration of quality of life (QoL).

When the efficacy of CANH is in doubt, we should err on the side of preservation of life and CANH

can be instituted on a trial basis. Nevertheless, clinical justification should be continually reviewed; when the indication for CANH no longer exists, or complications related to CANH have surfaced, the clinician should be prepared to discuss the possibility of withdrawal of CANH with the patient's loved ones. In the event that CANH is to be stopped, it is standard of care to maintain the best possible QoL for the patient.

Contextual Features

Every patient's journey through life and our healthcare ecosystem is unique. This invariably influences their thinking and how they make decisions. It is crucial for the clinical team to engage a patient's loved ones to better understand the thought process behind their requests. While continuously engaging in these discussions can often be time-consuming and emotionally draining for the team, it is vital in helping our patients' caregivers and loved ones process their grief while witnessing their loved one decline physically. Illustrated below are two examples of common ethical dilemmas. While they have been intentionally simplified, oftentimes, other factors such as religious and health beliefs add different dimensions to decision-making, hence adding on even more complexity:

- i) *Disagreement between decision-makers and the medical team OR amongst decision-makers*: This is best handled with empathetic communication in relaying the rationale of the clinical team's treatment decisions. The team should also proactively engage and address concerns from the

IT IS PRUDENT THAT MEDICAL PERSONNEL ARE EDUCATED AND HAVE A HEALTHY UNDERSTANDING AND RESPECT OF PATIENTS' RELIGIOUS AND CULTURAL BACKGROUNDS AND BELIEFS THAT WILL INVARIABLY INFLUENCE THEIR DECISIONS AND ATTITUDES TOWARDS CANH. MEDICAL CARE PROVIDERS SHOULD ALSO BE CONSCIOUS OF THEIR OWN PERSONAL CULTURAL OR RELIGIOUS INCLINATIONS WHICH MAY INFLUENCE THEIR OPINIONS ON SUCH MATTERS, AND BE CAREFUL NOT TO IMPOSE THEM ON HIS/HER PATIENTS.

patient's loved ones as the lack of feeding is often associated with starvation or a lack of filial piety. In more challenging scenarios, an independent 2nd opinion can be sought.

- ii) *Voluntary refusal of fluid and nutrition in advanced dementia*: If a patient repeatedly attempts to remove a feeding tube or expresses refusal of essential nutrition, a decision for continuation or cessation of CANH should be made in accordance with his/her previous statements and life decisions. While there is strong consensus that providing nutrition against the will of a patient is generally prohibited, the challenge arises when the patient has no DMC and family members are visibly distressed by their loved one's food refusal. Education about the clinical trajectory of dementia, and the methods and benefits of careful hand-feeding often helps caregivers feel more assured with the decision not to initiate CANH.

C. LEGAL ASPECTS

In England and Wales, current BMA guidelines view the administration of CANH as a form of medical intervention. As such, court approval is not required to withdraw CANH in patients who

have been established to have no DMC, as long as there is a consensus on what is in the patient's best interests, and that professional guidelines have been adhered to. Historically, most cases that have gone to court to obtain permission to withdraw CANH revolved around patients in a chronic VS / MCS. In the local context, there has been no legal precedence to guide us, but the decision-making process should be made clearly documented and reviewed as needed (Figures 2 and 3).

D. CULTURAL / RELIGIOUS ASPECTS

In some cultures and religions which do not consider

CANH as a form of medical intervention but a basic necessity, withdrawal can sometimes only be done if the patient is at the end of life and has provided explicit wishes to end artificial hydration and nutrition. It is prudent that medical personnel are educated and have a healthy understanding and respect of patients' religious and cultural backgrounds and beliefs that will invariably influence their decisions and attitudes towards CANH. Medical care providers should also be conscious of their own personal cultural or religious inclinations which may influence their opinions on such matters, and be careful not to impose them on his/her patients.

SUMMARY

- ❖ CANH is widely recognized as a form of medical therapy from an ethical and legal standpoint.
- ❖ The attending clinician has the duty to consider the clinical indications of initiating, sustaining, withholding or withdrawing CANH in the context of the patient's previously expressed wishes (autonomy) and current QoL (beneficence / non-maleficence).
- ❖ Withdrawal of CANH should not translate to a withdrawal of comfort measures – consistent and empathetic communication about treatment decisions go a long way in making our patients' loved ones feel supported and comfortable with our recommendations.

Adapted from:

1. Druml C, Ballmer PE, Druml W, et al. ESPEN Guideline on Ethical Aspects of Artificial Nutrition and Hydration. *Clin Nutr*. 2016; 35 (3): 545 – 556. DOI: 10.1016/j.clnu.2016.02.006.
2. British Medical Association (2018). *Clinically-assisted nutrition and hydration and Adults who lack the capacity to consent: Guidance for decision-making in England and Wales*.

REFERENCES

1. Sampson EL, Candy B, Jones L. Enteral tube feeding for older people with advanced dementia. *Cochrane Database Syst Rev*. 2009; 2009 (2): CD007209. DOI: 10.1002/14651858.CD007209.pub2.
2. NICE (2018). *National Enteral (tube) feeding for people living with severe dementia – Decision aid: User guide and data sources*. Available from: <https://www.nice.org.uk/guidance/ng97/resources/enteral-tube-feeding-for-people-living-with-severe-dementia-user-guide-and-data-sources-pdf-4852697008>.
3. Li I. Feeding tubes in patients with severe dementia. *Am Fam Physician* 2002; 65 (8): 1605-1610, 1515.
4. Royal College of Physicians (2020). *Prolonged disorders of consciousness following sudden onset brain injury: National Clinical Guidelines*.
5. Bruera E, Hui D, Dalal S, et al. Parenteral hydration in patients with advanced cancer: a multicenter, double-blind, placebo-controlled randomized trial. *J Clin Oncol*. 2013; 31 (1): 111-118.
6. Jonsen AR, Siegler M, Winslade WJ (2015). *Clinical Ethics: A Practical Approach to Ethical Decisions in Clinical Medicine* (8th edition). McGraw-Hill Education, New York, USA.

DR LYNN WIRYASAPUTRA

is a Resident Physician (Integrative & Community Care) in the Department of Palliative Medicine, Tan Tock Seng Hospital.





FEATURE

CANCER REHABILITATION — ARE WE DOING ENOUGH?

INTRODUCTION

The word “cancer” may provoke emotional reactions that include fear, anxiety and sadness. Today, however, most cancer survivors can expect to pass the 5-year mark.^{1,2} To quote Lynn Gerber, MD, cancer has been transformed from “an acute lethal illness” to “a complex, chronic and common disorder.”³

Cancer rehabilitation aims to allow the patient to achieve optimal physical, social, physiological and vocational functioning within the limits imposed by the disease and its treatment.⁴ It is not too different from rehabilitation in other chronic conditions where the patient may experience a life changing event (e.g. stroke, amputation, etc.) resulting in a new impairment and therefore, leading to a need for rehabilitation interventions in order to improve function and quality of life. However, there are some important differences in rehabilitation for cancer patients. In some situations, rehabilitation takes place even in the setting of ongoing treatment. There is also the issue of prognostic uncertainty, secondary cancers, and sometimes even death. Given the challenges mentioned, together with high costs of treatment, rehabilitation in this group of patients have in the past tended to be very conservative or even avoided. However, with the increasing number of cancer survivors due in part to an aging population, there is now an emerging need to address the physical, cognitive and emotional sequelae after lifesaving treatments.¹

A PATIENT-CENTRED APPROACH WITH AN INDIVIDUALISED REHABILITATION PLAN MAY NEED TO BE DEVELOPED FOR EACH CANCER SURVIVOR. THIS IS BEST ACCOMPLISHED BY AN INTERDISCIPLINARY REHABILITATION TEAM WITH EXPERTISE IN PHYSIOTHERAPY, OCCUPATIONAL THERAPY, EXERCISE PHYSIOLOGY, PSYCHOLOGY, SPEECH LANGUAGE PATHOLOGY, NUTRITION AND, PHYSICAL MEDICINE AND REHABILITATION (PM&R), TO NAME A FEW.

IMPACT OF CANCER TREATMENT

There are several unique medical scenarios for rehabilitation professionals to navigate when treating cancer patients, for example, radiation and chemotherapy effects and how these impact upon function, chronic immunocompromised states, bony precautions in bone metastases, and bone fragility. Site specific rehabilitation strategies (e.g. Lymphedema and concomitant shoulder rehabilitation in breast cancer,

amputee rehabilitation in lower limb sarcoma patients) would have to be considered during every patient assessment. To further add to the complexity, there are many less recognized effects of cancer treatment such as myalgias, arthralgias, psychosocial and emotional dysfunction, as well as long term and late effects such as persistent fatigue and cognitive deficits.^{5,6} Research suggests that survivors are not prepared to manage many of the late and long-term chronic effects that arise as a result of treatment of cancer.⁷ These challenges line the long road to recovery, resulting in a daunting rehabilitation process for patients and their caregivers especially.

A patient-centred approach with an individualised rehabilitation plan may need to be developed for each cancer survivor. This is best accomplished by an interdisciplinary rehabilitation team with expertise in physiotherapy, occupational therapy, exercise physiology, psychology, speech language pathology, nutrition and, physical medicine and rehabilitation (PM&R), to name a few.

STRATEGIES AND PARADIGMS IN CANCER REHABILITATION

The concept of cancer rehabilitation is still relatively young compared to other more established disciplines. One of the first oncology rehabilitation programs was started in the 1960s in New York, USA, and the principles that guided their practice remain relevant today. Dietz, one of the pioneers in this field working at Memorial-Sloan Kettering Cancer Center then, classified cancer rehabilitation according to 4 categories:⁸

1. **Preventative:** Interventions that will lessen the effect of expected disabilities.
2. **Restorative:** Interventions that attempt to return patients to previous levels of physical, psychological, social, and vocational functioning.
3. **Supportive:** Interventions designed to teach patients to accommodate their disabilities and to minimize debilitating changes from ongoing disease.
4. **Palliative:** Interventions focused on minimizing or eliminating complications, and providing comfort and support.

While Dietz was insightful in his description, practical applications have not been straightforward. Rehabilitation programs in Singapore have been largely skewed towards restorative and supportive components, with lesser emphasis on preventative (‘prehabilitation’) and palliative aspects. Many rehabilitation programs in the various restructured hospitals in Singapore only take place after completion of treatment, with referrals initiated by the managing oncologist or surgeon. Common reasons for referral include weakness and deconditioning, lymphedema, breathing difficulties and peripheral neuropathy, with the resulting rehabilitation program focussed only on the impairment referred for.

It is important to recognise that some patients (such as the elderly and frail) have a lower baseline of fitness

and poorer reserves, and therefore will take much longer to recover compared to fitter patients. The rate of loss of fitness in this group of patients will also be higher than in other groups post-treatment (e.g. surgery, radiation, chemotherapy). By building up fitness and the physiological reserves of such patients even before treatment has commenced, patients will hopefully be better able to tolerate stresses associated with treatment and recover better, moving themselves up to pre-frail or even fit levels (Figure 1).

interventions to improve fitness in the pre-treatment/pre-surgical phase.^{11,12} Akin to undergoing training prior to running a marathon, the aim is to increase functional reserves so as to achieve better post-treatment functional recovery and reduced incidence of complications (Figure 1). The benefits of prehabilitation can be seen in as little as 2 weeks.¹³

For most patients undergoing a prehabilitation program, the benefits can include reduced length of stay, reduced

treatment with poorer aerobic fitness and muscle quality than when they began.²⁰ For this reason alone, education and/or prescriptive counselling on progressive aerobic conditioning, resistance training and, the benefits of exercise in general, should be integral to any cancer survivorship/rehabilitation program.

The evidence supporting exercise in cancer patients has been gradually growing and now, it can be considered as part of standard of care. Most studies describe exercise

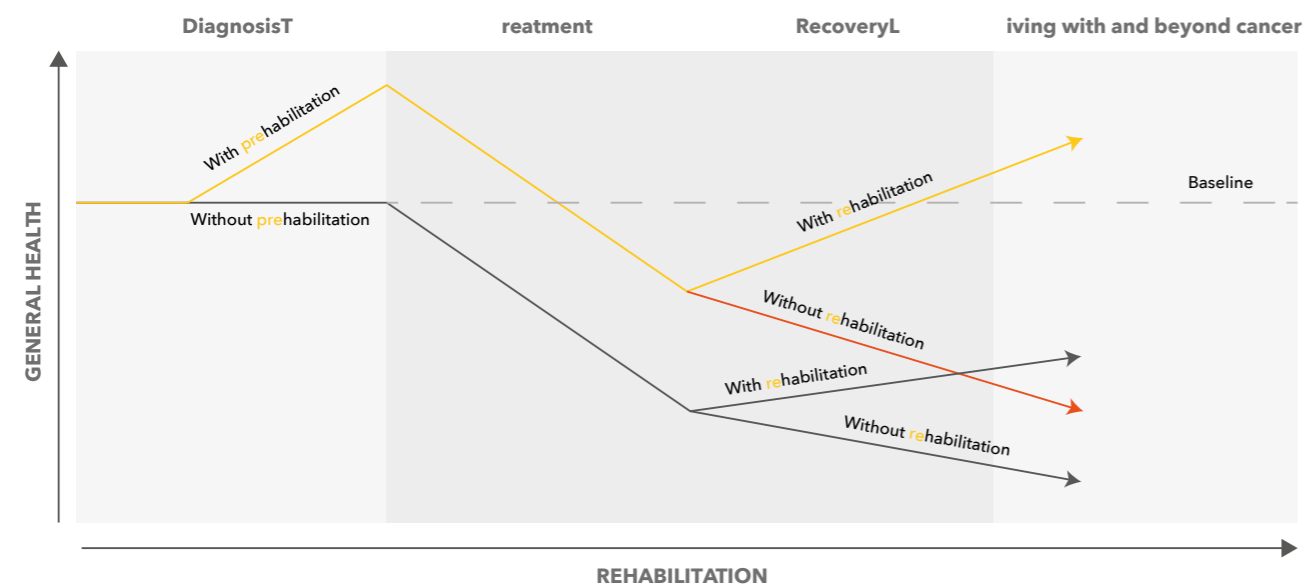


Figure 1. Relationship between prehabilitation and rehabilitation, and the proposed differences in outcome.¹⁹

Some common difficulties with prehabilitation include pain associated with exercise, financial burden associated with logistics, and a fixed negative mindset to physical activity. Despite these obstacles, it is becoming clear that better patient outcomes can only be achieved with a holistic approach that incorporates elements of prehabilitation and exercise.

Prehabilitation

While prehabilitation is fairly established in cardiovascular and thoracic surgery, there is also increasing research to support the idea of prehabilitation as an important part of the continuum in a cancer rehabilitation program.^{9,10} The concept involves physical, nutritional and psychosocial

post-treatment complications, improved cardiorespiratory fitness, and enhanced quality of life.¹⁴⁻¹⁷ Symptom-wise, prehabilitation has been shown to help maximise the outcomes of rehabilitation and minimise side effects of treatment such as fatigue and breathlessness. One of the earliest prehabilitation programs in Singapore was piloted by Khoo Teck Puat Hospital's Division of General Surgery in 2007, mainly in the colorectal surgery population. Their program described generally good outcomes with respect to functional recovery, complication and mortality rates.¹⁸

Exercise

In the absence of any cancer-specific morbidity, virtually all survivors of cancer emerge from their cancer

programs after cancer treatment, but there is sufficient evidence to show that exercise provides benefits in quality of life and muscular and aerobic fitness for people with cancer both during and after treatment, and that it does not cause harm.²¹

Many studies have described improvements in survival, quality of life and reduction in cancer-associated symptoms (e.g. fatigue, pain, constipation, dyspnea, weight loss, insomnia).²²⁻²⁴ In a review article, Ferioli et al. described the evidence-based benefits of different aspects of exercise on common cancer-related symptoms (Table 1).²²

Exercise and physical activity are two distinct entities. As defined by

Table 1. Physical exercises and their reduction of cancer-related symptoms.

| | Aerobic exercise | Resistance exercise | Strength exercise | Weight and impact exercise | Balance | Flexibility and relaxation exercise |
|---------------------------------|------------------|---------------------|-------------------|----------------------------|---------|-------------------------------------|
| PHYSICAL | | | | | | |
| Bone loss/disease | | • | | • | | |
| Muscle and fat mass dysfunction | • | | • | | | |
| Cachexia | • | • | | | | |
| Peripheral Neuropathy | | | • | | • | |
| Lymphedema | | • | | | | |
| PSYCHOSOCIAL | | | | | | |
| Pain | • | | | | | |
| Fatigue | • | • | • | | | • |
| Sleep disorder | • | | | | | • |
| PSYCHOLOGICAL | | | | | | |
| Depression, anxiety | • | | | | | |
| Quality of life | • | • | • | | | • |
| Self esteem | | • | | | | |

Adapted from Ferioli et al.²²

the World Health Organization, physical activity is any movement by the musculoskeletal system resulting in energy expenditure. Exercise is a planned, structured, and repetitive physical activity that has a purpose. It is common to hear from patients about their daily "exercise", which consists of walking to the market or to work. While their physical activity is likely to contribute

to some degree of reconditioning, most of the time, the intensity at which the activity is carried out is lacking; this brings us to the topic of exercise prescription in cancer patients.

Numerous guidelines exist and, utilising "FITT" [Frequency, Intensity, Type and Time (or, duration)], most of them recommend an end goal of 150 minutes of moderate to vigorous intensity exercise over 3-5 days, and at least 2 days of resistance exercise every week.^{21,25} The resistance exercise session should involve 2 sets of 8-10 major muscle groups repeated 8-10 times. Flexibility exercises should also include all major muscle groups, and balance exercises should be included for all elderly patients and for those who have balance difficulties (e.g. chemotherapy-induced neuropathy). Intuitively, more deconditioned patients should start with lower targets and increase accordingly.

Exercise programs in a supervised or group setting have many benefits, and are found to be superior in improving quality of life, fatigue, and muscular strength, compared to an individual exercising alone. These programs provide the right motivation, proper exercise technique, and a safe environment to exercise.²¹ In TTSH, the exercise program for oncology patients is conducted by a trained exercise physiologist, and takes

IN THE ABSENCE OF ANY CANCER-SPECIFIC MORBIDITY, VIRTUALLY ALL SURVIVORS OF CANCER EMERGE FROM THEIR CANCER TREATMENT WITH POORER AEROBIC FITNESS AND MUSCLE QUALITY THAN WHEN THEY BEGAN.²⁰ FOR THIS REASON ALONE, EDUCATION AND/OR PRESCRIPTIVE COUNSELLING ON PROGRESSIVE AEROBIC CONDITIONING, RESISTANCE TRAINING AND, THE BENEFITS OF EXERCISE IN GENERAL, SHOULD BE INTEGRAL TO ANY CANCER SURVIVORSHIP/REHABILITATION PROGRAM.



EXERCISE PROGRAMS IN A SUPERVISED OR GROUP SETTING HAVE MANY BENEFITS, AND ARE FOUND TO BE SUPERIOR IN IMPROVING QUALITY OF LIFE, FATIGUE, AND MUSCULAR STRENGTH, COMPARED TO AN INDIVIDUAL EXERCISING ALONE. THESE PROGRAMS PROVIDE THE RIGHT MOTIVATION, PROPER EXERCISE TECHNIQUE, AND A SAFE ENVIRONMENT TO EXERCISE.

place weekly over a period of 2-3 months. It is recommended for pre-exercise assessments to include the patient's general condition and special considerations (e.g. lymphedema, peripheral neuropathy, cardiovascular risk, musculoskeletal morbidities, cardiac issues, and special situations such as central lines, ostomies, or breast reconstruction). Patients with ongoing cancer-related complications (e.g. bone metastases) should be reviewed by an oncology rehabilitation specialist prior to commencement of exercise.²⁶

CONCLUSION

Rehabilitation in the cancer population is not too different from rehabilitation in other chronic conditions, where the patient may experience a life-changing event resulting in a new impairment. This leads to a need for rehabilitation interventions in order to improve function and quality of life. While the components for a successful cancer rehabilitation program exist within Singapore's healthcare system, there is currently a lack of synchrony between local clinical practice and the recommendations set by guidelines.

Firstly, there are clear pathways for rehabilitation interventions, including inpatient admission for functional decline because of injury, neurologic, degenerative, and other function-altering disorders. However, if a decline in functional status is caused by the effects of cancer or its treatment, then the likelihood of referral for rehabilitation is reduced.²⁷ This is also a common scenario overseas e.g. in the United States, patients with metastatic breast cancer

who have difficulty ambulating may not be referred to rehabilitation services.²⁸

Secondly, we observe that currently, rehabilitation takes place mainly after treatment and is often initiated for specific impairments/symptoms (e.g. lymphedema in breast cancer). However, other aspects such as prehabilitation, exercise, fatigue management and diet are neither evaluated nor optimised. Often, residual impairments like peripheral neuropathy lead to diminished function; however, therapy services are not sought. Common reasons include lack of awareness, financial difficulties, acceptance of "the new normal".²⁹

In order not to "miss" out on common impairments, cancer survivorship practitioners recommend an impairment-driven cancer rehabilitation model that includes screening and treating impairments all along the care continuum so as to minimize disability and maximize quality of life.³⁰

Finally, oncology care has made rapid progress in many areas, including screening and treatment. Oncology patients now have better access to life-saving treatment, and also benefit from earlier disease identification. However, for high-quality cancer care to be achieved, further improvements in the area of rehabilitation need to be made. To reduce morbidity and health care costs associated with cancer and disability, oncology-related endeavours and programs should, where possible, include a plan for rehabilitation.

REFERENCES

1. National Registry of Diseases Office (2017). Singapore Cancer Registry Annual Registry Report 2015. Available from: https://www.nrdo.gov.sg/docs/librariesprovider3/Publications-Cancer/cancer-registry-annual-report-2015_web.pdf?sfvrsn=10. Accessed on: 03 August 2020.
2. Rowland JH, Hewitt M, Ganz PA. Cancer survivorship: a new challenge in delivering quality cancer care. *J Clin Oncol*. 2006; 24 (32): 5101-5104.
3. Gerber LH. Foreword. In: Stubblefield M, O'Dell MW (2009). *Cancer Rehabilitation: Principles and Practices*. Demos Medical Publishing, LLC, New York, USA.
4. Cromes GJ. Implementation of interdisciplinary cancer rehabilitation. *Rehabil Counseling Bull*. 1978; 21: 230-237.
5. Holland JC, Weiss TR, Stiles J. Depression, anxiety and psychosocial dysfunction in the cancer patient; pp 841-854. In: Stubblefield M, O'Dell MW (2009). *Cancer Rehabilitation: Principles and Practices*. Demos Medical Publishing, LLC, New York, USA.
6. Institute of Medicine and National Research Council of the National Academies (2006). *From cancer patient to cancer survivor: lost in transition*. The National Academies Press, Washington DC, USA.
7. Aziz NM. Cancer survivorship research: challenge and opportunity. *J Nutr*. 2002; 132 (11 Suppl): 3494S-503S.
8. Dietz Jr JH. Rehabilitation of the cancer patient. *Med Clin North Am*. 1969; 53 (3): 607-624.
9. Asoh T, Tsuji H. Preoperative physical training for cardiac patients requiring non-cardiac surgery. *Jpn J Surg* 1981;11: 251-255.
10. van Adrichem EJ, Meulenbroek RL, Plukker JT, et al. Comparison of two preoperative inspiratory muscle training programs to prevent pulmonary complications in patients undergoing esophagectomy: a randomized controlled pilot study. *Ann Surg Oncol*. 2014; 21: 2353-2360.
11. Kabata P, Jastrzębski T, Kąkol M, et al. Preoperative nutritional support in cancer patients with no clinical signs of malnutrition--prospective randomized controlled trial. *Support Care Cancer* 2015; 23 (2): 365-370.
12. Silver JK, Baima J, Mayer RS. Impairment driven cancer rehabilitation: an essential component of quality care and survivorship. *CA Cancer J Clin*. 2013; 63 (5): 295-317.
13. Faithfull S, Turner L, Poole K, et al. Prehabilitation for adults diagnosed with cancer: A systematic review of long-term physical function, nutrition and patient-reported outcomes. *Eur J Cancer Care* 2019; e13023.
14. Rodriguez-Larrad A, Lascurain-Aguirrebena I, Abecia-Inchaurregui LC, et al. Perioperative physiotherapy in patients undergoing lung cancer resection. *Interactive Cardiovascular and Thoracic Surgery* 2014; 19 (2): 269-281.
15. Moran J, Guinan E, McCormick P, et al. The ability of prehabilitation to influence postoperative outcome after intra-abdominal operation: A systematic review and meta-analysis. *Surgery* 2016; 160 (5): 1189-1201.
16. Crandall K, Maguire R, Campbell A, et al. Exercise intervention for patients surgically treated for Non-Small Cell Lung Cancer (NSCLC): A systematic review. *Surg Oncol*. 2014; 23 (1): 17-30.
17. Hoon LS, Sally CWC, Hong-Gu H. Effect of psychosocial interventions on outcomes of patients with colorectal cancer: A review of the literature. *European Journal of Oncology Nursing* 2013; 17 (6): 883-891.
18. Wang Z, Tan KY, Tan P. Functional outcomes in elderly adults who have undergone major colorectal surgery. *J Am Geriatr Soc* 2013; 61: 2249-2250.
19. Macmillan Cancer Support, National Institute for Health Research and Nutrition, and the Royal College of Anaesthetists (2019). *Prehabilitation for people with cancer: Principles and guidance for prehabilitation within the management and support of people with cancer*. Available from: https://www.macmillan.org.uk/_images/prehabilitation-guidance-for-people-with-cancer_tcm9-353994.pdf. Accessed on: 03 August 2020.
20. Segal R, Zwaal C, Green E, et al. Exercise for people with cancer: a clinical practice guideline. *Curr Oncol*. 2017; 24: 40-46.
21. Ferioli M, Zauli G, Martelli AM, et al. Impact of physical exercise in cancer survivors during and after antineoplastic treatments. *Oncotarget* 2018; 9 (17): 14005-14034.
22. Schwartz AL, de Heer HD, Bea JW. Initiating Exercise Interventions to Promote Wellness in Cancer Patients and Survivors. *Oncology (Williston Park)* 2017; 31 (10): 711-717.
23. Gerritsen JK, Vincent AJ. Exercise improves quality of life in patients with cancer: a systematic review and meta-analysis of randomised controlled trials. *Br J Sports Med*. 2016; 50: 796-803.
24. Campbell KL, Winters-Stone KM, Wiskemann J, et al. Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable. *Med Sci Sports Exerc*. 2019; 51 (11): 2375-2390.
25. Gilchrist SC, Barac A, Ades PA, et al. Cardio-Oncology Rehabilitation to Manage Cardiovascular Outcomes in Cancer Patients and Survivors: A Scientific Statement from the American Heart Association. *Circulation* 2019; 139: e997-e1012.
26. Loh KW, Ng T, Choo SP, et al. Cancer Supportive and Survivorship Care in Singapore: Current Challenges and Future Outlook. *J Glob Oncol*. 2018; 4: JGO.17.00117. DOI: 10.1200/JGO.17.00117.
27. Cheville AL, Troxel AB, Basford JR, et al. Prevalence and treatment patterns of physical impairments in patients with metastatic breast cancer. *J Clin Oncol*. 2008; 26: 2621-2629.
28. Yang EJ, Chung SH, Jeon JY, et al. Current Practice and Barriers in Cancer Rehabilitation: Perspectives of Korean Physiatrists. *Cancer Res Treat*. 2015; 47 (3): 370-378.
29. Silver JK, Baima J, Mayer RS. Impairment-driven cancer rehabilitation: An essential component of quality care and survivorship. *CA Cancer J Clin*. 2013; 63 (5): 295-317.



DR WONG CHIN JUNG

is a Consultant (Integrative & Community Care) in the Department of Rehabilitation Medicine, Tan Tock Seng Hospital.

FEATURE

FLOWING ALONG THE RIVER OF LIFE IN CENTRAL HEALTH



LIFE IS LIKE A RIVER – ALWAYS MOVING, ALWAYS FLOWING. WE HAVE TO MOVE WITH IT, LIVE WITH IT, COME WHAT MAY.



Figure 1. NHG's population health framework, "River of Life", guides its evolving approach to health. It encapsulates NHG's ongoing transformation from care provider (providing episodic care and treating illnesses) to care partner (fostering the holistic health of the population).

Recognising the need to foster the holistic health of the population beyond simply treating illnesses, the National Healthcare Group (NHG) has devised a population health framework, "River of Life", as part of its evolving approach to health — helping people live well at every stage of their lives, from beginning to end (Figure 1). The River of Life (ROL) framework, which includes physical, mental and social dimensions, addresses care needs in 5 segments:

- LIVING WELL
- LIVING WITH ILLNESS
- CRISIS AND COMPLEX CARE
- LIVING WITH FRAILTY
- LEAVING WELL

In this feature, we will share some of the key community health programmes initiated by Central Health, how they tie in with the ROL framework, and how community health partners have contributed, or can further contribute, towards caring for our population.



Table 1. Activities and programmes conducted by Health Coaches.

| Screening Events | Health Coaching & Monitoring @ Community Health Posts | Mass Activities @ Community Health Posts | Structured Programmes @ Community Partner Site(s) |
|---------------------------|---|---|---|
| Chronic Illness Screening | Coaching on diet and lifestyle changes | Be Active! • Health Talk • Mass Exercises | Strong (Frailty) • Rolling with Wellness • Stronger Joints, Steadier You! |
| Functional Screening | Monitoring of blood pressure, blood glucose level and weight management | Cooking Workshops | Lean (Metabolic Syndrome) • Walking Foodpedia • Make it "Siew Dai" |
| Falls Screening | | | |
| Nutrition Screening | | | |

LIVING WELL, WITH PREVENTIVE CARE

Studies have shown that early life health choices can affect health in later life – poor health choices and adverse conditions can have deleterious impacts as we age, affecting us as individuals and also, as a society. Healthcare has long been evolving from just treating illnesses, towards including preventive strategies, and this has yielded positive dividends. **Living Well** focuses not only on prevention, but encourages a ‘culture of health ownership’, engaging the population as agents of their own health.

Focusing on *Lean and Strong* as the key priorities for preventive care, Central Health looks into the development and delivery of a range of programmes that impart knowledge and practical skills that participants can incorporate into their daily lives, with the aim of encouraging behavioural changes which:

- Encourage maintenance of healthy lifestyles and prevent onset of metabolic syndrome or delay frailty;
- Delay the onset of complications for those newly diagnosed with metabolic syndrome or who are at the early stages of frailty; and,
- Manage complications and delay disability for those with more complex issues relating to metabolic syndrome and frailty.

Health Coaches, part of TTSH’s Community Health Teams (CHTs), encourage healthier active living in residents through these programmes (Table 1). CHTs offer personalised guidance and set personalized care goals based on what matters to the participants, thereafter motivating participants to make sustainable lifestyle changes through exercise and diet (Figure 2). Interaction among participants during these activities also encourages the building and strengthening of peer support groups, further contributing toward the goal of activating the community to not just look after themselves, but their peers and the community as well.



Figure 2. NHG’s Health Coach sharing about the various services available at Community Health Posts (CHPs) to participants at a community partner’s event.



LIVING WITH ILLNESS, WITH PRIMARY CARE

With our rapidly ageing population and sedentary lifestyles, coupled with the consequent rise in incidences of chronic diseases, the role of primary care in the community is expanding.

TTSH’s Primary Care Partners Office (PCPO), with the support of primary care partners such as General Practitioners (GPs), Primary Care Networks (PCNs), Family Medicine Clinics (FMCs) and Polyclinics, has developed a suite of partnership initiatives to foster better collaboration for seamless, affordable and accessible care for patients; facilitating proactive management of chronic conditions; providing care for residents that is closer to home; and, supporting the Nation’s Vision of “One Singaporean, One Family Doctor” (Figure 3).

Community Right-Siting Programme (CRiSP)

The Community Right-Siting Programme allows patients with stable chronic conditions to be discharged and managed closer to home, either by Family Physicians or GPs in the community. GP partners are empowered to provide quality care, through clinical up-skilling, and have access to affordable clinical support services including medication, diagnostic-testing, and community health services from our partners - NHG Pharmacies, NHG Diagnostics and, Community Health Centres (CHCs).



Figure 3. TTSH’s Primary Care Partners Office (PCPO) team led by A/Prof David Foo (Clinical Lead, Primary Care) with the close support of Right-Siting Officers and Community Operations Team (Primary Care).

To ensure patients' smooth transition into primary care, a team of Right-Siting Officers (RSOs) serve as a vital point of contact between specialist outpatient clinics (SOCs), GPs and patients. RSOs provide essential financial counselling and patient education to patients, enabling patients to make informed decisions pertaining to their follow-up care in the community. As patients' case managers, RSOs are able to track patients' post-discharge health outcomes; as GPs' aides, RSOs connect with TTSH specialists for case discussions and enquiries.

Since CRiSP's official launch in 2014, 3,700 patients across 36 chronic conditions and at more than 140 GP partner clinics have benefitted from being right-sited to primary care, and these achievements are set to grow.

TTSH Community Right-Siting Programme - Shared Care

Initiated in April 2017 as an extension of CRiSP, the TTSH Shared Care Programme enables the co-management of moderately-stable to stable patients by SOC's and primary care, through the facilitation of care coordination across these healthcare settings. By developing co-management care protocols and channels of communication, the specialist and primary care provider can effectively share care management for the patient in 9 conditions (including diabetes, hypertension, asthma, chronic obstructive pulmonary disease (COPD), and rheumatoid arthritis).

Shared Care is envisioned to be expanded to the GP network through further leveraging on CRiSP's infrastructure, overcoming limitations including those faced in clinical notes-sharing.

GPNext

GPNext recognises the pivotal role hospital partners play in ensuring the continuum of care for patients' post-emergency treatment. Under GPNext, patients who visit the Emergency Department (ED) but are assessed to be stable, and with minor or low-complexity conditions, can be referred to partner GPs. By reducing referrals from ED to SOC's for such patients, GPNext increases resource-utilisation efficiency and also ensures more appropriate care management for these patients by our primary care partners.

Currently, 15 GPNext conditions (including urinary tract infection (UTI), abdominal pain, low back pain, dizziness, upper respiratory tract infection (URTI) and, the most recent addition of toe fracture) can be referred to a partner GP for follow-up treatment. The number of GPNext conditions is slated to increase to 18 in the following months, with the addition of acute dyspepsia, heartburn and gastroenteritis. Instead of waiting for an unnecessary follow-up with the specialist, patients will instead obtain the care they need within a week from the GP.

Coordinating & Advisory Care Team (CoACT)

To enable these community-based primary care initiatives, there is an evident need for effective communication between the hospital and primary care partners. Thus, together with administrators and RSOs from PCPO, the Coordinating & Advisory Care Team (CoACT) acts as a point of liaison with primary care partners.

CoACT, which is a team comprising specialists from 20 clinical specialties, communicates with specialists through dedicated email and phone channels to discuss care paths of patients who have been 'discharged' from SOC's. This way, the hospital provides the GP with administrative and clinical support, allowing both specialists and GPs to discuss care management plans for the patient. Such collaboration ensures positive health outcomes for the patient.



To find out more about our partnerships, or if you are interested to join us as a GP partner, email us at gp@ttsh.com.sg.



Figure 4. TTSH's Community Nurse conducting basic medication reconciliation with a resident at a Community Health Post (CHP) in Novena-Kallang-Rochor (Top). Functional Assessment for a resident at a CHP in Ang Mo Kio (Left). A mass exercise session led by TTSH's Health Coach at a CHP in Novena-Kallang-Rochor (Right).

AGEING IN PLACE

Ageing in Place, with Community Care by Community Health Teams

To support our seniors in managing their chronic conditions well at home, it is important for health teams to be anchored in the community.

Within each subzone of Central Health, there is a designated Community Health Team (CHT) which plays a major role in coordinating care, building relationships and enabling health engagement with social care partners to support ageing-in-place. CHTs support and empower residents and their caregivers to better care for themselves in the community, through the efforts of a multi-disciplinary care team (including Doctors, Nurses, Health Coaches, Pharmacists and Allied Health Professionals), in collaboration with primary care and community service providers (Figure 4). CHTs collaborate with partners within the vicinity to operate





Figure 5. An Occupational Therapist and Community Nurse from the Geylang Community Health Team (CHT) on a home visit to assess a resident's mobility status in the neighbourhood.

Community Health Posts (CHPs) which are located in Central neighbourhoods such as Care Corner Senior Activity Centres (SACs), Residents' Committees (RCs) and mosques. Residents may be referred to a CHT by a primary care provider, or walk in to any CHPs, to be reviewed and obtain personalised advice on appropriate interventions in areas such as medication reconciliation, assessment and education on fall risk, nutrition, and lifestyle education. CHTs can also provide links to nearby GPs for continued follow-up on the issues identified. For home-bound residents and those with complex health and/or psychosocial needs, CHTs may provide medical and nursing interventions through home visits and telephonic reviews (Figure 5). Charges may be applicable for home visits, depending on the type of service provided. CHTs will discuss with clients or caregivers on the relevant schemes and subsidies where applicable. Additionally, CHTs will also coordinate required health and social services to ensure continuity of care.

Today, TTSH has put in place 80 CHPs, each working closely with their community partners in Central Singapore, to deliver more integrated care to residents with complex care needs. Besides health talks, mass exercises and healthy cooking demonstrations, CHTs also conduct structured group programmes which are focused on encouraging physical activity, healthy eating, prevention of falls and, prevention and management of diabetes. CHTs also work with residents and caregivers to determine their care goals and craft customised care plans to achieve these goals.



Scan the QR code to find out more about CHT services or to locate a CHP near you. If you are a GP practising in the Central region of Singapore who is keen to refer a resident for care coordination with our CHTs, email us at chp@ttsh.com.sg

Ageing in Place, with Home Care Services

Home care services play a critical role in delivering care for home-bound patients in the community. Patients who receive home care are less likely to be admitted to the hospital, as their needs are addressed in the comfort of their own home. Home care services include:

- **INTERIM CAREGIVER SERVICES (ICS):** Provides home care of up to 2 weeks upon patient discharge to give time for families to make permanent arrangements
- **INTERIM CAREGIVER SERVICES+ (ICS+):** Provides home care for an additional 2 weeks after Interim Caregiver Services, in the event permanent care arrangements have yet to be made (approval for ICS+ is on a case-by-case basis)
- **MEALS ON WHEELS:** Meal delivery for patients who struggle with meal preparation
- **MEDICAL ESCORT AND TRANSPORTATION:** For patients who are unable to travel from one place to another independently (inclusive of medical appointments)
- **HOME SAFETY ASSESSMENT:** A review of the patient's home environment to ensure occupants' safety
- **HOME PERSONAL CARE:** Companionship and assistance with Activities of Daily Living (ADLs)
- **HOME THERAPY:** Home-based rehabilitative services for patients who show rehabilitative potential but experience difficulties accessing centre-based rehabilitative services
- **HOME NURSING:** Nursing care and procedure-based services such as wound dressing, injections, change of catheters, medication packing and vital signs monitoring
- **HOME MEDICAL:** Medical consultation and treatment via home visits
- **HOME HOSPICE:** Palliative and long-term care via home visits

In the event that the patient becomes home-bound and requires assistance at home, the GP may liaise with CHTs to do the necessary screening and assessment. Together, the patient can be directed to the relevant home care services to address his/her needs. Patients can receive services from home care partners indefinitely, for as long as he/she remains home-bound*.



*Note: Private home care providers such as Homage and Jaga-Me are able to provide services for ambulatory patients.

LEAVING WELL, WITH END-OF-LIFE & LONG-TERM CARE

Palliative care is increasingly vital as the number of frail elderly in Singapore grows, indicating a need to establish palliative care networks that support End-of-Life (EoL) and Long-Term Care in the community. A survey by Lien Foundation revealed that while the majority (77 %) of Singaporeans would prefer to die at home, only 27% actually do. A more concerted effort in primary care can help increase the chances of a terminally ill patient realising this wish.

Central Health has developed 2 programmes – Programme IMPACT and Project CARE – run by multi-disciplinary teams of doctors, nurses, medical social workers and administrative staff to help support patients and primary care providers to care for persons at their end of lives.

Programme IMPACT

In 2015, NHG had 1,993 organ-failure decedents – with AIC-Home (previous non-cancer palliative pilot) serving about 350 patients annually – leaving approximately 1,600 patients unable to receive home care. With established providers focusing only on cancer in the past decade (e.g. Dover Park, HCA), Programme IMPACT (Programme of Integrated Management & Palliative Care for the Terminally-ill non-cancer patients) began in 2017 to fill this gap by linking the hospital (organ specialists), home palliative team, and community providers to help patients ‘Leave Well’ at home. Programme IMPACT ensures good palliative care at home for persons with end-organ failure who have opted against aggressive treatment, e.g. a person with end-stage kidney failure who has not opted for dialysis (Figure 6). Patients do not need to stay or return to the hospital, and are able to pass on with dignity in their preferred place e.g. at home.

In CY2018, 75% of the decedents in Programme IMPACT were able to pass on according to their preferred place of death (i.e. at home), with reductions of 47% in ED admissions and 70% in inpatient admissions. For patients with reconciled SOC visits, an average of 50% of appointments were cancelled. This positively impacts patient care and patient experience, reducing the need for hospital utilisation- especially so when they are at the end-of-life. Family anxiety is also reduced, with patients well-supported at home. From a population health perspective, the work of the Programme IMPACT team has also helped to reduce healthcare utilisation (ED/inpatient/SOC).

To help build a sustainable model of care, Programme IMPACT also works with Dover Park Hospice on capability building, with the goal of passing on the care for this group of non-cancer palliative patients to them.



Figure 6. A Programme IMPACT nurse educating a patient on the use of a portable oxygen concentrator.

Project CARE

Palliative care has become increasingly vital as the number of frail elderly in Singapore rises. Many patients are instituted in Nursing Homes (NHs) during their EoL because of limitations in bodily functions and inadequate community support. Often, residents are sent to hospitals in their last hours even though further hospitalisation is unlikely to improve their condition. NHs face challenges of limited resources such as stretched manpower and limited medical care support for palliative residents, resulting in limited EoL discussions.

Tan Tock Seng Hospital (TTSH) was the first hospital to launch Project CARE (Care At the end of life for Residents in the homes for Elderly) in 2009, a palliative care scheme in partnership with NHs in the Central Region of Singapore. Project CARE aims to enable good palliative care in nursing homes for persons with estimated life expectancy of less than 12 months by improving their quality of life and quality of care, who themselves or whose families have opted for the comfort of care in a nursing home setting (Figure 7).

With Project CARE, hospital admissions in FY2017 and FY2018 for residents who opted for limited intervention or comfort measures reduced by 75.7% after enrolment in the scheme; furthermore, NH residents’ ED visits were also reduced by 70.7%. Of the 179 residents who passed away in FY2018, 93.8% of Project CARE patients had passed away in their preferred place of death, and 98.3% passed away according to their preferred treatment preference (in the context of preference for cardiopulmonary resuscitation).

Slowly but surely, palliative care is taking root in our healthcare system. We hope to reach out to interested GPs to join us in this work to provide good palliative care for patients in the community. Together we can better enable ageing with grace and dying with dignity for our population.



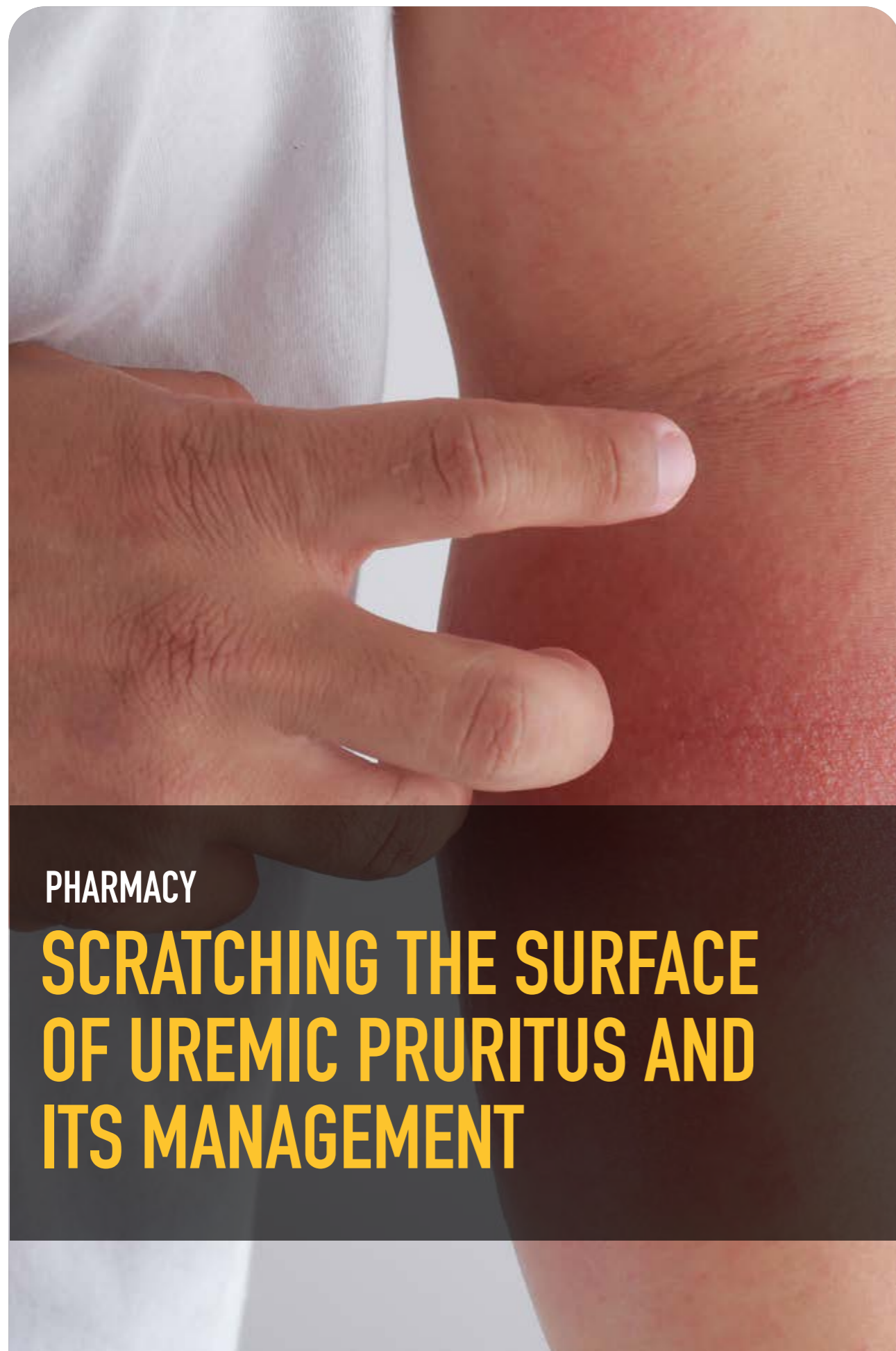
Figure 7. A Project CARE doctor conducting an assessment on a patient at a nursing home.

We would love to train and connect with you! If you are a GP practising in the central region of Singapore and are interested in finding out how you could provide palliative care in your neighbourhood, email us at gp@ttsh.com.sg.



DR TAN KOK HENG ADRIAN is a Senior Consultant and Family Physician in the Department of Continuing and Community Care, Tan Tock Seng Hospital.





PHARMACY

SCRATCHING THE SURFACE OF UREMIC PRURITUS AND ITS MANAGEMENT

Uremic pruritus (UP or chronic kidney disease (CKD)-associated pruritus) is a frequent complication in renal patients, particularly those with end-stage renal failure (ESRF). A large study, *Dialysis Outcomes and Practice Patterns Study (DOPPS)*, showed that the prevalence of moderate pruritus has not reduced over the years, remaining constant at 18% from 1996 to 2001 and 2012 to 2015.¹ Patients with UP report reduced quality of life and sleep quality, as well as depression and mortality.² In the DOPPS cohort, patients with moderate to extreme pruritus were found to be more likely to feel drained [adjusted odds ratio (AOR) = 2.3 - 5.2, $P < 0.0001$], have poor sleep quality (AOR = 1.9 - 4.1, $P < 0.0002$), and have physician-diagnosed depression (AOR = 1.3 - 1.7, $P < 0.004$).¹

In this article, we will review the pathophysiology of UP, the pharmacological options available and, the general treatment approach for UP.

PATHOPHYSIOLOGY OF UREMIC PRURITUS

The pathophysiology of UP is poorly understood. Several hypotheses have been proposed, including the following:³

- (i) *Immune hypothesis*: UP is the result of systemic inflammation, rather than being a local skin disorder. Elevated levels of C-reactive protein (CRP) are observed in the serum of hemodialysis patients with chronic pruritus; furthermore, relatively increased

proinflammatory T-helper-1 cell numbers and raised interleukin-6 concentration are detected in these patients. These observations suggest that there is an association between UP and the inflammatory response, as better outcomes are achieved by suppressing many of the inflammatory mediators.

- (ii) *Opioid hypothesis*: Imbalances in the expression of mu (μ) and kappa (κ) opioid receptors cause UP. UP is increased by μ -receptor activation and κ -receptor blockade, and decreased by κ -receptor activation and μ -receptor blockade. This hypothesis was based on an observation from a single study which showed a substantial reduction of itching in uremic patients after the oral application of naltrexone, a μ -opioid receptor antagonist.⁴

CLINICAL FEATURES OF UREMIC PRURITUS

Symptoms associated with UP are largely non-specific. Hence, UP is a diagnosis of exclusion. In general, UP tends to occur on the back, face and arms. Other characteristic symptoms are worsening of symptoms at night (therefore affecting the quality of sleep of these patients) and aggravation by heat (especially with excessive perspiration) and stress.^{3,5} Physical findings of the affected skin include xerosis (or dry skin), excoriations with and without impetigo, linear crusts, papules and ulcerations.

TREATMENT OPTIONS FOR UREMIC PRURITUS

Despite the high prevalence and life-altering potential, UP remains poorly characterized and lacks effective treatment because of the poorly understood pathophysiology mechanism. Before considering treatment, an evaluation should be performed to exclude other possible causes of pruritus such as dermatologic or systemic disease such as hyperparathyroidism, hyperphosphatemia and anemia.⁶

Treatment options can be classified into three categories: topical, physical and systemic.

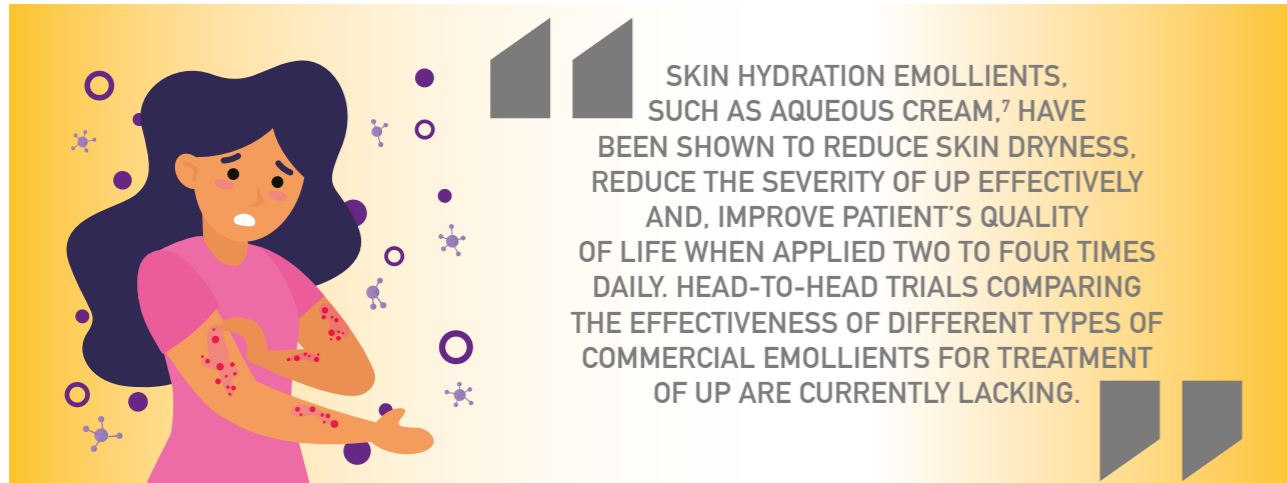
1) Topical treatment **Emollients**

Daily topical treatment with emollients is considered to be the cornerstone of UP treatment.^{3,5} This is because xerosis is found in most patients with ESRF and frequently aggravates pruritus. Skin hydration emollients, such as aqueous cream,⁷ have been shown to reduce skin dryness, reduce the severity of UP effectively and, improve patient's quality of life when applied two to four times daily. Head-to-head trials comparing the effectiveness of different types of commercial emollients for treatment of UP are currently lacking.

Tacrolimus ointment

Topical treatment with tacrolimus ointment has been shown to be effective in relieving pruritus. Tacrolimus

SYMPTOMS ASSOCIATED WITH UP ARE LARGELY NON-SPECIFIC. HENCE, UP IS A DIAGNOSIS OF EXCLUSION. IN GENERAL, UP TENDS TO OCCUR ON THE BACK, FACE AND ARMS. OTHER CHARACTERISTIC SYMPTOMS ARE WORSENING OF SYMPTOMS AT NIGHT (THEREFORE AFFECTING THE QUALITY OF SLEEP OF THESE PATIENTS) AND AGGRAVATION BY HEAT (ESPECIALLY WITH EXCESSIVE PERSPIRATION) AND STRESS.^{3,5} PHYSICAL FINDINGS OF THE AFFECTED SKIN INCLUDE XEROSIS (OR DRY SKIN), EXCORIATIONS WITH AND WITHOUT IMPETIGO, LINEAR CRUSTS, PAPULES AND ULCERATIONS.



exerts its effect by targeting the microinflammatory process. In a prospective proof-of-concept study in which pruritus was assessed with a modified pruritus assessment score, tacrolimus reduced the score significantly (by 81.8%) after 6 weeks' treatment [median (interquartile range) score: 11 (6–16) at Week 0 vs. 2 (0–5.25) at Week 6; $P < 0.0001$].⁸ Tacrolimus was well tolerated, with no reports of serious adverse events. Transient stinging and burning sensation were reported by four patients in the first week of the trial, while one patient experienced a mild skin rash. No systemic exposure to tacrolimus was detected.⁸ A recent double-blinded, vehicle-controlled study to assess the efficacy of tacrolimus ointment 0.1% for the treatment of haemodialysis-related pruritus found that all patients experienced significant improvement regardless of treatment arm by week 4, with no demonstrable difference between tacrolimus and vehicle.⁹

**2) Physical treatment
Phototherapy**

Gilchrest et al. first reported the effectiveness of sunburn-spectrum UVB-phototherapy in patients with UP.¹⁰ Nine out of 10 subjects treated with UVB phototherapy reported a marked reduction in pruritus. The beneficial effects of UVB therapy are thought to be due to a decrease in proinflammatory cytokine levels and the induction of mast cell apoptosis.¹¹ However, UVB therapy failed to demonstrate a significant benefit in a more recent randomized controlled trial published in 2011.¹² UVB therapy is associated with an increased risk of carcinogenesis, and this possibility should be discussed with patients prior to treatment.

Additionally, other long-term effects of UVB therapy remain largely unknown.

**3) Systemic treatment
Gabapentin/pregabalin**

Gabapentin and pregabalin are gamma-aminobutyric acid analogs that moderate calcium influx at nerve terminals by binding to the alpha2-delta subunit of voltage-gated calcium channels within the central

nervous system. Both are commonly used in a variety of neuropathic pain syndromes, and have also been effective for UP. A randomized, single-blind clinical trial involving haemodialysis patients with UP found that, compared to doxepin (a potent antihistamine), pregabalin was more effective in decreasing UP measured on the visual analog scale (VAS) [mean \pm SD scores: 7.5 ± 1.4 (pregabalin) and 7.1 ± 1.3 (doxepin) at baseline to 2.1 ± 2.6 (pregabalin) and 4.2 ± 2.6 (doxepin) at the end of the study; $P < 0.001$].¹³ Similarly, another randomized, double-blind 12-week study of dialysis patients found that pregabalin was more effective in reducing the severity of pruritus (evaluated using VAS scores) than ondansetron or placebo.¹⁴ Two randomized trials evaluated the efficacy of gabapentin against placebo for the treatment of UP in haemodialysis patients. Gunal et al. found that gabapentin produced a more significant reduction in VAS score compared to placebo [mean \pm SD scores: 8.4 ± 0.94 at baseline to 1.2 ± 1.8 with gabapentin ($P = 0.0001$) and 7.6 ± 2.6 with placebo ($P = 0.098$) at the end of 4 weeks].¹⁵ Similar findings were reported by Nofal et al. where the reduction in VAS score after 4 weeks was greater in patients who received gabapentin than in those who received placebo [mean \pm SD scores: 7.63 ± 2.0 at baseline to 1.81 ± 2.2 with gabapentin ($P < 0.001$) and 6.9 ± 1.97 at baseline to 6.8 ± 2.48 with placebo ($P = 0.4$)].¹⁶ Overall, gabapentin or pregabalin show statistically significant benefit in the treatment of UP compared to placebo.

Mu-opioid receptor antagonists

Data on the effectiveness on naltrexone, a μ -opioid receptor antagonist, is conflicting. In a randomised, double-blind, placebo-controlled crossover trial involving haemodialysis patients with severe resistant pruritus, naltrexone 50 mg/day resulted in a significant reduction in pruritus score.⁴ However, the use of naltrexone in UP was re-evaluated in a randomized, double-blind, placebo-controlled crossover study more recently.¹⁷ Not only did the trial show no additional benefit with the addition of naltrexone, a higher incidence of toxicity, such as gastrointestinal side effects, was observed. Nine

out of 23 patients complained of gastrointestinal disturbances during the naltrexone period, compared to only one out of 23 patients during the placebo period ($P < 0.05$).¹⁷

Antidepressants

For patients with refractory UP, the use of sertraline, a selective serotonin reuptake inhibitor, has been studied. Chan et al. conducted a retrospective review of 20 consecutive patients who presented to the renal palliative care clinic with pruritus refractory to antihistamines.¹⁸ Sertraline was initiated at 25 mg daily orally for the first month, with dosage increments of 25 mg in monthly intervals based on clinical response, up to a maximum of 200 mg daily as necessary. In this review, low-dose sertraline was

effective for antihistamine-refractory UP in renal palliative care patients. Placebo-controlled, blinded, randomized studies are necessary to validate this observation.

GENERAL RECOMMENDATION FOR MANAGING UREMIC PRURITUS

Many ESRF patients suffer from pruritus. Its exact pathophysiology is not known, and many therapeutic options have been proposed. A stepwise approach is recommended when treating UP (Figure 1). A list of drugs which are commonly available and used is illustrated in Table 1. Physicians should teach patients to avoid potential exacerbating factors, and look into the adequacy of patients' dialysis sessions.

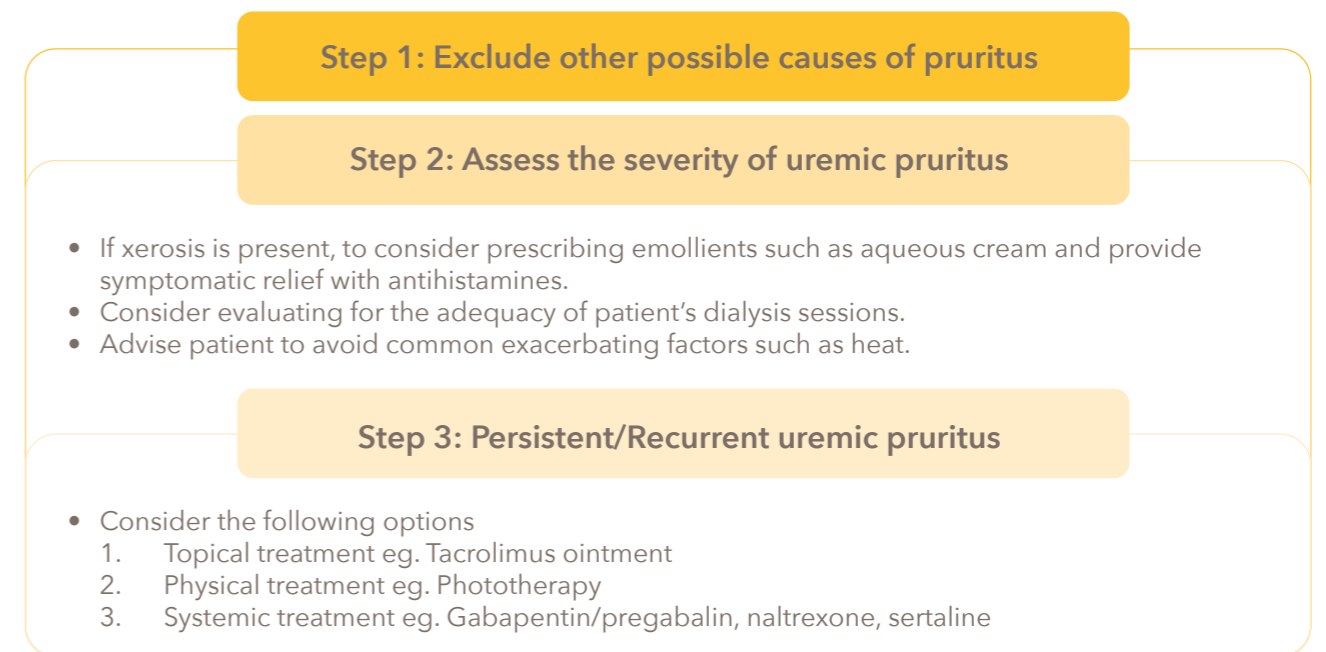


Figure 1. Recommended stepwise approach to manage uremic pruritus (UP).



Table 1. Common drugs (and their doses) which are available in Singapore for the treatment of UP.

| Treatment options | Dose | Side effects (Incidence)/ Monitoring |
|--|---|--|
| Emollients e.g. Aqueous cream | Topical application to the affected area twice daily | - |
| Tacrolimus ointment* (Available in 0.03% and 0.1% strengths) | Topical application to the affected area twice daily | <ul style="list-style-type: none"> • Dermatological: Burning sensation of skin (43% to 58%) Sunburn (1% to 2%) <p><i>Note: Although a causal relationship has not been established, rare cases of malignancy (i.e. skin cancer and lymphoma) have been reported in patients treated with topical calcineurin inhibitors, including tacrolimus ointment.</i></p> |
| Gabapentin | <p>Dosing is based on creatinine clearance.</p> <p>Patients with CKD Stage 3 and above: Initiate at 100 mg once daily and titrate upwards.</p> <p>Patients on haemodialysis: Initiate at 100 mg 3x/week post-HD; can be titrated up to 300 mg 3x/week</p> | <ul style="list-style-type: none"> • Neurological side effects: Ataxia (1% to 13%) Dizziness (17% to 28%) Drowsiness (19% to 21%) |
| Pregabalin | <p>Dosing is based on creatinine clearance.</p> <p>Patients with CKD Stage 3 and above: Initiate at 25 mg once daily and titrate upwards.</p> <p>Patients on haemodialysis: Initiate 50 mg every other day; to be given after dialysis on HD days</p> | <ul style="list-style-type: none"> • Cardiovascular: Peripheral oedema (4% to 16%) • Nervous system: Dizziness (3% to 45%) Drowsiness (≤ 36%) |
| Naltrexone | 50 mg (oral) once daily | <ul style="list-style-type: none"> • Central nervous system: Headache (25%) Insomnia (≤ 14%) • Gastrointestinal: Nausea (33%) Vomiting (14%) Anorexia (≤ 14%) Change in appetite (≤ 14%) Decreased appetite (≤ 14%) Diarrhoea (13%), Abdominal pain (11%) |
| Sertraline | 25 mg (oral) once daily; can be titrated upwards to a maximum dose of 200 mg/day | <ul style="list-style-type: none"> • Gastrointestinal: Diarrhoea (20%) Nausea (26%) Xerostomia (14%) • Nervous system: Dizziness (12%) Drowsiness (11%) |

*Off label indication.

CONCLUSION

UP can be a debilitating condition for many ESRF patients. The current evidence for treatment efficacy (with the exception of gabapentin) is weak due to a lack of large, rigorous multi-arm, randomized controlled

trials. No guidelines on the treatment of UP have been published. Thus, the onus is on physicians to be aware of the aetiological hypotheses of UP and the available treatment options. Prescribers should adopt a stepwise approach in the management of UP.

REFERENCES


1. Pisoni RL, Wikstrom B, Elder SJ, et al. Pruritus in haemodialysis patients: International results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant.* 2006; 21(12): 3495-3505.
2. Shirazian S, Aina O, Park Y, et al. Chronic kidney disease-associated pruritus: impact on quality of life and current management challenges. *Int J Nephrol Renovasc Dis.* 2017; 10: 11-26.
3. Mettang T, Kremer AE. Uremic pruritus. *Kidney Int.* 2015; 87(4): 685-691.
4. Peer G, Kivity S, Agami O, et al. Randomised crossover trial of naltrexone in uraemic pruritus. *Lancet.* 1996; 348(9041): 1552-1554.
5. Combs SA, Teixeira JP, Germain MJ. Pruritus in Kidney Disease. *Semin Nephrol.* 2015; 35(4): 383-391.
6. Schwartz IF, Iaina A. Management of uremic pruritus. *Semin Dial.* 2000; 13(3): 177-180.
7. Morton CA, Lafferty M, Hau C, Henderson I, Jones M, Lowe JG. Pruritus and skin hydration during dialysis. *Nephrol Dial Transplant.* 1996; 11(10): 2031-2036.
8. Kuypers DR, Claes K, Evenepoel P, Maes B, Vanrenterghem Y. A prospective proof of concept study of the efficacy of tacrolimus ointment on uraemic pruritus (UP) in patients on chronic dialysis therapy. *Nephrol Dial Transplant.* 2004; 19(7): 1895-1901.
9. Duque MI, Yosipovitch G, Fleischer AB, Jr., Willard J, Freedman BI. Lack of efficacy of tacrolimus ointment 0.1% for treatment of hemodialysis-related pruritus: a randomized, double-blind, vehicle-controlled study. *J Am Acad Dermatol.* 2005; 52(3 Pt 1): 519-521.
10. Gilchrist BA, Rowe JW, Brown RS, Steinman TI, Arndt KA. Relief of uremic pruritus with ultraviolet phototherapy. *N Engl J Med.* 1977; 297(3): 136-138.
11. Szepietowski JC, Morita A, Tsuji T. Ultraviolet B induces mast cell apoptosis: a hypothetical mechanism of ultraviolet B treatment for uraemic pruritus. *Med Hypotheses.* 2002; 58(2): 167-170.
12. Ko MJ, Yang JY, Wu HY, et al. Narrowband ultraviolet B phototherapy for patients with refractory uraemic pruritus: a randomized controlled trial. *Br J Dermatol.* 2011; 165(3): 633-639.
13. Foroutan N, Etmnan A, Nikvarz N, Shojai Shahrokh Abadi M. Comparison of pregabalin with doxepin in the management of uremic pruritus: a randomized single blind clinical trial. *Hemodial Int.* 2017; 21(1): 63-71.
14. Yue J, Jiao S, Xiao Y, Ren W, Zhao T, Meng J. Comparison of pregabalin with ondansetron in treatment of uraemic pruritus in dialysis patients: a prospective, randomized, double-blind study. *Int Urol Nephrol.* 2015; 47(1): 161-167.
15. Gunal AI, Ozalp G, Yoldas TK, Gunal SY, Kirciman E, Celiker H. Gabapentin therapy for pruritus in haemodialysis patients: a randomized, placebo-controlled, double-blind trial. *Nephrol Dial Transplant.* 2004; 19(12): 3137-3139.
16. Nofal E, Farag F, Nofal A, Eldesouky F, Alkot R, Abdelkhalik Z. Gabapentin: A promising therapy for uremic pruritus in hemodialysis patients: A randomized-controlled trial and review of literature. *J Dermatolog Treat.* 2016; 27(6): 515-519.
17. Pauli-Magnus C, Mikus G, Alscher DM, et al. Naltrexone does not relieve uremic pruritus: results of a randomized, double-blind, placebo-controlled crossover study. *J Am Soc Nephrol.* 2000; 11(3): 514-519.
18. Chan KY, Li CW, Wong H, et al. Use of sertraline for antihistamine-refractory uremic pruritus in renal palliative care patients. *J Palliat Med.* 2013; 16(8): 966-970.



MS AMANDA YONG MEI HUI is a Pharmacist from Singapore General Hospital who is currently undertaking her Drug Information clerkship in the Department of Pharmacy, Tan Tock Seng Hospital in fulfilment of her Doctor of Pharmacy (PharmD) candidature from the National University of Singapore.

THE ONUS IS ON PHYSICIANS TO BE AWARE OF THE AETIOLOGICAL HYPOTHESES OF UP AND THE AVAILABLE TREATMENT OPTIONS. PRESCRIBERS SHOULD ADOPT A STEPWISE APPROACH IN THE MANAGEMENT OF UP.





RADIOLOGY QUIZ

TRY OUR RADIOLOGY QUIZZES OF INTERESTING CASES SEEN IN TTSH. PUT YOUR KNOWLEDGE TO THE TEST WITH THIS ISSUE'S SCENARIO.

A 34-year-old female had been working in Singapore for 4 months as a domestic helper when she presented with a fall and head injury. She reported a 3-day history of vertigo and tinnitus associated with vomiting prior to the fall. She had a past medical history of premature menopause at age 30.

Physical examination was normal, and she did not display any neurological deficit. No cerebellar signs were elicited. There was no palpable breast mass or lymphadenopathy.

INVESTIGATIONS

- WCC 13.5, Hb 12.2, Platelets 562
- Na 143, K 4.0, Cr 46
- Serum calcium 2.2, Adjusted serum calcium 2.39
- Anti-HBc/HBsAg/anti-HCV negative
- HIV negative
- Myeloma panel negative

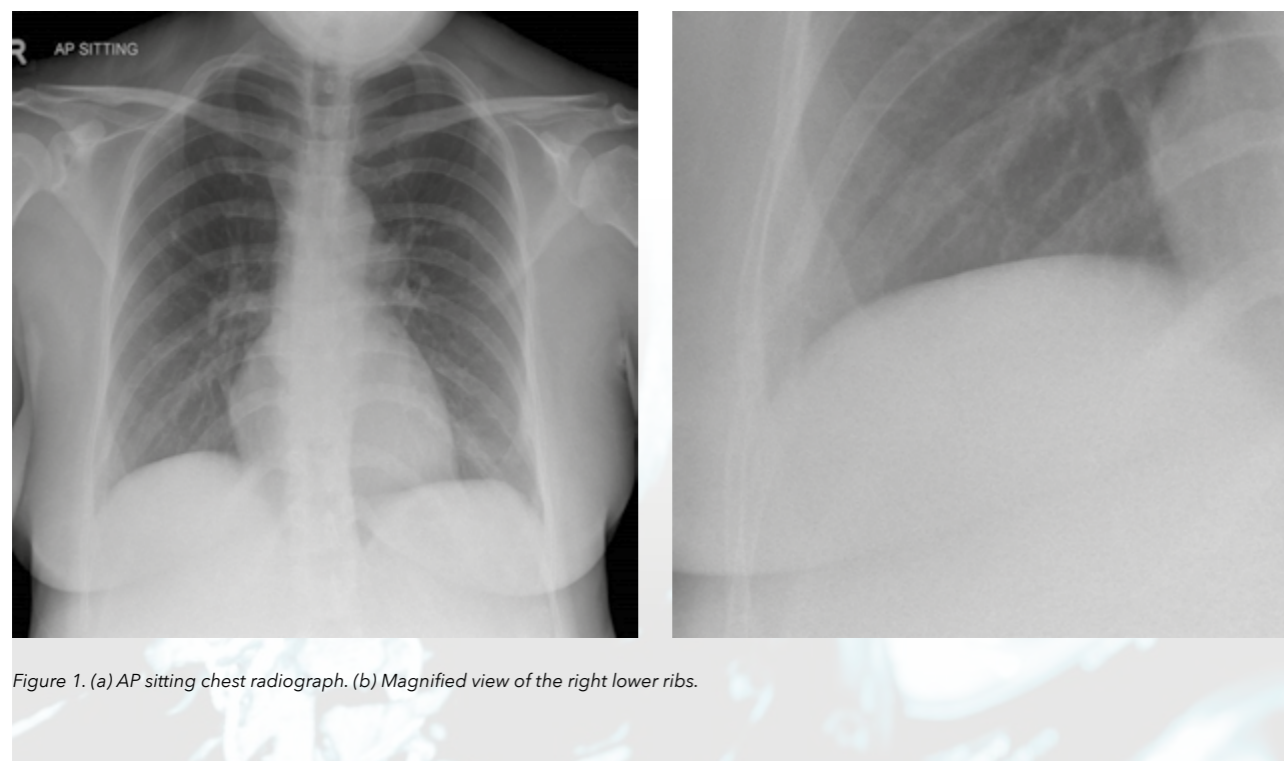


Figure 1. (a) AP sitting chest radiograph. (b) Magnified view of the right lower ribs.

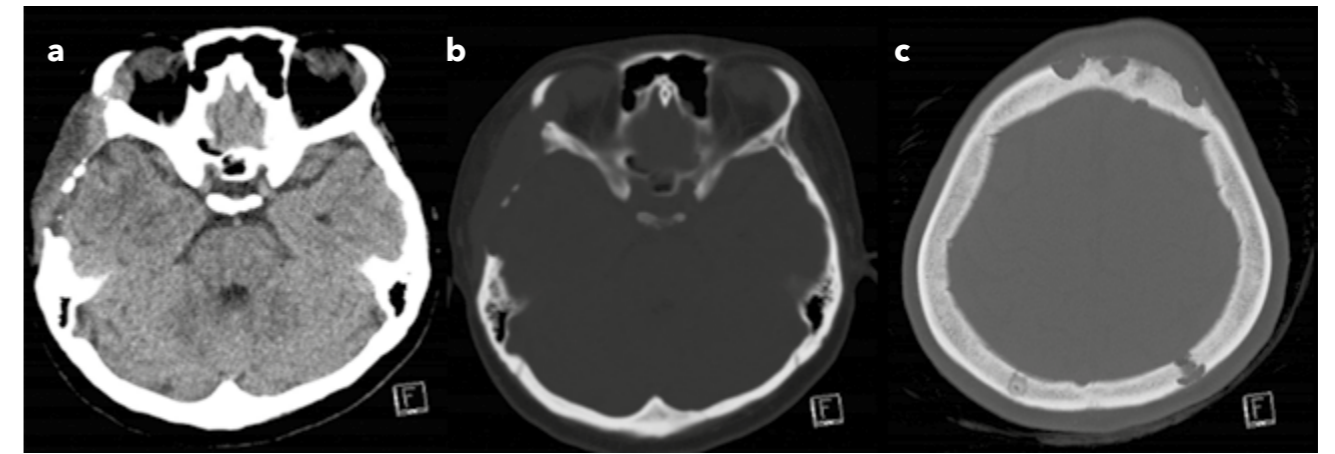


Figure 2. Axial non-contrast CT brain in (a) Soft tissue window and (b,c) Bone window.

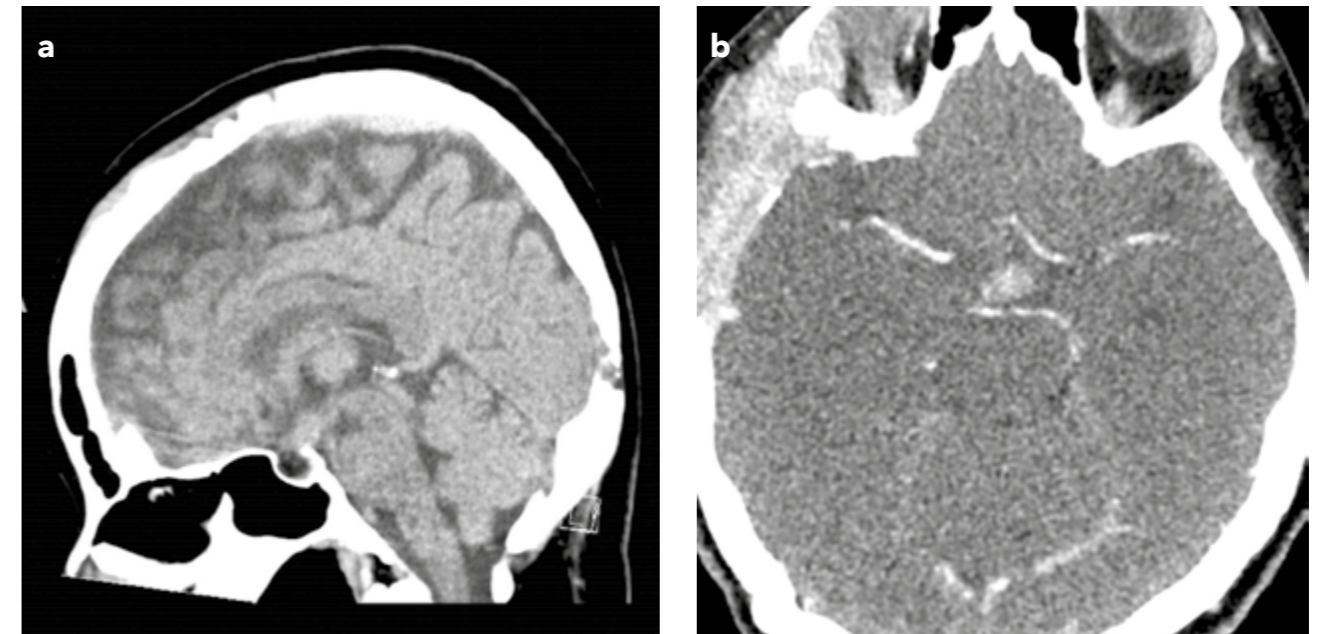


Figure 3. (a) Sagittal reconstruction of the non-contrast CT brain. (b) Axial contrast-enhanced CT brain.

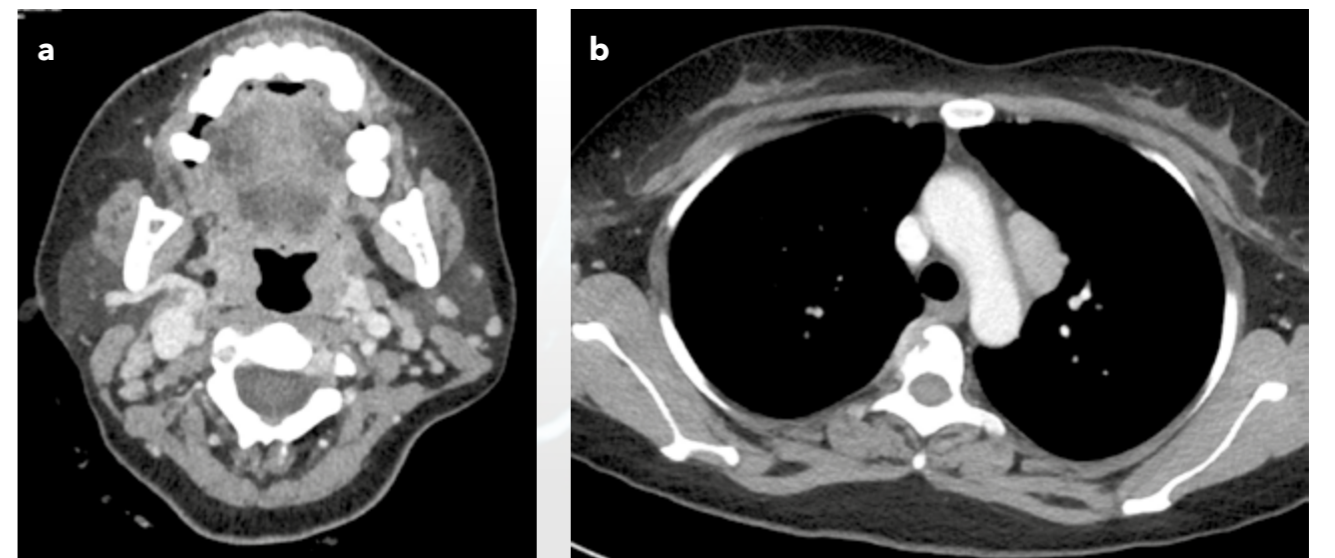


Figure 4. Axial contrast-enhanced CT of (a) Neck and (b) Thorax.

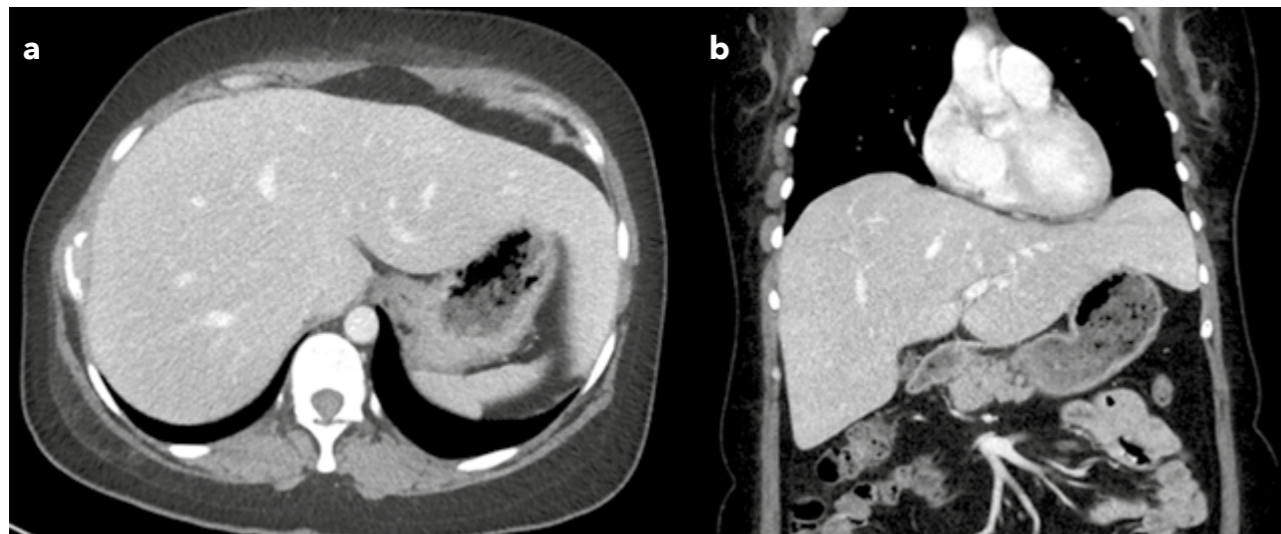


Figure 5. Contrast-enhanced CT abdomen (a) Axial and (b) Coronal.

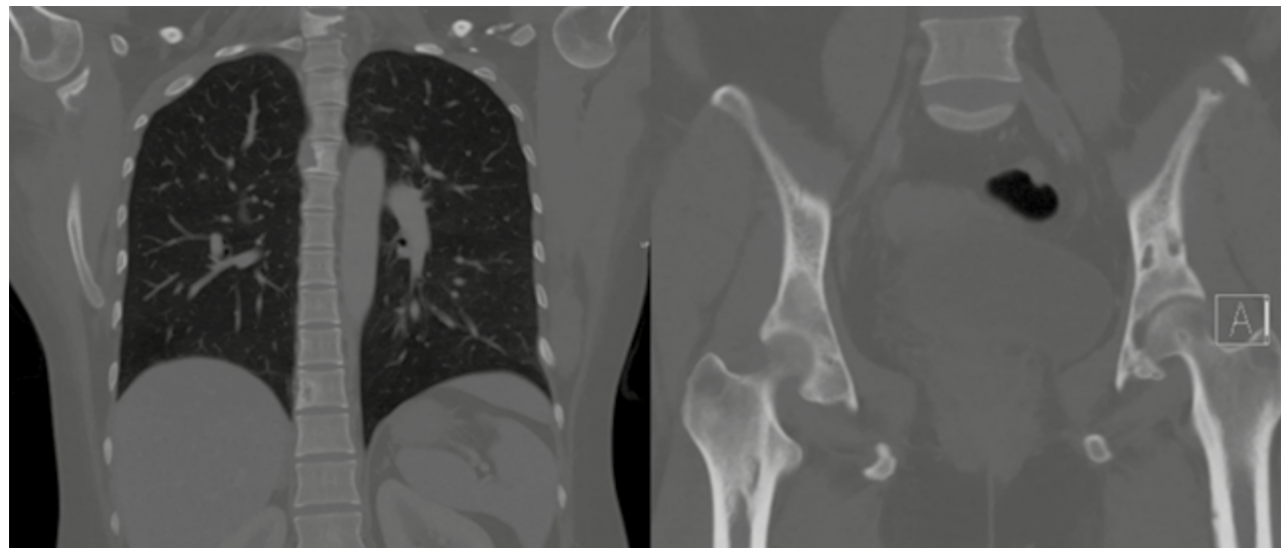


Figure 6. Coronal CT in bone window of the (a) Thorax and (b) Pelvis.

QUESTIONS

- 1) What is the finding on the chest radiograph (Figure 1)?
- 2) What do the plain (Figure 2) and contrast-enhanced CT brain (Figure 3) show?
- 3) What is seen on the CT neck and thorax (Figure 4)?
- 4) How does the liver appear (Figure 5)?
- 5) Do you spot any osseous abnormality (Figure 6)?
- 6) What are the differential diagnoses for the findings?

ANSWERS

- 1) There is erosion of the right 8th and 9th lateral ribs.
- 2) Plain CT brain shows a lytic lesion in the right temporal bone with associated soft tissue extending through the right lateral orbital wall which is also eroded (Figures 2a and 2b). Other similar lytic lesions with beveled edges are seen in the frontal and parietal bones (Figure 2c). The lesion in the right parietal bone has a button sequestrum appearance with a central bone opacity surrounded by a well-defined lucent area (Figure 2c).

On the sagittal reconstruction, there is thickening of the infundibulum and a suprasellar nodule (Figure 3a). On contrast-enhanced CT brain, the suprasellar nodule shows enhancement (Figure 3b).
- 3) Enlarged level II cervical lymph nodes are seen on the right as well as prominent left intraparotid lymph nodes (Figure 4a). CT thorax shows an enlarged para-aortic node (Figure 4b).
- 4) There is hepatomegaly, but no focal hepatic lesion is detected (Figure 5).
- 5) Multiple lytic lesions are present in the imaged bilateral proximal humeri, thoracic vertebral bodies, iliac bones and bilateral proximal femora (Figure 6).
- 6) Langerhans cell histiocytosis is the top differential given the overall findings (see Discussion below). The patient in this case is older than the usual age of presentation (childhood or adolescence).

Erdheim Chester disease, another histiocytic disorder with overlapping features such as bone lesions and sella involvement, is another differential. However, the bone lesions in Erdheim Chester tend to be osteosclerotic, although lytic lesions are possible. Retroperitoneal findings such as peri-renal or peri-aortic soft tissue, seen in a third of patients, are not present in this case.

Metastasis and lymphoma should always be considered as a differential for lymphadenopathy and osseous lesions in an adult patient. No primary malignancy was detected on clinical examination or imaging to support metastasis in this case. Lymphoma can be present with nodal and extranodal disease, but the lymphadenopathy tends to be more extensive.

DISCUSSION

Langerhans cell histiocytosis (LCH) is the most common dendritic cell disorder, with other dendritic cell disorders including Erdheim-Chester disease and juvenile xanthogranuloma.

LCH is classified into three groups based on the systems involved:

- The unifocal (localized) form is the most common (70%), with lesions in a single or few bones. Patients tend to present between the ages of 5 and 15 years.
- The multifocal unisystem (chronic recurring) form (20%) occurs in younger patients aged 1-5 years. They present with multiple bone lesions as well as involvement of the reticuloendothelial system.
- Lastly, in 10% of patients, the multifocal fulminant form typically leads to death from disseminated involvement of the reticuloendothelial system, complicated by anaemia and thrombocytopenia.

Radiological findings in LCH can be found in multiple systems. The most common radiographic manifestation is osseous lesions. LCH has a predilection for the skull, followed by the mandible, ribs, pelvis and spine. In the skull, lesions show a punched-out appearance

with a beveled edge due to asymmetrical destruction of the inner and outer cortices, which can be seen on radiograph or CT. Lesions may also display a button sequestrum appearance representing a central area of dead bone surrounded by erosive accumulation of histiocytes which appears lucent. In later stages, the lesions can coalesce and give rise to a geographic skull. Lesions are typically asymptomatic or present with focal pain. If the temporal bone is affected, the patient may experience dizziness, vertigo and otorrhoea.

In the spine, the vertebral body is usually affected with early lesions appearing lytic before resulting in uniform collapse of the vertebral body known as vertebra plana. There is preservation of the intervertebral disc space. In the long bones, lesions are found in the metadiaphysis with early lesions appearing lytic, expansile and aggressive later progressing to become sharply defined and sclerotic. Early bone lesions may show increased radiotracer uptake on nuclear medicine bone scan.

Involvement of the reticuloendothelial system denotes a worse prognosis. Hepatosplenomegaly and/or focal hypodense hepatic or splenic lesions may be seen

on CT. There may also be periportal fibrosis which appears as hypodensity along the biliary tracts on CT with corresponding low T1 and T2 signal on MRI. Lymphadenopathy is usually seen in the neck but can develop elsewhere.

Central nervous system (CNS) involvement in LCH tends to present as diabetes insipidus or growth hormone deficiency secondary to infiltration of the pituitary gland. MRI most often shows thickening of the pituitary stalk (70%) as well as loss of the normal posterior pituitary bright spot on T1. Other less common imaging findings include T2 hyperintense lesions in the cerebellum, basal ganglia and white matter as well as meningeal and choroid plexus lesions.

LCH in the lung is more common in adults, and is almost always associated with smoking. In early disease, CT shows centrilobular micronodules in a bilateral upper-to-mid lung distribution with characteristic sparing of the costophrenic angles. These micronodules later become small cysts (<1 cm) of varying sizes which can coalesce to form bulla which may be complicated by pneumothorax.

Treatment of focal LCH osseous lesions is with radiotherapy. Vertebral involvement resulting in neurologic symptoms may be treated with spinal fusion or bracing. Reticuloendothelial, CNS and pulmonary LCH requires chemotherapy and/or steroids. Retinoic acid and IVIG are also used to treat neurodegenerative symptoms.

LEARNING POINTS

- Langerhans cell histiocytosis is a rare multisystem histiocytic disorder with variable extent of involvement.
- It is classified into unifocal, multifocal unisystem and multifocal fulminant forms based on the systems affected.
- It affects the bones, reticuloendothelial system, CNS and lungs with various radiologic findings.
- Treatment includes radiotherapy for localized lesions, chemotherapy and steroids for systemic disease.



REFERENCES

1. Zaveri J, La Q, Yarnish G, Neuman J. More than Just Langerhans Cell Histiocytosis: A Radiologic Review of Histiocytic Disorders. *RadioGraphics* 2014; 34: 2008-2024.
2. Krasnokutsky, MV. The Button Sequestrum Sign. *Radiology* 2005;236: 1026-1027.

DR EMMA LEE

is a Resident in the Department of Diagnostic Radiology, Tan Tock Seng Hospital.

LESIONS MAY ALSO DISPLAY A BUTTON SEQUESTRUM APPEARANCE REPRESENTING A CENTRAL AREA OF DEAD BONE SURROUNDED BY EROSION ACCUMULATION OF HISTIOCYTES WHICH APPEARS LUCENT. IN LATER STAGES, THE LESIONS CAN COALESCE AND GIVE RISE TO A GEOGRAPHIC SKULL.

ECG QUIZ

CHALLENGE YOURSELF WITH OUR ECG QUIZ. YOU WILL LEARN SOMETHING NEW EVERYTIME.



An elderly Chinese gentleman with history of diabetes, hypertension, ischaemic heart disease and permanent atrial fibrillation consulted his family physician for routine follow-up and medications. His usual medications include Apixaban, Amlodipine, Glipizide and Metformin. His resting 12 lead electrocardiogram (ECG) performed last year is shown in Figure 1:

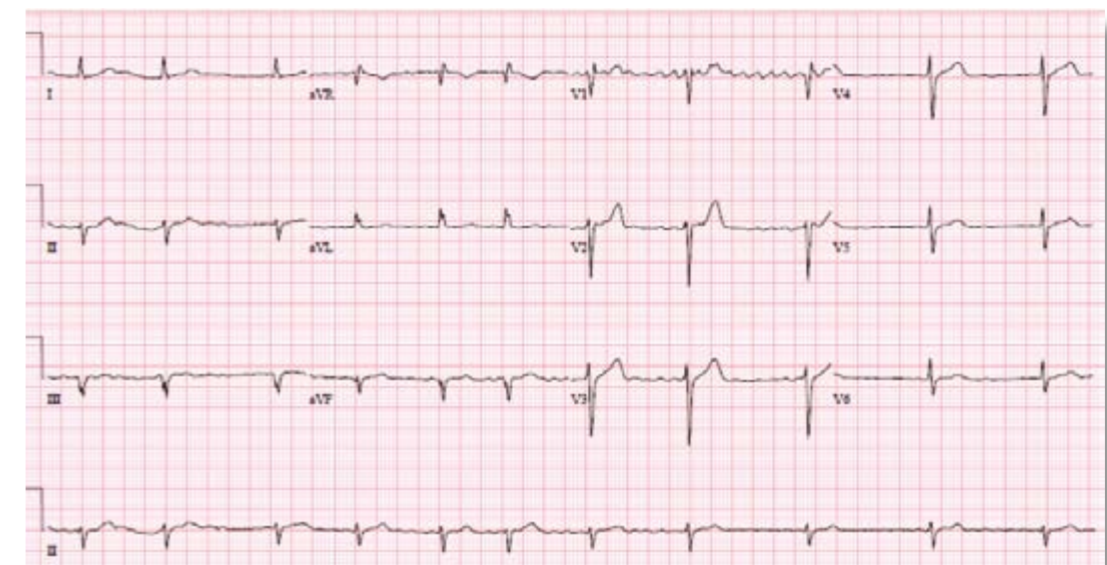


Figure 1. Resting 12 lead ECG from the previous year.

He reported having 3 episodes of transient loss of consciousness over the past few months. The family physician thus ordered an ECG (Figure 2):

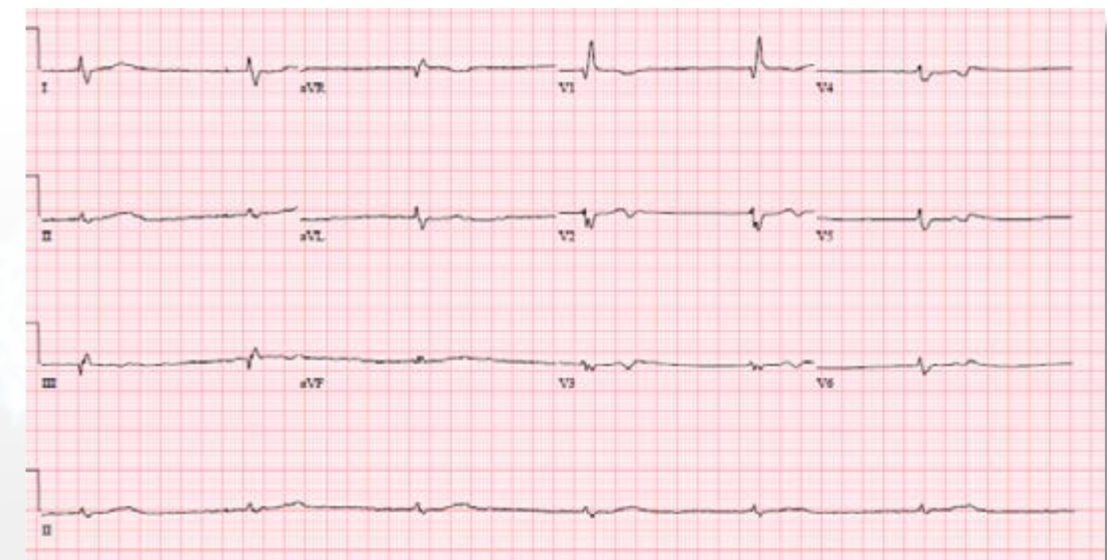


Figure 2. Resting 12 lead ECG performed immediately in the clinic.

QUESTIONS

- 1) What does the ECG in Figure 2 show?
- 2) What is the definite management for this patient?

ANSWERS

- 1) Bradycardia (36 beats/min) with broad QRS complexes. No clear P waves can be seen. The baseline does not appear flat, and small fibrillatory waves may be seen on close inspection. The ECG diagnosis is atrial fibrillation (AF) with complete heart block (CHB).
- 2) Implantation of a permanent pacemaker (PPM) (Figure 3).



Figure 3. Single chamber PPM was implanted in this patient.

DISCUSSION

This elderly patient presented with several episodes of unexplained transient loss of consciousness. A good history is important to exclude common causes such as cardiac, orthostatic hypotension (as patient is on multiple antihypertensives), cerebrovascular event (for which AF is a risk factor) or seizures, and hypoglycaemia (especially if patient is on oral hypoglycaemic agents).

In the absence of interventions such as ablation or rhythm control drugs, a regular cardiac rhythm in a patient known to have permanent atrial fibrillation (AF) is worrisome for development of complete heart block (CHFB). Also known as 'regularised AF', the ECG reveals regular bradycardia that may be wide complex if the

escape rhythm originates from the ventricles. As there is still fibrillatory activity at the atria level, no clear P waves can be seen, and the baseline is also not completely flat (unlike junctional bradycardia).

CHB is considered a high grade atrio-ventricular block and requires PPM implantation, especially in the presence of symptoms such as syncope. The chest X-ray in Figure 3 shows a single pacing lead in the right ventricle, consistent with the presence of a single chamber pacemaker. A dual chamber pacemaker (with an additional lead in the right atrium) is not indicated in this case as there is no need to either sense atrial activity or pace the atrium in a patient with permanent AF.



DR YEOW MIN SEN is a consultant in the Department of Cardiology, Tan Tock Seng Hospital.