TAN TOCK SENG HOSPITAL

MEDICAL DIGEST

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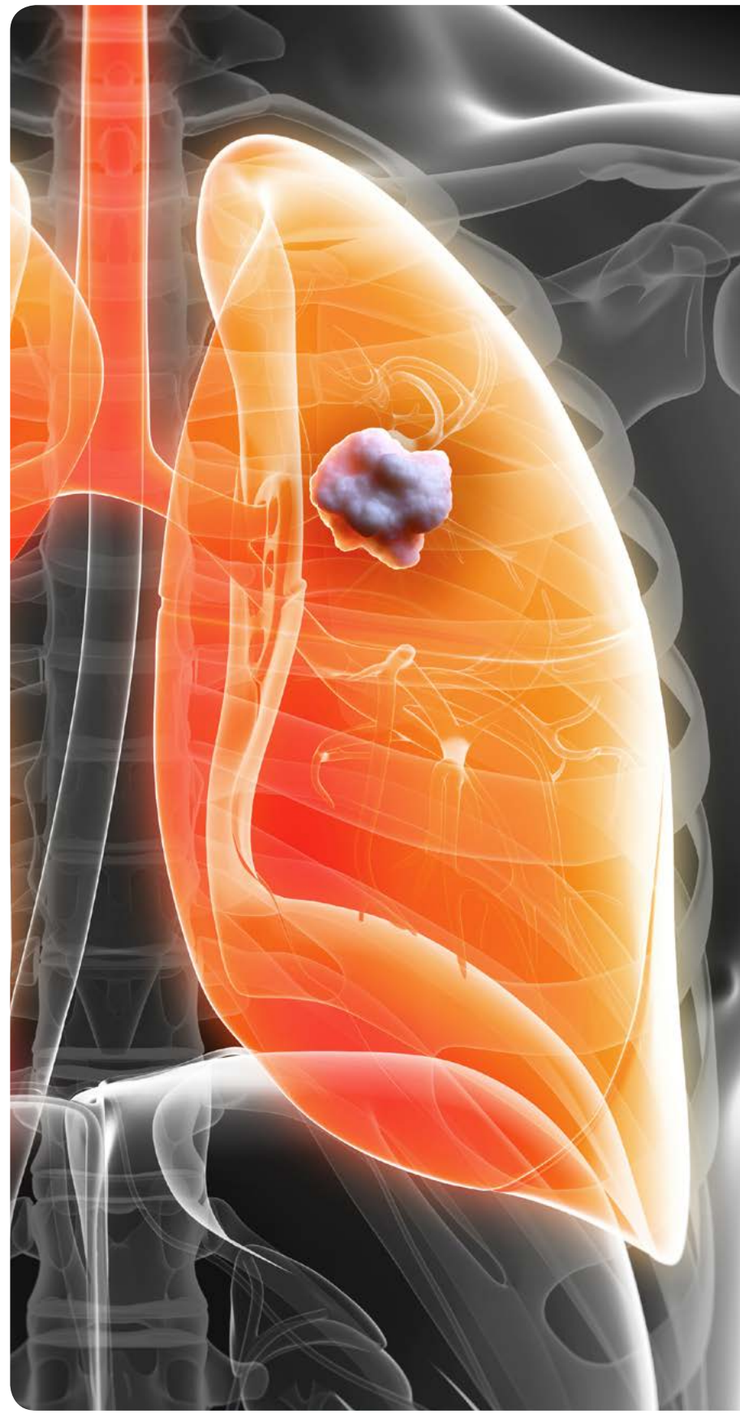

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Tan Tock Seng
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FROM THE EDITOR

I believe that there is a role for intuition in Medicine. No, I do not mean jumping to conclusions after taking a perfunctory history and performing a cursory examination. I mean seeing the truth in one's mind's eye, cutting through a confusing deluge of data that has defied analysis by clinical algorithms, computer programmes and rational thought.

Intuition, defined by the Oxford English Dictionary as 'the immediate apprehension of an object by the mind without the intervention of any reasoning process; a particular act of such apprehension', is celebrated in the medical literature. "Intuition is part of what makes a great doctor; be sure you always listen to it", Dr Peterkin recounted what he was told in CMAJ 2017; 189(14):E544. "Intuition is more than simply a 'gut feeling', it is a process based on knowledge and care experience and has a place beside research-based evidence" (Melin-Johansson C, et al. J Clin Nurs. 2017 Mar 22). Mathematician Raymond Louis Wilder argued that intuition is something we develop only after working deeply on a problem (Science 1967; 156:605-10). He quoted Descartes: 'By intuition I understand, not the fluctuating testimony of the senses, nor the misleading judgment that proceeds from the blundering constructions of imagination, but the conception which an unclouded and attentive mind gives us so readily and distinctly that we are wholly freed from doubt about that which we understand'.

As we practise in a crucible of increasingly complex medical conditions, multitudinous test and imaging results, coupled with burgeoning medical knowledge in the background, I argue that intuition becomes more rather than less important. The majority of clinical problems are solved by application of rules, by invoking patterns in our memory, or by seeking expert help, but there will be defining moments when none of these will do. The best clinicians will reach in and extract the right diagnosis, without necessarily being about to explain how he or she did it.

I am not sure if some of us lack intuition (maybe the men), or perhaps we have never exercised it and therefore dare not trust it. It is probably more often used than talked about. It is certainly never taught in medical school. But an everyday manoeuvre will tell if our intuitively derived diagnosis is correct – a trial of therapy.

In the Dune books, faster-than-light travel was made safe because navigators under the influence of spice melange could plot the route presciently. In this complex medical environment, under the right circumstances, we should consider employing our gift of intuition.

Dr Leong Khai Pang
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Medical Digest

MEDICAL DIGEST

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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. The theme this issue are medical disciplines.

RESEARCH EXCERPT 1

Role of Bronchoscopy in Prompt Discharge from the Intensive Care Unit

Verma A, Sim WY, Tai DY, Goh SK, Kor AC, Phua CK, Ho B, Lim AY, Lew SJ, Xu H, Puah SH, Abisheganaden J. J Bronchology Interv Pulmonol. 2016; 23(2):123-30.

IMPORTANCE IN CLINICAL PRACTICE

Intensive care imposes substantial financial burden on health care systems and has been reported to be 2.5 times more costly than other hospital stays that do not involve time in the ICU. The commonest reason for ICU use (93.3%) is for respiratory disease requiring ventilator support. Therefore, the management of respiratory diseases requiring mechanical ventilation must be reevaluated continually so that ICU resources are deployed efficiently. Apart from reducing economic burden, early liberation from mechanical ventilation and extubation brings a multitude of clinical benefits such as reducing the risks of ventilator associated pneumonia, sedation, and critical care neuropathy. Our study demonstrated that the majority of patients in our cohort (75%) with benign and malignant diseases could be promptly transferred out from the ICU to a general ward after successful discontinuation of mechanical ventilation and extubation after bronchoscopic intervention. We therefore advocate early recognition of the indications for bronchoscopic intervention in suitable patients.

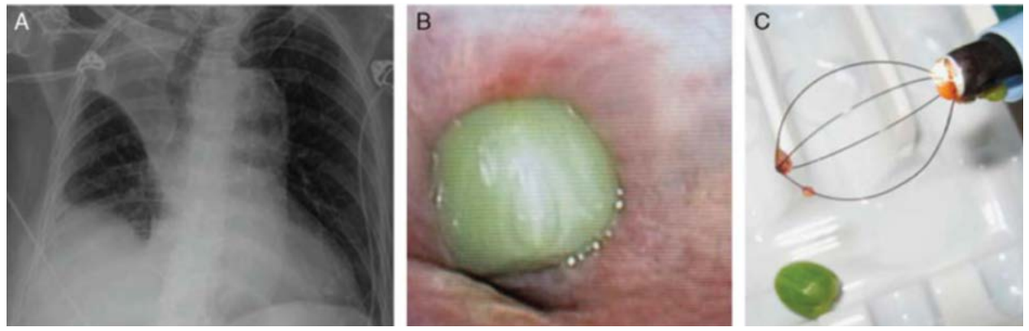
This study was undertaken to assess the role of bronchoscopy on the discontinuation of mechanical ventilation and prompt discharge from the intensive care unit (ICU) in our institution.

A retrospective analysis of 12 critically ill patients admitted to the ICU or high dependency unit (HDU) for the management of "respiratory failure from central airway obstruction" from August 2014 to September 2015 was performed.

The primary end points were: the proportion of patients in whom mechanical ventilation could be discontinued, the proportion of patients who could be extubated, and the proportion of patients who could be discharged from ICU to general wards after the bronchoscopic intervention. Nine patients (75%) had an endotracheal tube, and three (25%) had a tracheostomy tube. Nine (75%) patients admitted to the ICU could be transferred to a general ward after a median interval of 2 days (range, 1 to 7 days) after the intervention. Median pre-bronchoscopy and post-bronchoscopy ratio of arterial oxygen partial pressure to fractional inspired oxygen was 102.8 (range, 99.2 to 328) and 180 (range, 129 to 380), respectively, with significant improvement post-intervention (p=0.002). Radiologically, all eight patients with lung atelectasis on presentation experienced complete re-expansion of the lung on the day after bronchoscopic intervention.

This summary was prepared by Dr Akash Verma, a consultant in the Department of Respiratory and Critical Care Medicine, Tan Tock Seng Hospital.

Figure 1. Although uncommon, foreign body aspiration is a potentially fatal event and may require stay in the intensive care unit. The figure shows a representative case of a foreign body in the central airway. (A) Chest radiograph showing right upper lobe atelectasis. (B) Bronchoscopy showing a green pea in the right upper lobe. (C) Removal of green pea using the dormia basket.



RESEARCH EXCERPT 2

Analysis of Genetic Variation in CYP450 Genes for Clinical Implementation

Goh LL, Lim CW, Sim WC, Toh LX, Leong KP. PLoS ONE. 2017;12(1):e0169233.

IMPORTANCE IN CLINICAL PRACTICE

The genetic determinants of drug response are constant throughout life and offer great promise in optimising patient-tailored drug therapy. The implementation of PGx testing in patient care requires accurate, cost effective and rapid genotyping. We took into account factors such as cost, ease of workflow, turnaround time and flexibility of the assay when choosing the genotyping approach. The simplicity and robustness of this PGx panel is found to be highly suitable for use in a clinical laboratory. The finding that 98% of our population have at least one actionable genotype even among the small range of drug-gene rules provides impetus to incorporate PGx genotyping. For example, our study showed a high prevalence of CYP2D6 ultra-metabolisers (~18%) in our population. This group of people are at increased risk for toxicity for CYP2D6 substrates such as codeine, some anti-depressants and antipsychotics, and could potentially benefit from genotyping.

In this study, we aim to develop an appropriate panel relevant to the prescription patterns and genotype prevalence in this country. The performance of a custom designed panel for pharmacogenomics (PGx) testing was evaluated and used to analyse 506 genomic samples across three major ethnic groups of Singapore (Malay, Indian and Chinese).

The testing includes the detection of 32 key variants of CYP2C9, CYP2C19, CYP3A5 and CYP2D6 as well as two copy number assays for CYP2D6. Our genotyping results using HapMap reference controls demonstrated high call rate accuracy in terms of concordance with genotypes identified by independent analyses on the Sequenom MassARRAY system and droplet digital PCR. The study showed that the vast majority of individuals (98%) from our population carry one or more actionable variants (table 1) annotated in the Clinical Pharmacogenetics Implementation Consortium (CPIC). The major alleles detected include CYP2C9*3, CYP2C19*2, CYP2D6*2A, CYP2D6*10, CYP2D6*36, CYP2D6*41, CYP3A5*3 and VKORC1*2. These translate into a high percentage of intermediate and poor metaboliser phenotypes for these genes in our population and suggest that genotyping may be useful to identify patients who are prone to drug toxicity with standard doses of drug therapy.

This summary was prepared by Dr Goh Liuh Ling, a principal scientific officer from the Molecular Diagnostic Laboratory, Tan Tock Seng Hospital.

Table 1. Recommendations for actionable pharmacogenomic markers based on CPIC guidelines (Adapted from Goh LL, et al, 2017).

Gene	Actionable SNP	MAF	Clinical Pharmacogenetics Implementation Consortium		
			Evidence level	Drug	Dosing guidelines
CYP2C9	rs1799853	0.015	1A	Warfarin	Pharmacogenetic algorithm-based dosing available on http://www.warfarindosing.org is used for patients with different combinations of CYP2C9 and VKORC1 genotypes.
	rs1057910	0.072	1A		
VKORC1	rs9923231	0.597	1A		
CYP2C19	rs4244285	0.342	1A	Clopidogrel, Amitriptyline	An alternative antiplatelet therapy to clopidogrel is recommended for CYP2C19 poor or intermediate metabolizers.
	rs4986893	0.025	1A		
	rs72552267	0.002	1A		An alternative drug to amitriptyline is recommended for CYP2C19 ultrarapid metabolizers.
	rs12248560	0.062	1A		
CYP2D6	rs16947	0.207	1A	Codeine, Amitriptyline, Nortiptyline	Alternate analgesics to codeine are recommended for CYP2D6 ultrarapid and poor metabolizers due to potential toxicity and lack of efficacy, respectively.
	rs1135840	0.617	1A		
	rs1080985	0.146	1A		Alternative drugs to amitriptyline and nortriptyline are recommended for CYP2D6 ultrarapid metabolizers and poor metabolizers.
	rs3892097	0.040	1A		
	rs1065852	0.411	1A		
	rs28371725	0.069	1A		
CYP3A5	rs776746	0.653	1A	Tacrolimus	Increasing the starting dose by 1.5 to 2 times is recommended for CYP3A5 intermediate or extensive metabolizers.

SNP, single-nucleotide polymorphism; MAF, minor allele frequency.

FEATURE ARTICLE 1

HOME VENTILATION AND RESPIRATORY SUPPORT SERVICE

Since antiquity, humans have sought to support or replace inadequate or absent bodily functions for survival and comfort. We may not think of crutches and wheelchairs as "life support", but they have probably cumulatively contributed more to the survival of humans (especially war victims, amputees and people with neurologic illness) than dialysis machines, ventilators and ECMO machines.

Artificial enteral nutrition via nasoenteral or percutaneous enteral tubes, are similarly now commonplace interventions that support inadequate vital functions, viz. mastication and swallowing. Mechanical ventilation should be seen as a part of this continuum.

Bellows were employed for resuscitation of drowning victims in the 17th century. In the early 20th century, the "Iron Lung" saved the lives of polio patients and miners with coal gas inhalation poisoning. During the Second World War, endotracheal ventilation and positive pressure ventilation helped countless pilots with hideous facial and body burns.

During the 1950s, the worldwide polio epidemic killed thousands. The Danish Anaesthesiologist, Bjorn Ibsen, turned the tide on the polio epidemic in Copenhagen by instituting positive pressure ventilation via tracheostomy. Many polio survivors were dependent on either negative pressure ventilation via the iron lung, or positive pressure ventilation via tracheostomies or mouthpieces. In Europe and North America, this sparked a movement to help such ventilator assisted individuals go home, with a view of increasing their autonomy and dignity and hence improving their quality of life. This was not a cost-cutting measure by government authorities; on the contrary, families and friends of polio patients in France, at the spearhead of this movement, established associations, lobbied the Government, raised funds and trained caregivers, so that this "right-siting" could happen.

Singapore, a third world country till the late 80s, escaped this trend and hence prolonged mechanical ventilation was seen as something extraordinary and prohibitive. It was not until the early 2000s that a paediatric home care unit capable of looking after ventilated patients was established in Kandang Kerbau Children's Hospital.

The situation for adults was dire. A few families had brought their ventilator-dependent loved ones home in anecdotal incidents, but they had no public funding or trained healthcare personnel to support them. The follow-up model was the specialist outpatient clinic – imagine a ventilator-dependent tetraplegic attending separate appointments with ENT (for tracheostomy care), Orthopaedics (for management of spinal cord injury) and Rehabilitation!

The TTSH Home Ventilation and Respiratory Support Service (HVRSS) was established in 2009, with the support of TTSH senior management, and through the effort of doctors from Anaesthesiology, Respiratory Medicine, Continuing and Community Care, Palliative Medicine, Rehabilitation Medicine, as well as nurses, physiotherapists, respiratory therapists, occupational therapists, speech therapists and medical social workers. It began, and remains, a true multidisciplinary team.

Casemix

Respiratory failure can be simplistically divided into oxygenation failure (due to V/Q mismatch) and ventilatory failure. Ventilatory assistance is needed in patients with inadequate ventilatory capacity due to neurological or muscular inadequacies, or increased load due to chest wall restriction.

The majority of HVRSS patients have ventilatory insufficiency due to neuromuscular weakness, such as motor neuron disease, cervical cord injuries and other neuropathies and myopathies. A smaller number have ventilatory insufficiency due to catastrophic critical illness; in these cases, a combination of cardio-renal insufficiency, lung parenchymal disease and ICU-acquired weakness contribute to the breathing failure.

Ventilatory assistance is delivered with a variety of devices depending on patient needs:

a) Multimode home ventilators are prescribed for patients needing tracheostomy ventilation or near continuous (> 16 hr/day) non-invasive ventilation (NIV); and
b) Pressure-limited portable ventilators (also known colloquially as BiPAPs (bilevel positive airway pressure devices)) for patients needing nocturnal ventilation or nocturnal plus minimal daytime ventilation.

Figure 1. A lady on tracheostomy ventilation enjoying an outdoor moment.

The TTSH Home Ventilation and Respiratory Support Service (HVRSS) was established in 2009, with the support of TTSH senior management, and through the effort of doctors from Anaesthesiology, Respiratory Medicine, Continuing and Community Care, Palliative Medicine, Rehabilitation Medicine, as well as nurses, physiotherapists, respiratory therapists, occupational therapists, speech therapists and medical social workers.

Invasive ventilation at home is delivered via a tracheostomy. Contrary to common misconception, tracheostomised patients with intact bulbar functions can talk as long as airflow is directed through the vocal cords. We typically employ leak speech with additional positive end expiratory pressure (PEEP). A small group of patients are unable to tolerate this due to severely limited lung or chest wall compliance.

Figure 2. Gentleman on non-invasive ventilation which allows for intimate family time.

Swallowing is possible for tracheostomised patients with intact bulbar function, but the recovery of full swallowing function typically takes many weeks, with intense coaching by a speech therapist.

Non-invasive ventilation may be delivered via oronasal masks, total face masks, nasal pillows or mouthpieces. Side effects include dry eyes, stuffy nose, aerophagia, and skin breakdown over pressure areas. Again, contrary to common misconception, NIV may actually be more challenging than tracheostomy ventilation for the patient, family and healthcare team if the patient requires it round the clock. Secretions and bulbar dysfunction used to be listed as "contraindications" in older textbooks, but it is now recognised that some of these patients may tolerate NIV with assiduous airway clearance and careful adjustment of ventilatory settings.

Costs

Currently, the purchase of respiratory equipment is subsidised by the Ministry of Health's pilot funding, or by charitable organisations. A full set of equipment for a patient needing tracheostomy ventilation round the clock typically includes a multimode ventilator, cough assist machine, suction machine, oxygen concentrator, heated humidifier, cuff pressure manometer, manual resuscitator and pulse oximeter. The patient will in addition often need a hospital bed with a pressure relief mattress, and an appropriate wheelchair and commode. All these could add up to $30,000. Is this wise spending of healthcare dollars? With care, these equipment may be functional for five years, therefore the cost per day is $30,000/(365 x 5) or $16.50. As such, the TTSH HVRSS tries its utmost to ensure that equipment cost does NOT deter patients who need ventilatory assistance from using it.

Ongoing costs generally include increased utilities, consumables, as well as the cost of foreign domestic workers (two workers may be optimal if the patient is completely paralysed). As such, the monthly cost for a fully ventilated tetraplegic patient is typically between $1500 and $2500. Note two important caveats:

a) This cost is almost completely borne by the patient and family members, save for certain reliefs and subsidies; and
b) The cost of one day's hospitalisation in an acute care hospital is about $1000.

Managing the patient at home is cheaper, but unfortunately most of the cost of care at home is borne by patients and families. As such, we are grateful for all the help the Ministry of Health and various charities

Figure 3. Our patient and her family enjoying an outing with members of the TTSH Home Ventilation and Respiratory Support Service.

Figure 4. A patient on non-invasive ventilation via a nasal interface.

have provided for our ventilator assisted individuals and their families.

Survival

The literature suggests that NIV prolongs survival by months to a year in patients with advanced amyotrophic lateral sclerosis. Tracheostomy ventilation is known to prolong survival by years. Our experience matches these published data.

The results in COPD are more conflicting, but a recent German publication suggests that nocturnal NIV significantly improves both survival and quality of life.

Quality of Life

Are we prolonging life at the expense of multiplying suffering? Or as some euphemistically put it, are we prolonging dying? This is a suspicion and fear borne by many healthcare professionals.

Again, our local experience and published literature indicate that ventilator-assisted individuals generally enjoy reasonable satisfaction with life. Most ventilator-assisted individuals, when asked if they would choose mechanical ventilation again if given a chance, indicate in the affirmative.

We noticed that our neurologically disabled patients undergo a significant period of grieving before recovering equanimity and a positive outlook. Our cumulative experience in looking after more than a hundred ventilator-assisted individuals and their families has given us the confidence to reassure our patients and encourage them to wait out the blackest moments of grieving, while pointing them to strategies that might help – restoring patient autonomy, family engagement, physical exercise (active or passive), and social, cultural and religious activities that are meaningful to the patient.

We also notice that there is often an existential fear of death, and a clinging to life, even in the face of significant suffering. We have learnt that life and death cannot be weighed dispassionately on a scale of values. Every patient has to take his own time

to walk this last phase of his life. Many still make important discoveries, and still contribute positively to the lives of their families in this phase. Our role is to humbly accompany them, helping them to make the best choices in their unique situations.

Caregivers

Published research indicates a high level of caregiver stress and burnout. Our experience is not different. Do we then shorten the journeys of ventilator assisted individuals to avoid traumatising caregivers?

We are constantly humbled by the love and dedication of family members. Many are in the middle to lower middle income strata, yet they spare no effort to make life more comfortable and meaningful for their loved ones. We constantly share with families the pragmatic coping strategies we picked up from other households. It is truly a community of learning.

The Healthcare Team

Who should look after ventilator-assisted individuals? Many overseas centres deploy a tertiary hospital team providing follow-up for ventilation, with or without home visits. General medical and nursing needs are often provided by Family Physicians and nurses who make house calls.

Our team incorporates both elements, as GPs do not commonly perform house calls, and we do not have a district nursing system.

Each and every one of the doctors, nurses, therapists, social workers and administrators who have worked with the TTSH HVRSS have contributed tremendously to this pioneering work in Singapore. It is not possible to thank them individually here, but their names will always be remembered in the hearts of our patients and their families.

Figure 5. Some of the team members from the TTSH Home Ventilation and Respiratory Support Service team.

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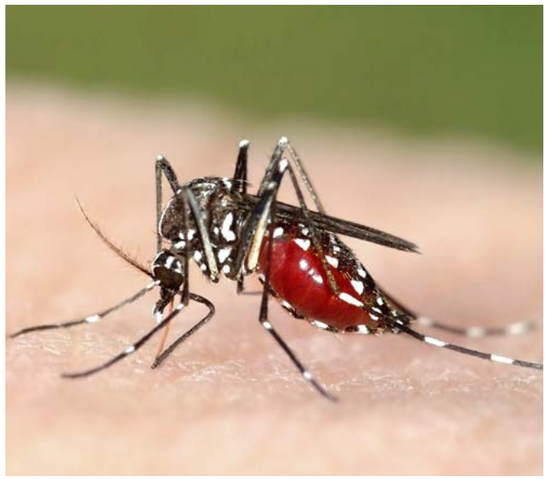
FEATURE ARTICLE 2

THE DENGUE VACCINE: CONFIDENCE AND HESITANCY

In October 2016, the Singapore Health Sciences Authority (HSA) approved Dengvaxia® (previously known as CYD-TDV), a newly developed dengue vaccine from Sanofi.[1] Dengvaxia is the result of decades-long research to develop a safe and effective vaccine for dengue – a mosquito-borne virus which causes hundreds of millions of infections worldwide. Over the past 40 years, dengue incidence has been increasing in Singapore and the region due to urbanisation.[2]

Dengvaxia is a quadrivalent, live-attenuated, chimera of the yellow fever vaccine virus, and the dengue virus. Both viruses are of the *Flavivirus* genus. Proteins on the surface of the yellow fever vaccine virus envelope have been replaced with counterparts from the dengue virus. The dengue virus can be grouped into (at least) four different strains – known as serotypes – because of differences in these surface proteins. Each vaccination shot is a mixture of these four serotypes.

Introducing new vaccines, and promoting the uptake of currently recommended ones, presents a number of challenges. The World Health Organisation (WHO) groups those challenges which underpin public acceptance of vaccines under the umbrella terms 'vaccine confidence' and 'vaccine hesitancy'.[3] These terms largely describe how the public perceives a vaccine's safety, effectiveness, and necessity.



Public perception of the need for a dengue vaccine in Singapore is perhaps assured. Intensive efforts have been put into education, surveillance and vector control by the National Environment Agency (NEA) and other government bodies, to limit dengue morbidity and mortality. As a testament to the success of these, the incidence of dengue is surprisingly low in Singapore, compared with our neighbours in South East Asia. From 2007-2015, the annual incidence of dengue averaged just 179 cases per 100,000, with only a small number of deaths.[4] An improved understanding of dengue pathophysiology has also helped to significantly reduce the proportion of people with dengue infections who need inpatient care or platelet transfusions.[5,6]

It is this relatively low incidence of dengue in Singapore, and the unusual nature of dengue virus immunology which limits the utility of the vaccine locally, and has also raised concerns about its safety.

Infection with one serotype of dengue does not provide protective immunity against other serotypes. Instead, second infections are more likely to result in serious consequences – such as the dengue shock syndrome.[7] Infection with two serotypes, however, is thought to provide sufficient cross-protection so that a third infection is unusual. Overcoming this interaction is a critical issue for a safe dengue vaccine.

Two large phase III clinical trials have been performed with Dengvaxia.[8,9] Both trials were performed in children younger than 16 years; one trial in Latin America and one in Asia. In both regions, dengue incidence is high compared with Singapore. Together, more than 35,000 children were enrolled. Pooling results across trials and all age groups, the vaccine reduced virologically-confirmed dengue infections by 60% in the 25 months following the first vaccine dose administered.[10] Over this period there was also a reduction in severe dengue by 93% and a reduction in hospitalisations by 81%. The vaccine also appeared to be safe with an incidence of serious adverse events (SAE) similar to placebo.[11]

While these headline results were encouraging, further analysis of the trial data highlighted a significant limitation: the efficacy of the vaccine was strongly affected by the presence of pre-existing immunity. In those who were seropositive prior to vaccination – i.e. they had previously been infected with at least one serotype of dengue – the efficacy was 78%. If the participants were seronegative, this fell to 38%. This role of pre-existing immunity was also evident when vaccine efficacy was analysed by age. In young children – who are more likely to be seronegative – efficacy was 34%, whereas in older children efficacy increased to 74%.

These data suggest that Dengvaxia might not reliably induce sustained serotype cross-protection. In the clinical trials, this vaccine provided better protection against dengue serotypes DEN-3 and DEN-4, compared with DEN-1 and DEN-2. Follow-up data to 5 years after vaccination also uncovered an increased risk for hospitalisation and severe dengue at 3 years after vaccination in those aged below 9 years. This could indicate that the immune response to vaccination is akin to a single infection. In people who are seronegative at vaccination, the response to an infection subsequently might be as if it was a second infection, with a higher risk of serious disease. Whereas, if seropositive at vaccination, the response to subsequent infection would be as if it was a third or later infection – and not associated with a higher risk of serious disease.

The significance of this finding from longer term follow-up data remains uncertain. It is based on a relatively small number of events, and hospitalisation risk was not significantly increased at year 4 or 5. It is also important to note that despite these concerns, the vaccine does represent a useful public health tool for countries with a high burden of disease. For example, overall (from year 1 to 5) the risk of hospitalisation was lower in children who received the dengue vaccine. It is estimated that in the Asia-Pacific and Latin American trials, the vaccine prevented 638 and 239 hospitalised dengue cases per 100,000 persons vaccinated, respectively.[12]

But in countries like Singapore, with a low burden of dengue, its role is much less certain. Plausibly a window of opportunity exists in which the vaccine is clinically useful – after the first infection, but before the second. As a result, it is recommended to screen for pre-existing dengue immunity prior to vaccination, to identify who is likely to benefit and least likely to experience complications. Such a test has recently become available locally – though positive serology will only confirm previous exposure to dengue, and not how often it may have occurred. Vector control remains the most important measure to reduce the chance of being bitten by an infected mosquito – while also reducing the risk of other mosquito-borne diseases such as Zika.

The uncertainty surrounding the best use of Dengvaxia in Singapore has resulted in a rather limited approval from the HSA – restricting its use to those aged between 12 and 45 years. In addition, the vaccine has not been added to the regular schedule and injection fees cannot be recovered from Medisave. In Singapore, confidence in its safety in the approved age group should not displace hesitancy about its benefits.

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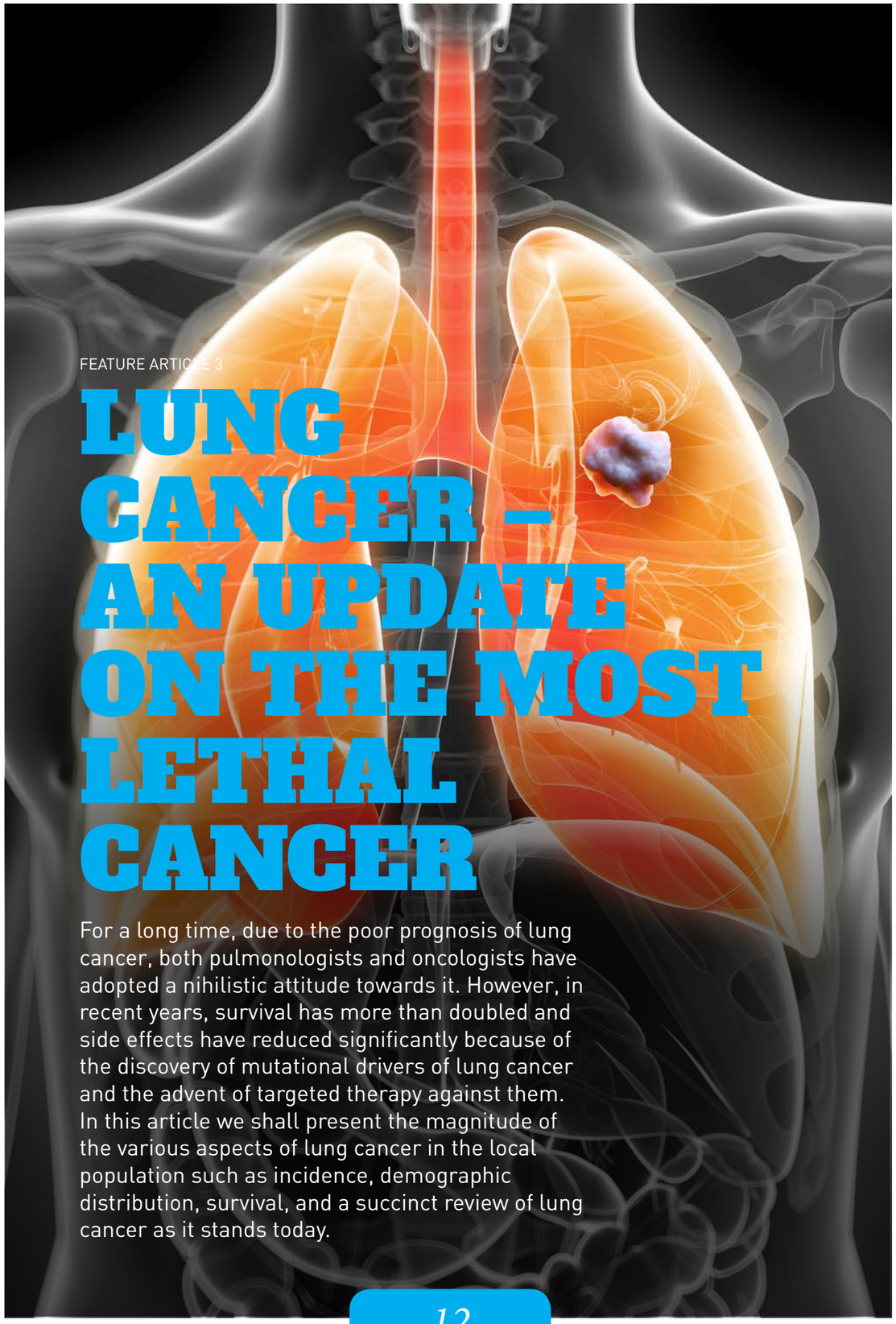

FEATURE ARTICLE 3

LUNG CANCER – AN UPDATE ON THE MOST LETHAL CANCER

For a long time, due to the poor prognosis of lung cancer, both pulmonologists and oncologists have adopted a nihilistic attitude towards it. However, in recent years, survival has more than doubled and side effects have reduced significantly because of the discovery of mutational drivers of lung cancer and the advent of targeted therapy against them. In this article we shall present the magnitude of the various aspects of lung cancer in the local population such as incidence, demographic distribution, survival, and a succinct review of lung cancer as it stands today.

Statistics of Lung Cancer

Lung cancer kills more people than the other four most common cancers (breast, colon, pancreas and prostate) combined.[1] It is the second most common cancer after prostate cancer in men, and breast cancer in women. Approximately 1500 people are diagnosed with lung cancer every year in Singapore.[2] Adenocarcinoma is the most common sub-type, affecting 43.5% of patients with lung cancer.[3] Women affected are more frequently diagnosed with adenocarcinoma (43% of all lung cancer subtypes) than men (21%), and the age of onset of adenocarcinoma can be as early as 31 years.[3] Approximately 32% of all lung cancer patients and 55% of patients with adenocarcinoma sub-type are non-smokers, dispelling the notion that only smokers are at risk.[3] The right and left upper lobes are the most affected sites, leading to the frequent misdiagnosis of tuberculosis. Eighty-two percent of patients present with central lesion adjacent to the large airways either in the form of parenchymal lesion located next to the airways, mediastinal lymph node, or mediastinal infiltration.[3] Thirty-two percent of patients with adenocarcinoma carry activating epidermal growth factor receptor (EGFR) mutation. Most patients (68%) present in advanced stage, and median survival among all cancer sub-types locally in advanced lung cancer is 122 days.[3]

Diagnosis

Chest radiographs can only pick up early-stage cancer if the lesion is more than 1 cm in size; anything smaller is missed. Chest radiography is limited in that it fails to diagnose early cancer when there is potential cure with resection (figure 1). Computed tomography (CT) is needed in each and every patient to guide the choice of modality for tissue diagnosis. On CT, lung cancer manifests in five radiological patterns: peripheral nodule or mass, discreet mediastinal lymph node, mediastinal infiltration, endobronchial lesion with distal lung atelectasis, and pleural effusion (figure 2).[4] In order to confirm the diagnosis, a tissue sample is needed. This is best obtained by transthoracic needle aspiration (TTNA) or navigation bronchoscopy for peripheral lesions, convex probe endobronchial ultrasound-guided trans-bronchial needle aspiration (EBUS-TBNA) for discreet mediastinal lymph node or mediastinal infiltration, bronchial biopsy for endobronchial lesion, and pleural tap followed by thoracoscopic biopsy for pleural effusion (figure 3). TTNA entails passing the biopsy needle percutaneously through the chest wall, into the lesion in the lung under CT guidance. Although TTNA is associated with a 24-40% risk of pneumothorax, the detection rate is close to 90%.[4] EBUS-TBNA is a technique that uses a bronchoscope fitted with an ultrasound probe at its tip to visualise structures outside the trachea and bronchi. When the ultrasonic bronchoscope is connected to the processor, it is possible to view the sonographic images of the structures outside the airways or inside the mediastinum. This enables biopsy of mediastinal or hilar lesions under real-time ultrasonographic image guidance. The diagnosis detection rate of EBUS-TBNA for such

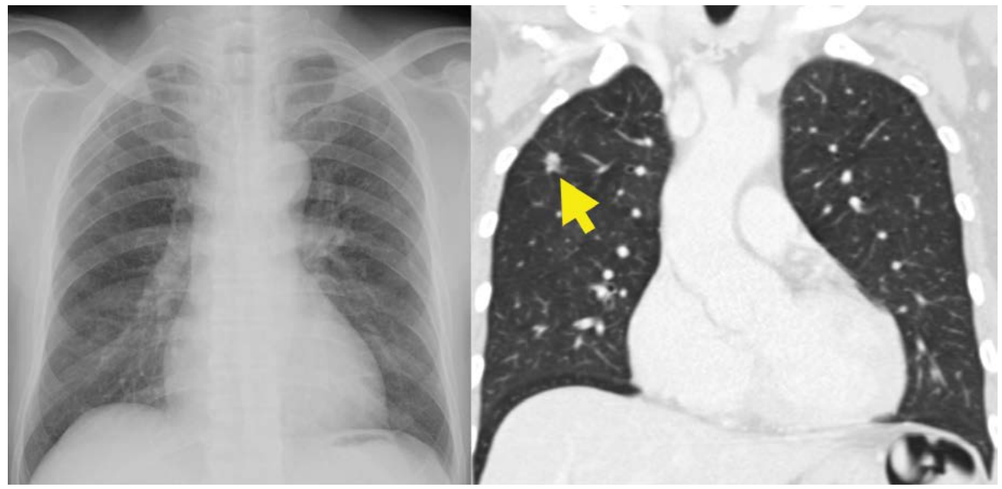

Figure 1. The right upper lobe pulmonary nodule (1 cm in size) is not visible on the radiograph (left) and only seen in the CT scan (right).

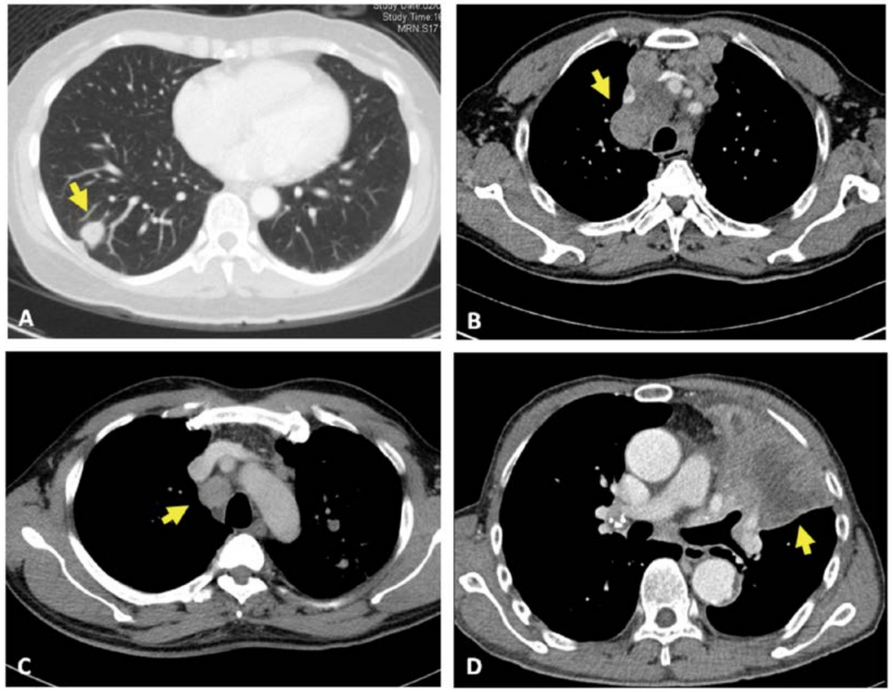

Figure 2. Common radiological patterns of lung cancer on CT scan. A: peripheral nodule or mass; B: discreet mediastinal lymph node; C: mediastinal infiltration; and D: endobronchial lesion with distal lung atelectasis.

lesions is close to 80%.[3] The historical alternative to EBUS-TBNA had been mediastinoscopy, but it is more invasive, requires an incision in the neck, and requires general anaesthesia. However, EBUS-TBNA can be performed via the trans-oral route under moderate sedation. The detection rate of bronchoscopic biopsy for endobronchially visible lesions is close to 70%, and for pleural tap, and thoracoscopic biopsy in cases of pleural effusion is 50% and 98% respectively.[5]

Surgical resection

Since surgical resection carries the highest chance of survival, this is the most important form of therapy. Lung cancer in stages I and II, and in some cases stage III (IIIA) are resectable, whereas stages IIIB and IV are not. Staging is determined in two ways. Some physicians prefer to perform a CT scan of the brain, abdomen and pelvis, and a bone scan, whereas others prefer a brain MRI and a PET scan (figure 4). Brain MRI and PET scan are more accurate and is the preferred strategy, but a PET scan is more expensive (~SGD1600) than a bone scan.[6] Any deposit outside the chest, in the contralateral lung, or pleural effusion renders the cancer stage IV.

Feasibility of surgical resection

Some patients, despite early stage lung cancer, are not physically fit to endure removal of a part of or the whole lung, especially if they have COPD and poor lung function from smoking. FEV1 and DLCO below 60% of predicted carry an increased risk from surgery. In addition, patients with poor heart function or advanced age are also contraindicated for surgical resection. Patients unfit for surgery are treated with radiation therapy, specifically stereotactic body radiation therapy. However, best supportive care or palliative care is not the only option left for the advanced stage cancer patients.

On CT, lung cancer manifests in five radiological patterns: peripheral nodule or mass, discreet mediastinal lymph node, mediastinal infiltration, endobronchial lesion with distal lung atelectasis, and pleural effusion.

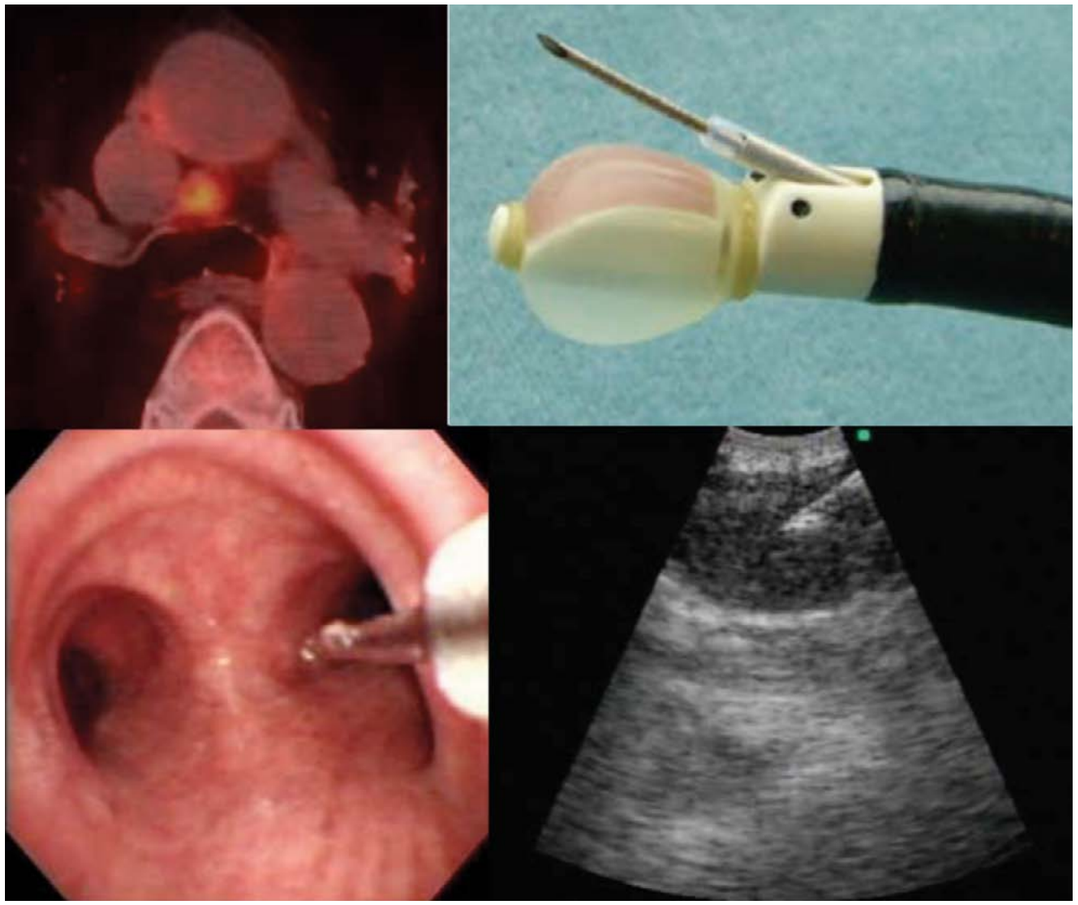

Figure 3. Convex Probe EBUS-TBNA, showing, clockwise from upper left, the lesion on CT scan, the tip of the probe, the passage of the probe into the bronchus and the ultrasound image.

Targeted Therapy

Median survival in "untreated" advanced lung cancer is 4-5 months, and 10% survive more than a year.[7] Platinum-based doublet chemotherapy has been the mainstay of treatment of advanced lung cancer in the last four decades but response rates and survival have remained dismal and largely unchanged from 13% in 1975 to 16% thirty years later in 2003.[7] Median survival in advanced lung cancer treated with platinum-based doublet chemotherapy is 8-12 months, and 33% survive more than a year.

However, over the last decade, there are new insights into the molecular pathogenesis of lung cancer. Lung cancer is more diverse at a molecular level than is apparent on histological appearance. The histological description of adenocarcinoma, for example, may encompass close to 10 different types of lung cancer from the genomic aberration point of view, each requiring a potentially different therapeutic agent (figure 5). This is in complete contrast with the historical practice of treating all adenocarcinoma patients with the same platinum-based doublet chemotherapy indiscriminately.

The identification of several activating mutations driving lung cancer, such as EGFR, ALK and ROS1, has significantly changed the outcome of lung cancer. The resulting emergence of therapy targeted at blocking the carcinogenic pathways activated by these mutations has proven to be twice as effective as standard chemotherapy.[8,9] Median survival in advanced lung cancer treated with EGFR-TKIs is 22 months and about 53% survive more than a year.[10] Targeted therapy carries minimal side effects (such as acne and diarrhoea) and can be administered orally, in contrast to conventional chemotherapy which is relatively more toxic and requires in-

hospital drug administration. Most therapeutic benefit has so far been seen in patients with "adenocarcinoma", which, anyway, affects the majority of patients. The striking success in treating adenocarcinoma has provided the impetus to harness similar benefits in squamous cell and small-cell carcinoma sub-types of lung cancer as well. In addition to targeted therapy, immunotherapy, which makes use of the patient's immune system to inhibit proliferation of lung cancer cells, is emerging as another option. Although limited to clinical trials currently, it carries significant promise.

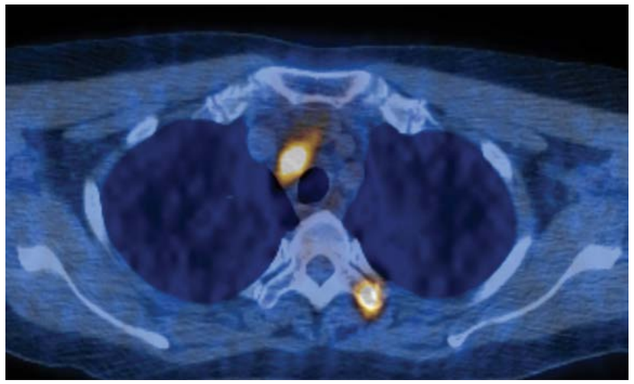

Figure 4. An example of a PET scan showing two lesions.

In conclusion, the long-standing nihilism surrounding lung cancer is fading. Better understanding of the molecular profile of lung cancer and of the role of the immune system is making novel therapies available. It is hence necessary for doctors treating lung cancer to stay abreast of new developments to provide updated treatment strategies to patients.

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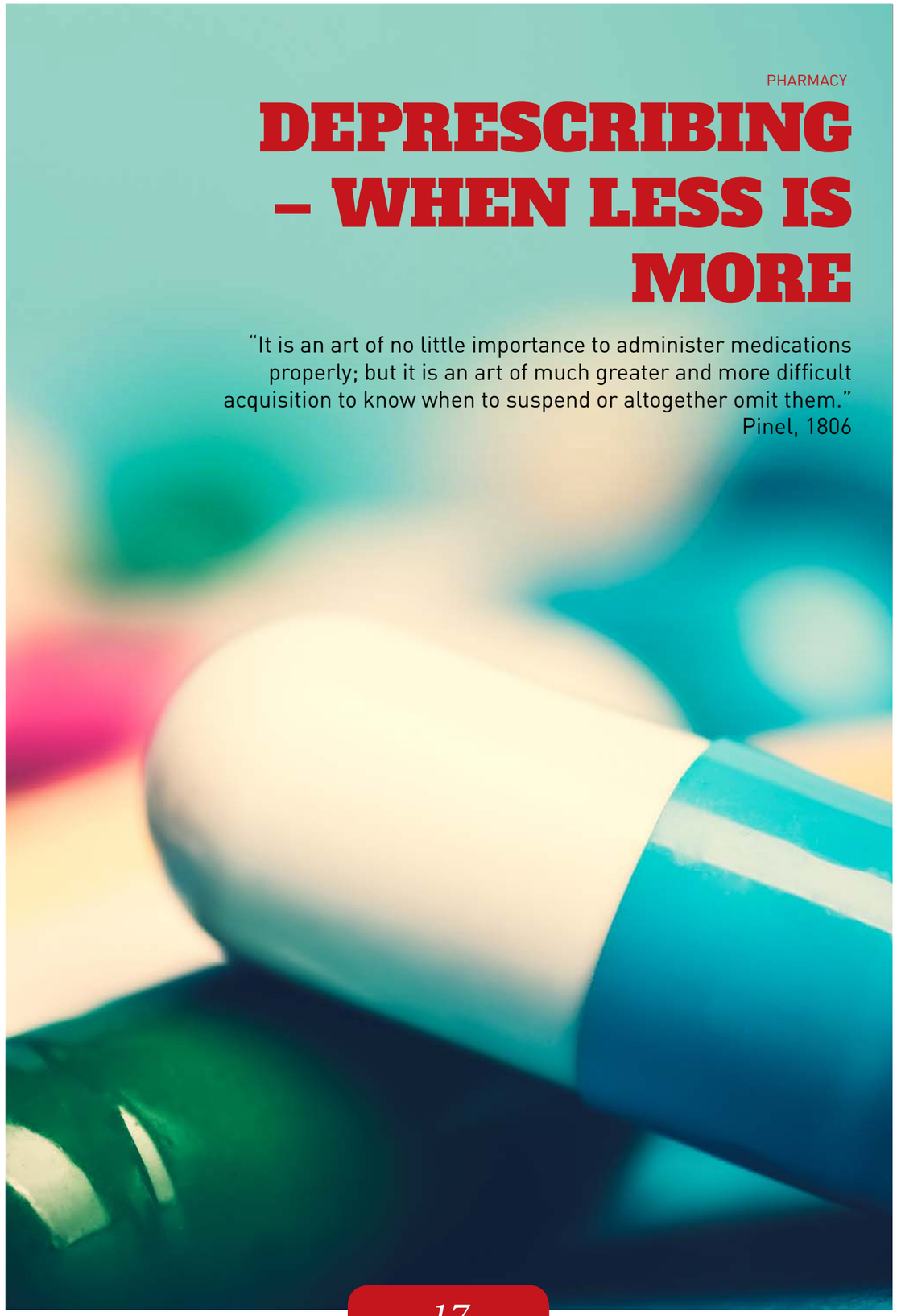
PHARMACY

DEPRESCRIBING – WHEN LESS IS MORE

"It is an art of no little importance to administer medications properly; but it is an art of much greater and more difficult acquisition to know when to suspend or altogether omit them."
Pinel, 1806



CASE EXAMPLE:

Mdm Lim is a 92-year-old Chinese lady on regular follow-up at your clinic. Today she is accompanied by her daughter, Stacey. Her medical history includes hypertension, dyslipidaemia (last lipid panel in December 2016: LDL 1.6 mmol/L, triglyceride 1.4 mmol/L), stage 3-4 chronic kidney disease and recurrent falls.

On examination, you noticed several bruises on her arms and minor forehead lacerations. Stacey reports that Mdm Lim had fallen twice in the past 6 months, and she complains of giddiness and confusion at times. The blood pressure while seated is 110/70, without postural drop on assuming the standing position. Stacey recounts that "Mum is taking too many pills that she sometimes refuses to take her medications" and "Mum often forgets her night dose of medications apart from the sleeping pill."

Her medication list consists of:

1. Aspirin 100 mg once daily;
2. Calcium/vitamin D 2 tab once daily;
3. Lovastatin 20 mg nightly;
4. Nifedipine LA 60 mg once daily;
5. Renal Vitamin 1 tab once daily;
6. Vitamin B complex 1 tab once daily;
7. Omeprazole 20 mg twice daily;
8. Lorazepam 1 mg nightly; and
9. Chlorpheniramine 4 mg three times a day, as needed (she has been taking this regularly for itch for the past 2 weeks).

Mdm Lim is a typical geriatric patient prescribed multiple medications whom we encounter commonly. With advances in medicine and accessibility to affordable healthcare, Singapore is facing the challenge of an ageing population with increasing life expectancy[1] and the attendant escalating healthcare cost.[2] The number of residents aged 65 years and above has more than doubled from 200,000 in the year 2000 to 487,000 in 2016, and is expected to reach 900,000 by 2030.[3,4] Annual elderly healthcare costs in Singapore are projected to rise 10-fold to more than $66 billion by 2030, the highest in the Asia-Pacific region.[2]

With increasing age, the accumulation of chronic diseases and the resultant care complexity make polypharmacy prevalent in the geriatric population (broadly defined as individuals aged 65 years and over) and increases our healthcare expenditure. Polypharmacy is often compounded by the fragmented care delivered by multiple prescribers across numerous settings, as well as the patients' and physicians' reluctance to modify treatment regimens initiated by other physicians. This frequently gives rise adverse drug reactions and drug interactions, poor adherence and increased rates of readmissions.[4]

In a local study of 454 nursing home residents aged ≥65 years, polypharmacy predisposed patients to inappropriate medication use.[5] The average number of medications prescribed per resident was 5.32, and 70% of the residents were evaluated to have inappropriate medication use.

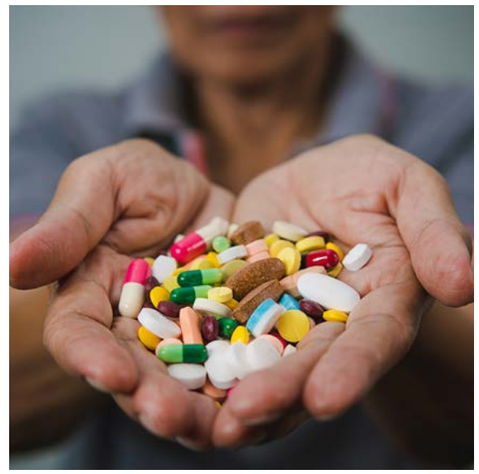
What is deprescribing?

The concept of 'deprescribing' has been described centuries ago but the term is relatively new, appearing in the literature approximately a decade ago.[6] In a recent publication, Scott et al.[7] defined deprescribing as the 'systematic process of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits within the context of an individual patient's care goals, current level of functioning, life expectancy, values, and preferences.'

The broad principles of deprescribing entail:[6,7]

1. A thorough review of the current medications and their indications;
2. Evaluation of the benefits and risks of drug-induced harm taking into account individual patient factors, life expectancy and goals of treatment;
3. Identification of medications to be ceased, substituted, or reduced; and
4. Planning and implementing a deprescribing regimen in partnership with the patient and/or carers involved in the patient's care.

It is important to recognise that deprescribing is part of the process of providing holistic patient-centred care, and plays a role as important as initiation or dose titration in the prescribing continuum. A systematic deprescribing process should be an integral part of medication review to ensure patients do not receive unnecessary treatment with little benefit and has the potential for causing harm. Deprescribing is neither about identifying a medication erroneously prescribed in the first place nor denying effective treatments to patients who may benefit, and should definitely not be viewed as such.



The deprescribing literature has been mostly centred on the geriatric population for several reasons. These patients have multiple diseases, there is substantial evidence of harm associated with inappropriate prescription, increased susceptibility to adverse effects due to altered drug disposition, and weaker evidence-based treatment recommendations for geriatric patients. As such, the risk of polypharmacy may outweigh the combined benefits of the multiple drugs prescribed for these individuals. Nevertheless, the principles of deprescribing provide a framework for systematic review of drug therapy and can be applied beyond the geriatric population to any individuals with multiple comorbidities and chronic medications.

Benefits of deprescribing

As shown in a recent comprehensive review, evidence supporting deprescribing is limited to medication withdrawal trials or trials improving the appropriateness of medications prescribed.[7] In general, most of the available studies demonstrate that deprescribing is not harmful in the majority of older adults and may be beneficial in improving quality of life,[8,9] as well as reducing risk of falls and cognitive impairment,[10] mortality[9,11] and costs.[9]

In a systematic review of 31 medication withdrawal trials among individuals aged ≥65 years, it was found that specific drug classes (antihypertensives, psychotropics, benzodiazepines) can be withdrawn without harm in carefully selected patients with judicious monitoring.[12] Of note, withdrawal of psychotropics and benzodiazepines was associated with a marked reduction in falls and improvement in daily function and cognition. This was similarly observed in a more recent review.[10] Garfinkel et al.[8,9] applied the Good Palliative-Geriatric Practice algorithm for drug discontinuation to nursing home residents and community-dwelling elderly in Israel. In the first study among nursing home residents, 332 different drugs were discontinued in 119 patients without significant adverse effects.[9] Patients in the study group had an observed reduction in mortality rates and referrals to acute care facilities compared to the control group. A follow-up study involving 70 community-dwelling elderly successfully discontinued 81% of the medications, which included antihypertensives, nitrates, frusemide, acid suppressant therapy, and benzodiazepines.[8] Although 2% of the discontinued drugs required re-initiation due to symptom recurrence, 88% of the elderly rated an improvement in perceived general health.[8] An unblinded, randomised pragmatic clinical trial showed that statins could be safely discontinued in patients with life expectancy of less than 1 year, with benefits such as improved quality of life, use of fewer non-statin medications and a corresponding reduction in drug costs.[13]

There are many ongoing studies that will add to the growing evidence for deprescribing. For instance, a multinational randomised controlled trial utilising electronic decision support to guide deprescribing in elderly patients with multiple chronic diseases (PRISMA-eDS) was recently started in Europe. Several trials investigating relevant patient outcomes following interventions to reduce polypharmacy are under way in Australia (the Opti-Med study), Canada (WiseMed) and the Netherlands (DIM-NHR). In addition, various organisations such as the

> Deprescribing is neither about identifying a medication erroneously prescribed in the first place nor denying effective treatments to patients who may benefit, and should definitely not be viewed as such.

Ontario Pharmacy Research Collaboration are at the forefront in developing evidence-based guidelines on deprescribing specific drug classes.

Barriers to deprescribing

As French psychiatrist Phillipe Pinel's quote illustrates, deprescribing may be a daunting task for most physicians. It is more intuitive to prescribe medications than to deprescribe them, as medical training offers little to no grounding on the subject. This is worsened by the general paucity of data and the lack of a comprehensive framework to guide this process. Disease-specific guidelines typically recommend medication initiation based on clinical trials which predominantly exclude the multimorbid elderly, yet rarely provide guidance when risks outweigh the benefits of continuing pharmacotherapy. Poor communication between healthcare providers and inadequate transfer of information at transitions of care further contribute to this knowledge deficit. As a result, deprescribing is often fraught with anxiety and uncertainty, leading to the reluctance to 'rock the boat' because of the perception of disrupting the clinical stability of an existing medication regimen.

Some physicians may feel solely responsible for medicine management within their own speciality. Even if one identifies a potentially inappropriate prescription in a patient, he or she may be reluctant to interfere with medications prescribed by other physicians or specialists, lest this leads to conflicts. Other barriers cited by physicians include heavy workload, time constraints, patients' ambivalence or resistance to change, and non-specific fears about the consequences of drug discontinuation.[14,15]

From the patients' perspective, the deprescribing process is similarly challenging.[14,16] Patients' demands and expectations, as well as those of their families, may be a hindrance to deprescribing. Patients may be reluctant to stop medications which they perceive to be necessary or beneficial. Some who experience problems with their medications may unintentionally withhold information, either because they attribute side effects to ageing or they have difficulties communicating with their healthcare providers due to cognitive impairment or poor health literacy. Some may also resist deprescribing due to fear of withdrawal reactions or even of abandonment by their physicians. Nonetheless, a survey showed that more than 90% of patients are willing to cease a medication that their prescriber deemed to be no longer required.[17]

The deprescribing process

To date, most guidelines are written for the management of single disease. None have been designed specifically to guide deprescribing, nor do they fully address the interconnected factors associated with multimorbidity. With recent interest in deprescribing as a means to tackle polypharmacy and improve health outcomes, a variety of structured frameworks and tools have emerged to encourage deprescribing in practice (table 1).

Generic algorithms typically outline common elements for deprescribing in a sequence. Examples include the 5-step deprescribing protocol by Scott et al.[7] and the Good Palliative-Geriatric Practice algorithm.[8] Explicit medication lists are often employed as screening instruments to identify inappropriate drugs that are amenable for deprescribing. In the realm of geriatric medicine, the Beer's criteria[18] and STOPP/START[19,20] criteria are commonly used. However, these medication lists are not exhaustive, and withdrawal of medications not on these lists should also be considered. In addition to the generic approach, drug-specific evidence-based clinical deprescribing guidelines have also been developed as tools to support deprescribing. For instance, the Canadian Deprescribing Network has published decision-support algorithms for proton pump inhibitors (PPIs), benzodiazepines, antipsychotics and antihyperglycemics.

RESOURCE	BRIEF DESCRIPTION
The 5-step deprescribing protocol[7] (Australia)	• Proposed by Scott and colleagues based on their research • Key steps in the deprescribing protocol: 1. Reconcile medications and ascertain indications for each drug 2. Consider overall risk of drug-induced harm 3. Assess each drug for its eligibility to be discontinued 4. Prioritise drugs for discontinuation 5. Implement and monitor drug discontinuation regimen
The Good Palliative-Geriatric Practice algorithm[8,9] (Israel)	• Consensus-based flow chart first developed in 2004 for nursing homes to reduce polypharmacy. Use has been further evaluated in community dwelling older adults. • The algorithm may be used to re-evaluate individual drug therapy for each patient, systematically guiding healthcare professionals to decide whether to continue with the same dose, reduce it, discontinue the drug completely, or switch to another drug.
Scottish Polypharmacy Guidance (Scotland)	• Developed jointly by the Scottish government, NHS Education for Scotland and two subgroups of the Polypharmacy Guidance Review Group • Provides tools for medication review, including the '7-steps' review process, medicines to be cautious of (in terms of their need, effectiveness, safety and adherence/patient-centredness), and collated number needed to treat/adverse drug reaction charts to aid informed decisions on drug efficacy and safety. • Available at: http://www.polypharmacy.scot.nhs.uk/
Deprescribing For Better Health Outcomes (Australia)	• Collaboratively developed by Primary Health Tasmania and Consultant Pharmacy Services • A suite of evidence-based fact sheets to guide deprescribing in older people • Fact sheets available for allopurinol, antihypertensives, antiplatelets, antipsychotics, benzodiazepines, bisphosphonates, cholinesterase inhibitors, glaucoma eye drops, NSAIDs, opioids, proton pump inhibitors, statins, sulfonylureas, calcium/vitamin D • Available at: http://www.cpsedu.com.au/posts/view/47/2016-Deprescribing-Resources
Beers criteria[18] (United States)	• Updated in October 2015 by a workgroup convened by The American Geriatrics Society, comprising of experts in geriatric medicine, nursing, pharmacy practice, research, and quality measures • Explicit list of individual drugs or drug combinations that have an unfavourable balance of benefits and harms in many older patients that prompts for close review of the necessity and cautious prescribing/monitoring if the medication is prescribed
STOPP/START criteria[19,20] (United Kingdom/ Ireland)	• STOPP = Screening Tool of Older Persons' Prescriptions • START = Screening Tool to Alert doctors to Right (i.e. appropriate, indicated) Treatment

	• First developed in 2008 by experts in geriatric pharmacotherapy across UK and Ireland. Last updated in 2014 to take into account an expanding therapeutics base. • Evidence-based sets of criteria that aid healthcare professionals to systematically identify potentially inappropriate medications (STOPP) and potential prescribing omissions (START)
Medstopper	• Developed by a team of Canada's experts in gerontology, polypharmacy, pharmacology, pharmacy, patient advocacy, and family medicine • Free online web application to aid deprescribing decisions based on three key criteria: 1. Potential of the drug to improve symptoms 2. Potential to reduce risk of future illness 3. Likelihood of causing harm • Incorporates recommendations in Beers criteria and STOPP/START criteria • Creates a list of a patient's drug-indication pairs and prioritises drugs to deprescribe, as well as provides suggestions on how to taper identified medications and possible symptoms to be monitored • Plans to validate Medstopper in a trial setting underway • Available at: http://medstopper.com/
Medication Appropriateness Index[21] (United States)	• Originally developed by an expert panel in the Duke University Medical Center in 1992 to assist physicians and pharmacists in assessing drug therapy appropriateness in elderly patients • Implicit criteria consisting of 10 elements considered necessary for appropriate prescribing, including indication, effectiveness, appropriate dose, practical and correct directions, absence of interactions, lack of therapeutic duplication, appropriate duration and low cost • Requires comprehensive clinical details, medical knowledge and clinical judgment to assess each criterion on a three-point Likert scale • Applicable to any drug and to any clinical condition in any clinical setting. However, it does not address under-prescribing and may be time consuming to use.
Deprescribing.org (Canada)	• Developed by the Canadian Deprescribing Network • Evidence-based deprescribing guidelines/algorithms for healthcare professionals and deprescribing information pamphlets for patients • Algorithms available for proton-pump inhibitors, benzodiazepines, antipsychotics and antihyperglycemics • Available at: http://deprescribing.org/
NO TEARS tool[22] (United Kingdom)	• May be used as a mental prompt to aid efficient medication review within a 10-minute consultation • **N**eed and indication; **O**pen questions; **T**ests and monitoring; **E**vidence and guidelines; **A**dverse events; **R**isk reduction or prevention; **S**implification and switches

Table 1. Resources available to guide decision-making in deprescribing.

The exploding growth in PPI utilisation, accompanied by the emerging data on potential harm, has attracted attention in re-appraising the use of PPIs.

Deprescribing efforts in Singapore: The example of proton pump inhibitors

The past decade has seen efforts at promoting awareness and utility of deprescribing in local settings. The Institute of Mental Health has successfully achieved a reduction of antipsychotic polypharmacy in chronic schizophrenia inpatients with no documented relapses within 6 months of implementation, aided by the development of in-house protocols to guide dose titration and monitoring.[23] Khoo Teck Puat Hospital initiated Project Cut-a-piller to create a systematic workflow to detect and rectify inappropriate polypharmacy, and this project has been expanded to look at various deprescribing initiatives, such as a PPI deprescribing framework implemented in inpatient settings. The National Healthcare Group is also embarking on a stepped-wedge randomised controlled trial looking at the implementation of team-care deprescribing in nursing homes.[24]

The Pharmaceutical Society of Singapore has contributed towards the deprescribing effort. As part of Pharmacy Week 2015, the Society launched a deprescribing kit (figure 1) and a joint position statement on polypharmacy in Singapore. Since then, polypharmacy and deprescribing have been part of the key messages for the annual Pharmacy Week, in order to continually promote awareness and empowerment amongst physicians and patients. PPIs were also identified as the first drug class proposed to be deprescribed at a national level, due to its heavy overutilisation worldwide including our home ground. In 2014 alone, 59 million units of PPIs costing $19 million were dispensed from restructured hospitals.[25]

The exploding growth in PPI utilisation, accompanied by the emerging data on potential harm, has attracted attention in re-appraising the use of PPIs. In a study examining inpatients prescribed PPIs at Tan Tock Seng Hospital (TTSH), almost half of the patients were on PPIs without the presence of an FDA- or guideline-approved indication. PPI overutilisation may be attributed to its revolutionary efficacy in upper gastrointestinal disorders overshadowing its potential for adverse effects, namely hypomagnesaemia, vitamin B12 deficiency, pneumonia, fractures, *Clostridium difficile* infection, and chronic kidney disease. Many healthcare practitioners have the false impression that PPIs are a harmless and inexpensive option for any gastrointestinal condition, or are necessary for

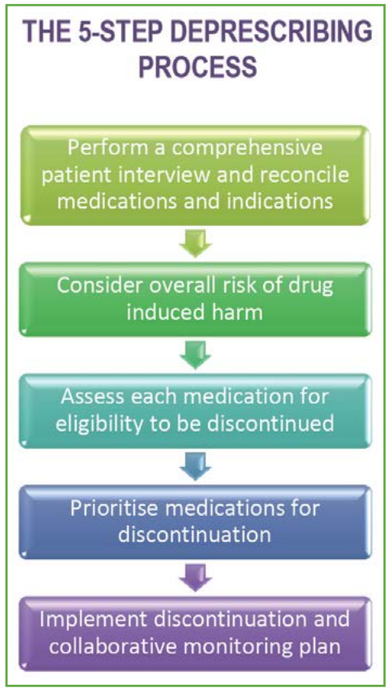


Figure 1. Pocket card from the "Introducing Deprescribing to Singapore" Kit, Pharmacy Week 2015 (with courtesy from the Pharmaceutical Society of Singapore).

prophylaxis against possible gastric problems which a patient has yet to encounter. The failure to reassess the individual patient's needs for continuation of PPIs as long-term therapy during care transition contributes to inappropriate overutilisation and unnecessary expenditure.

Recently, the Ontario Pharmacy Evidence Network (OPEN) published a decision-support algorithm which strongly recommends deprescribing PPIs (reducing dose, discontinuing, or using "on-demand" dosing) in adults who have completed a minimum of 4 weeks of PPIs, except when used to treat selected conditions such as chronic NSAID users with bleeding risk or patients with documented history of a bleeding gastrointestinal ulcer.[26] This adds on to the armamentarium of evidence-based PPI deprescribing guidelines available in literature.

At TTSH, the Department of Pharmacy has developed the PPI Deprescribing Guideline in collaboration with the Department of Gastroenterology and Hepatology. Launched in October 2016, this in-house guideline serves as a quick point-of-care reference on guideline-based recommendations of PPI indications, dose and duration, with the intent to support clinicians in reducing or stopping PPIs when no longer indicated. Roadshows have been conducted since its launch to raise awareness of the need to deprescribe PPIs, and anecdotally there is a general trend towards incorporating PPI deprescribing into daily practice. Further work is currently being done to assess the effects of implementing the PPI deprescribing guidelines.

While it may seem that overseas organisations and local restructured hospitals have been proactive in the area of deprescribing, we must recognise that efforts should not be limited to selected clinical settings, healthcare professionals or patient populations. Each health care encounter provides an opportunity to engage patients and their caregivers in understanding the role of deprescribing in ensuring optimal and judicious medication use.

Conclusion

The single-disease approach towards prescribing has inevitably resulted in polypharmacy, a 21st century medical phenomenon that increases the risk of adverse drug reactions and non-adherence. Deprescribing addresses this by shifting the focus from the number of medications to the appropriateness of the medications to address specific patient needs and goals. It involves a critical review of medications, identifying and discontinuing those that have lost their indication, have no clear benefit for the patient or are not aligned with the patient's goals of care. This is a process that requires no less diligence and care that physicians exercise when prescribing. While various resources have been developed to support this process, the success of deprescribing highly depends on a concerted effort amongst healthcare professionals across settings and full engagement with patients and their caregivers.

As part of Pharmacy Week 2015, the Society launched a deprescribing kit and a joint position statement on polypharmacy in Singapore. Since then, polypharmacy and deprescribing have been part of the key messages for the annual Pharmacy Week, in order to continually promote awareness and empowerment amongst physicians and patients.

CASE EXAMPLE (continued):

Mdm Lim needs to take more than 10 tablets daily and it is not surprising that Stacey is concerned. You review Mdm Lim's medications and identify several medications which you can consider discontinuing.

Medication	Remarks
Aspirin	Mdm Lim has no history of coronary, peripheral or cerebral symptoms or occlusive events. In a meta-analysis conducted by the Antithrombotic Trialists' (ATT) Collaboration, aspirin use in primary prevention only provided a marginal benefit in preventing major cardiovascular events (number needed to treat=246) but increased major gastrointestinal and extracranial bleeds. The evidence supporting the use of aspirin in primary prevention is weak, and this should be weighed against Mdm Lim's risk of bleeding due to her history of recurrent falls.
Lovastatin	There is no compelling indication for lovastatin given Mdm Lim's well-controlled LDL levels and the paucity of evidence supporting the prescribing of statins in primary prevention in elderly patients with low cardiovascular risk.
Renal Vitamin	Mdm Lim is not on dialysis and is eating well. There is no indication for Renal Vitamin as it is meant to replace water soluble vitamins that are lost during dialysis.
Vitamin B complex	Non-essential supplement; may be stopped to reduce pill burden.
Lorazepam	Mdm Lim has been complaining of having difficulty sleeping. You probed further and realised that she has poor sleep hygiene. She drinks coffee three times a day (including at night). Her sleep is also disrupted in view of frequent urination at night. In view of her history of falls and confusion, you would like to stop lorazepam. However, as Mdm Lim has been taking lorazepam regularly for the past 2 months and you are concerned about rebound insomnia, you decide to taper the dose gradually and reinforce good sleep hygiene habits.
Chlorpheniramine	Mdm Lim complains of itchiness that requires her to take regular chlorpheniramine. She likes its "sedating effect" that helps her sleep. After examination, you suspect that the itch may be attributed to her dry skin. Concerned that prolonged use (>1 week) of first-generation antihistamines may increase risk of falls and worsen cognition in the elderly, you advise Mdm Lim to stop chlorpheniramine and apply topical moisturisers regularly. You also prescribe a short course of second-generation non-sedating antihistamine to be used when necessary for the itch.
Omeprazole	Standard dose omeprazole is effective in reducing the incidence of peptic ulcers in low-dose aspirin users. Mdm Lim denies any dyspepsia symptoms with aspirin, but finds it difficult to remember to take her night doses of medications. You decide to reduce to standard dose PPI (i.e. 20 mg once daily).

Stacey is rather apprehensive about stopping aspirin and requests for some time to think about it. You agreed to continue aspirin till the next visit (planned for 4 weeks' time) and reinforce fall precautions. At the end of the consultation, Mdm Lim's prescription is as follows:

1. Aspirin 100 mg once daily;
2. Calcium/vitamin D 2 tab once daily;
3. Nifedipine LA 60 mg once daily;
4. Omeprazole 20 mg once daily;
5. Lorazepam 0.5 mg nightly;
6. Aqueous cream apply twice daily; and
7. Loratadine 10 mg once daily as needed for 1 week.

Mdm Lim thanks you for reducing the number of pills that she needs to take, from ten to five every morning.

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RADIOLOGY QUIZ

Every issue, we present radiology and ECG quizzes of interesting cases seen in TTSH. Put your knowledge to the test with this issue's scenarios.

QUESTION 1

This 56-year-old gentleman, a non-smoker, presented to the GP with a six-month history of intermittent non-specific chest pain and a dry cough. The patient had no significant past medical or family history. ECG findings were unremarkable. A chest X-ray was performed in the polyclinic (figure 1). What does it show?

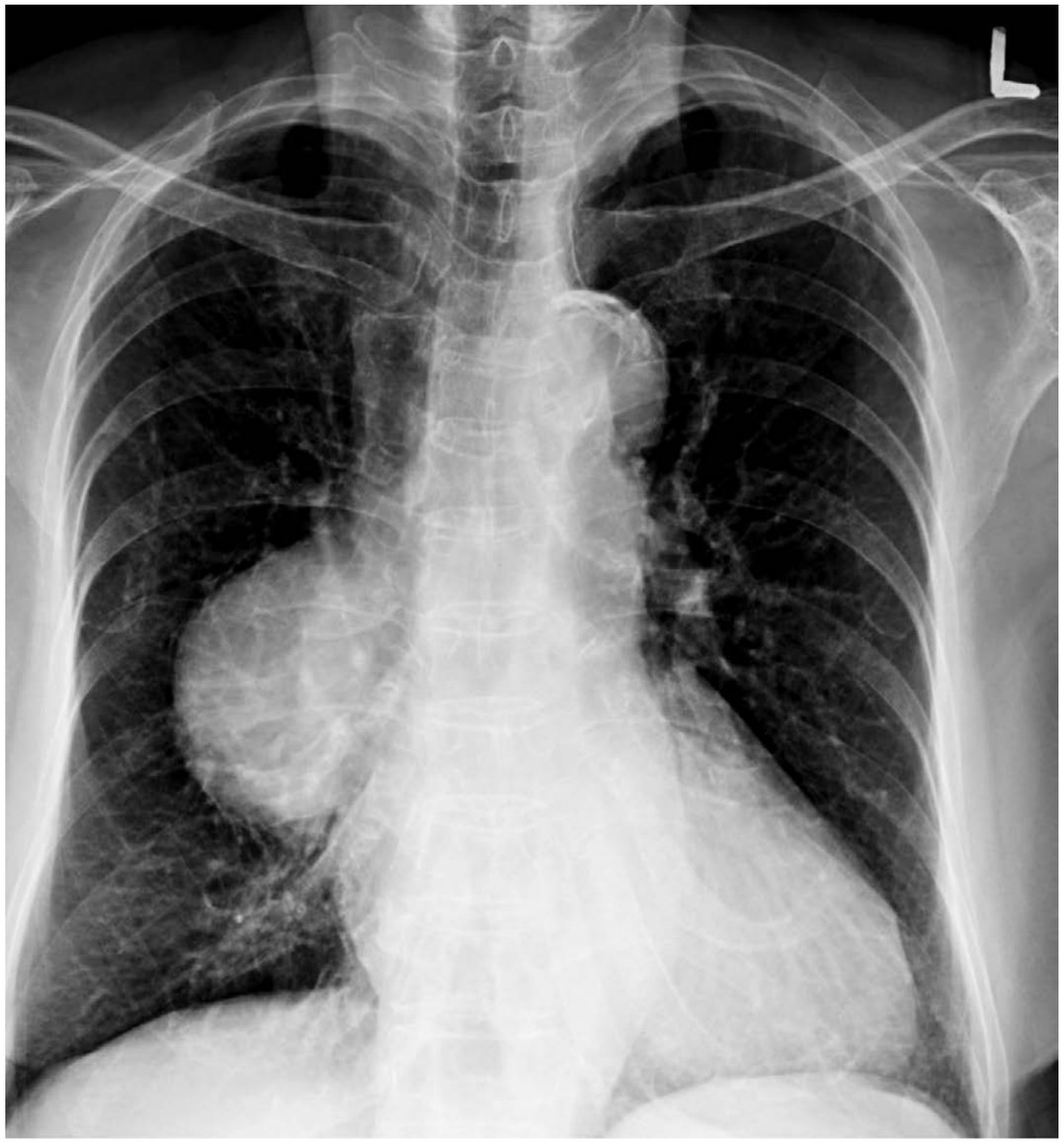
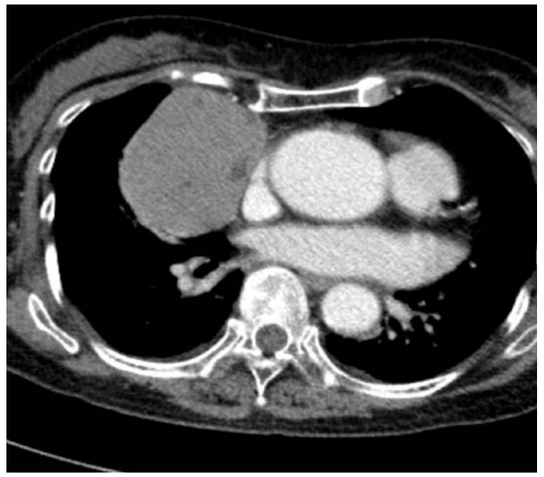


Figure 1. Chest X-ray of a man complaining of intermittent chest pain.



QUESTION 2

A contrast CT scan was subsequently performed for this patient. What do the selected images show (figures 2 to 4) and what are your differentials for a mass lesion in this location?

Figure 2. Selected axial CT slice, soft tissue windows.

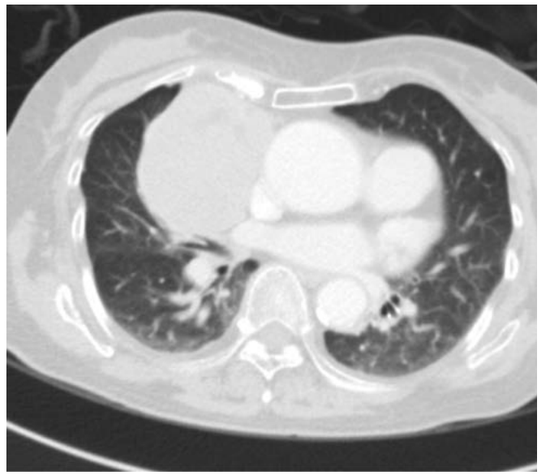


Figure 3. Selected axial CT slice, lung windows.

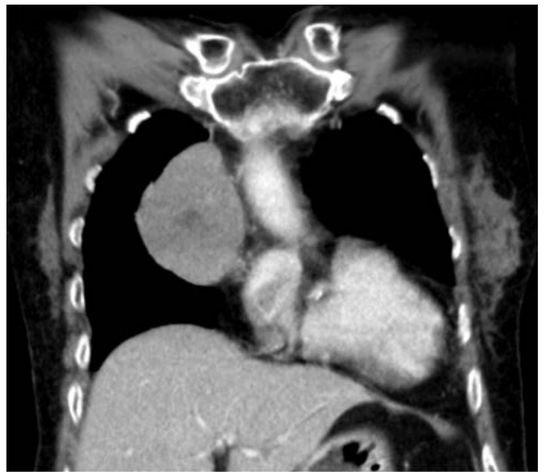


Figure 4. Selected coronal CT slice, soft tissue windows.

ANSWER 1

The heart is not enlarged. The lungs are clear. There is a large soft-tissue opacity in the right hilar region. No internal calcification or fat density is seen within. The margins of the mass are smooth and appear confluent with the mediastinum. The hilar vessels as well as the right main bronchi can be seen through the mass (hilar overlay sign) without any silhouette, indicating that this is most likely not arising from the middle mediastinum. Further, the absence of posterior rib splaying or bony destruction suggests that is the mass most likely arises from the anterior mediastinum. Overall, there is a large mass originating from the right mediastinum, most likely in the anterior compartment.

ANSWER 2

The contrast CT images confirm the presence of a smoothly marginated, soft-tissue mass in the right anterior mediastinum. There are a few small hypodense areas within, most likely representing areas of necrosis. No internal calcification or fat density is seen within. There is no associated pericardial effusion or invasion of the adjacent vascular structures. The middle lobe bronchus posteriorly is compressed. No lung parenchymal involvement, mediastinal nodes or pleural effusion is seen.

The differentials for an anterior mediastinal mass are the 4 'T's – Thymoma, Thyroid goitre, Teratoma, and Terrible lymphoma. In this case, thymoma is the most likely differential given the absence of any enlarged thyroid gland or tracheal deviation on the chest X-ray, the absence of fat within the lesion and the absence of any other enlarged nodes in the thorax or the neck.

The patient was referred to interventional radiology for a CT guided biopsy and the histology results confirmed the diagnosis of a thymoma (figure 5).

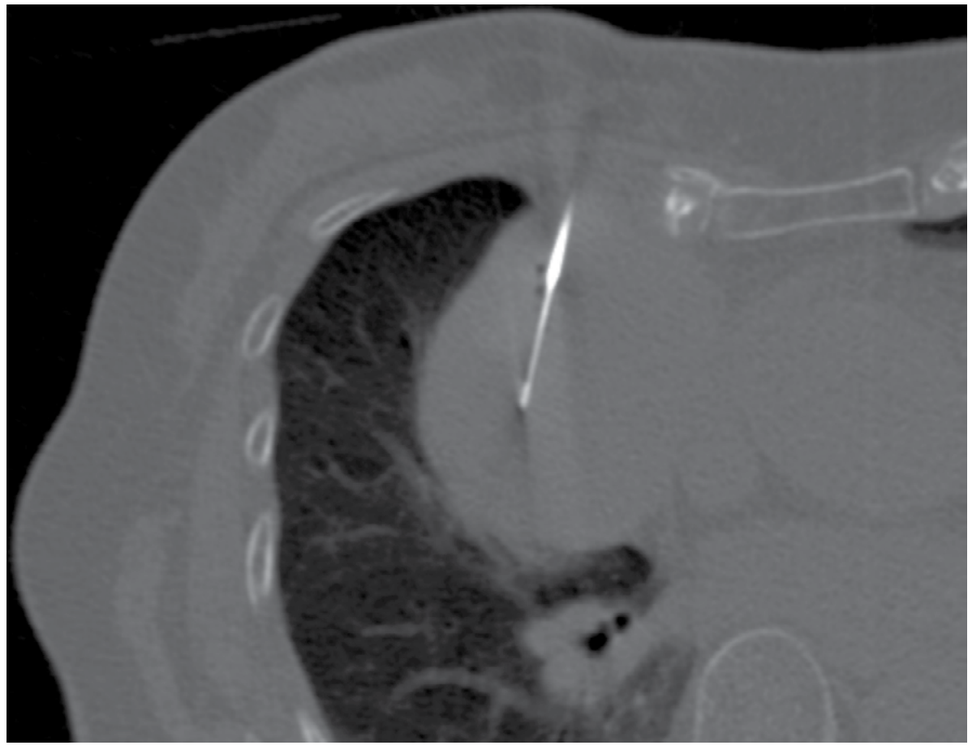


Figure 5. CT guided biopsy showing presence of thymoma.

Discussion

Thymomas are relatively rare tumours arising from the thymus in the anterior mediastinum of middle-aged patients. They are however still the most common primary neoplasm of the thymus and of the anterior mediastinum.

It typically presents in the 5th to 6th decades, without gender predilection. These lesions can be asymptomatic or cause with non-specific symptoms such as chest pain, persistent cough or shortness of breath. Large tumours may present with venous obstruction, dysphagia or stridor due to the mass effect.

Numerous conditions have been associated with thymomas. Those with the strongest correlation and most frequently encountered include myasthenia gravis (10-20% of patients with myasthenia gravis have a thymoma and 30-50% of patients with a thymoma have myasthenia gravis), pure red cell aplasia (50% of patients with pure red cell aplasia have a thymoma and 5% of patients with a thymoma have pure red cell aplasia), systemic lupus erythematosus (SLE) and rheumatoid arthritis.

Thymomas are invasive in nature and the WHO classification scheme divides them according to histological appearance, which correlates with the likelihood of invasiveness and thus correlates with staging. The Masaoka staging system is also commonly adopted to assess invasion and is assessed at surgery.

On plain radiographs, they are often seen as a well-defined, lobulated soft tissue density slightly towards one side of the mediastinum. On CT, thymomas are usually of soft tissue attenuation and are usually located between the sternum and great vessels. A cystic component is common and calcification can be seen in as high as 10-50% of patients which tend to be small and more commonly peripherally located.

Treatment depends on the stage as well as the presence of myasthenia gravis. Complete surgical excision usually results in cure. For invasive thymoma, surgery may still be contemplated if complete excision is thought possible. If not, then down-staging with preoperative chemotherapy may be employed. Radiotherapy is not usually employed for stage I thymomas, but has a role in both post-surgical management of resected invasive thymoma or for inoperable invasive tumours, including thymic carcinoma. Prognosis is significantly influenced by the histological type and surgical staging.

FURTHER READING

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ECG QUIZ

A 50-year-old male tourist presented to the Emergency Department (ED) with a three-day history of vomiting, diarrhoea, fever and vague chest discomfort. He has no cardiovascular risk factors apart from a family history of premature coronary artery disease. A resting 12-lead electrocardiogram (ECG) was performed when he arrived at the ED (figure 1). The serum troponin level was 0.15 ug/L (normal < 0.5ug/L).

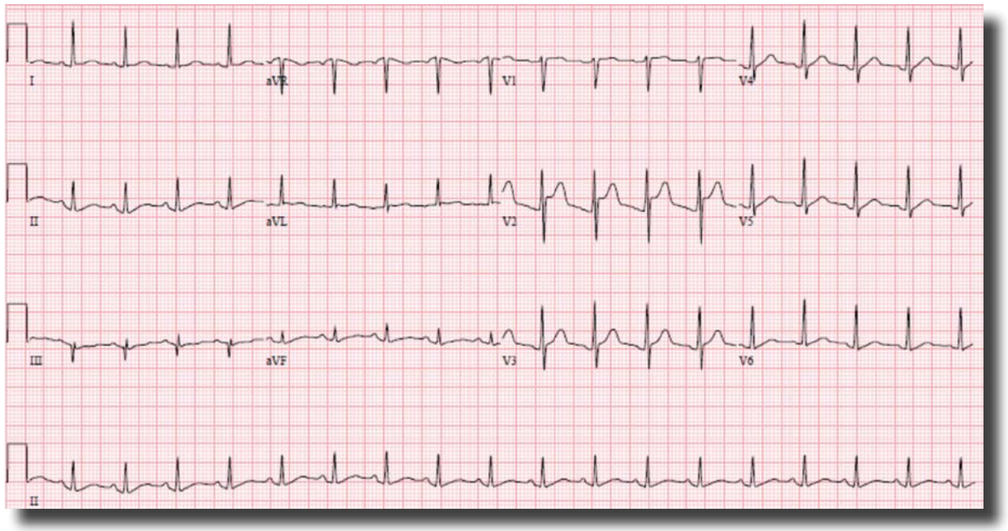

Figure 1. ECG performed on arrival to ED.

He was observed in the ED and a repeat ECG was performed 6 hours later (figure 2). The repeat serum troponin rose to 4.68 ug/L. The patient was still experiencing mild chest discomfort although he remained haemodynamically stable.

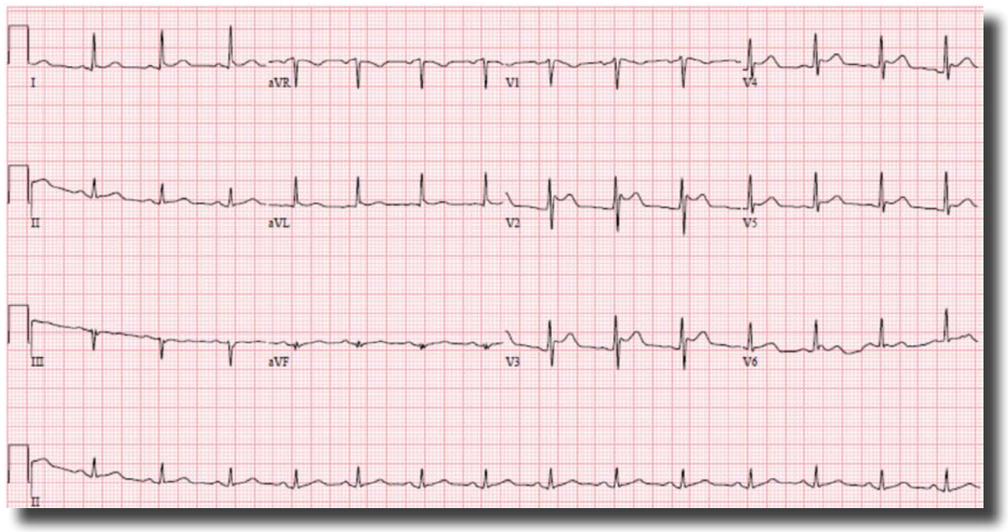

Figure 2. ECG performed 6 hours later.

QUESTION

What is the most likely diagnosis?

ANSWER

The most likely diagnosis in the given scenario is myopericarditis.

Discussion

This patient with minimal cardiovascular risk factors presented with symptoms consistent with viral gastroenteritis and vague chest pain. His initial 12-lead ECG (figure 1) revealed sinus tachycardia with isolated ST segment elevation over lead V2. The repeat ECG (figure 2) performed 6 hours later showed new ST segment elevation over leads V2-V6, with no reciprocal ST depressions in other leads. On closer examination, the PR segment (especially over lead II) appears depressed. There is also PR segment elevation and ST segment depression in lead aVR. Given the elevated troponin level, a diagnosis of myopericarditis was made. A transthoracic echocardiogram revealed a normal left ventricular ejection fraction (LVEF) with no wall motion abnormalities or pericardial effusion. An invasive coronary angiogram performed the next day revealed normal coronaries. The patient declined further investigations in view of cost and was discharged well.

Acute pericarditis contributes to 5% of all ED visits for chest pain. Viral infection (such as enteroviruses, herpesviruses, adenoviruses, parvovirus B19) is the most common cause. The chest pain is typically described as sharp, pleuritic and improved by sitting forward. Physical examination may reveal a pericardial rub in a third of cases.

The ECG changes in acute pericarditis evolve through different stages over time and with treatment. The earliest and most classical ECG changes include diffuse concave ST elevation with PR segment depression. Reciprocal ST segment depression and PR segment elevation in lead aVR is also seen. However, these typical ECG patterns are seen in only 60% and other non-specific ST and T wave changes can also occur. Other causes of ST segment elevation such as ST segment elevation myocardial infarction (STEMI) and early repolarisation should be excluded.

Apart from the 12-lead ECG, serum cardiac biomarkers (e.g. troponin) should be performed to detect concomitant myocardial injury. In the absence of other features suggestive of myocardial ischaemia, the elevated troponin levels are not diagnostic for a myocardial infarction. Instead, a diagnosis of myopericarditis is made if there is predominant pericarditis in the presence of myocardial involvement.

The 2015 European Society of Cardiology Guidelines for the diagnosis and management of pericardial diseases recommends further investigations such as transthoracic echocardiogram and cardiac magnetic resonance imaging. Coronary angiography should also be performed to exclude coronary artery disease in the presence of a troponin rise.

As with acute pericarditis, non-steroidal anti-inflammatory drugs (NSAIDs) are the first line medications for myopericarditis. Despite myocardial involvement, myopericarditis generally carries a good prognosis with no increased risk of heart failure or mortality.

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