

# MEDICAL DIGEST



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In this year-end edition of *Medical Digest*, I wish to talk about the generosity of spirit of clinicians. I define this as the willingness to share and do more, especially for those who cannot conceivably benefit us. An expression of this big-heartedness is the willingness to spend time to listen and communicate, and to share our humanity. These can manifest as taking care to choose the most appropriate doctor to refer the patient to if the medical problem is beyond us, willingness to write a note to the patient's employer to ease his workload, helping the patient navigate the byzantine medical system, and visiting the patient when he is admitted to hospital. A little effort by the doctor can make a disproportionately large impact on the perception and outcome of the patient.

These acts are not merely something nice that we can do. The clinician may well be the best educated, most connected, and best resourced person that a patient will ever encounter. If this doctor, in this privileged position and with full knowledge of the patient's circumstances, does not walk the extra mile, who will? Dr Jeffrey wrote: *"Unkindness to patients is often more subtle; by using distancing tactics such as appearing busy, concentrating on scans and the results of tests, and ignoring patients' anxieties, doctors can leave patients feeling isolated. In a management culture which measures success in numbers, league tables and throughput, time spent with the patient addressing their concerns is not valued so is not seen as an essential part of a doctor's duty"* (J Royal Soc Med 2016;109:261-263).

Let us be conscious of the things that stop us from being generous: lack of time, discontent with our lot, unconducive environment, burnout and distraction. Let us bring all your attention to bear on the patient's needs by giving yourselves. We should show generosity of spirit not only to the well-behaved and well-heeled patient, but especially to the indigent and difficult-to-manage ones.

And on that note, we end our tirade. The Editorial team of *Medical Digest* wishes all readers a blessed 2020.

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.



## CHARACTERISTICS AND CLINICAL OUTCOMES OF OPEN SURGERY FOR TRIGGER DIGITS IN DIABETES

Ho SWL, Chia CY, Rajaratnam V. *Journal of Hand and Microsurgery* 2019; 11(2): 80-83.

Diabetes carries a 10-15% lifetime risk of trigger digit development. Diabetics who develop trigger digits are thought to suffer from poorer long-term clinical outcomes due to of persistent pain, recurrence of triggering, and poorer patient satisfaction after treatment. Treatment of trigger digit can be non-surgical (splints and corticosteroid injections) and surgical (open or percutaneous release).

This was a retrospective study of all patients who underwent open surgical release under local anaesthesia for trigger digit in a single institution from 2012 to 2013. A total of 191 patients were recruited, on whom 260 open releases were performed. More than half (54.5%) were females. The majority (92.1%) were right-hand dominant, with the trigger digit occurring more frequently in the dominant hand in both diabetic (68.9%) and non-diabetic (75.4%) patients. The middle finger was most commonly involved (43.5%).

Fewer than one-third (31.9%) of patients had diabetes. The diabetic group was significantly older than the non-diabetic group (58.2 vs. 54.2 years,  $p < 0.05$ ). There was no significant difference between both groups with regard to multiple-digit presentation, the average number of digits affected, and the severity of trigger digits. Both groups reported high post-operative satisfaction after surgery and had good or excellent clinical outcomes at 2-year follow-up, with similarly low rates of complications such as stiffness and pain.



TTSH Research News is curated and edited by DR MELISSA TIEN, consultant in the Department of Ophthalmology, Tan Tock Seng Hospital.

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

Polypoidal choroidal vasculopathy (PCV), an affliction of the choroidal vasculature, is a sub-type of neurovascular age-related macular degeneration (nAMD). Multimodal imaging is necessary for the accurate diagnosis of both PCV and nAMD, which share common clinical and imaging features.

Fluorescein angiography (FA) is the gold standard test for diagnosing nAMD while indocyanine green angiography (ICGA) holds the same position for PCV. In real-world clinical practice, patients with features of nAMD are often investigated with FA alone without further confirmatory tests. Hence, PCV may be misdiagnosed as nAMD since FA features of both may appear analogous. As ICGA may not be readily available or may be contraindicated because of shellfish or iodine allergy, alternative imaging methods to confirm PCV are needed. In such clinical scenarios, it is useful for retina specialists to be able to identify FA features which differentiate PCV from nAMD, and to be aware of their predictive values.

Image sets from the EVEREST study (a prospective, multi-centre study conducted in patients with symptomatic macular PCV from Apr 2008 to May 2009 across 7 centres in Asia) were analysed. 61 patients were diagnosed with PCV, and 15 with nAMD. FA features with a positive predictive value for PCV > 80% were: (i) nodular hyperfluorescence (corresponding to polyp location on ICGA), (ii) blocked fluorescence (corresponding to submacular haemorrhage on colour

fundus photography), (iii) leakage characteristic of occult choroidal neovascularization (CNV), and (iv) pigment epithelial detachment (PED). However, the features of occult CNV and PED had low specificity (< 30%), as these could also be suggestive of nAMD.

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

### IMPORTANCE IN CLINICAL PRACTICE

In practices where ICGA is not routinely performed, identification of specific features on FA suggestive of PCV may serve as a signal for retina specialists to carry out ICGA to confirm the diagnosis. In cases where ICGA is unavailable or contraindicated, these FA features may function as an alternative imaging modality to support the diagnosis of PCV.

Though PCV and nAMD share similar presentation and risk factors, there are differences in their pathophysiology, visual prognosis and clinical course. Misdiagnosis of PCV as nAMD is a common reason for poor response to anti-vascular endothelial growth factor treatment. Nearly 50% of nAMD patients with a poor response to treatment require revision of the primary diagnosis. Hence, it is clinically relevant to differentiate PCV from nAMD from the outset.

## EVEREST STUDY REPORT 4: FLUORESCIN ANGIOGRAPHY FEATURES PREDICTIVE OF POLYPOIDAL CHOROIDAL VASCULOPATHY

Tan CS, Ngo WK, Lim LW, Tan NW & Lim TH. *Clin. Experiment. Ophthalmol.* 2019; 47: 614-620.





## CONTROVERSIAL TOPIC

# EVALI: E-CIGARETTE OR VAPING PRODUCT USE-ASSOCIATED LUNG INJURY

### CASE VIGNETTE

A 22-year-old man with no prior medical history presented to the Emergency Department with abdominal pain, nausea and vomiting of a week's duration. At triage, it was found that he had low grade fever of 37.9°C and borderline oxygen (O<sub>2</sub>) saturation of 89% on room air. Lab tests showed mild transaminitis and neutrophilia. Chest radiograph (CXR) showed bilateral interstitial opacities. He was put on supplemental oxygen and empirically treated for bacterial pneumonia.

Further history revealed that he had consulted his family physician three weeks ago for dyspnoea, cough and fever, which were attributed to viral respiratory tract infection and treated symptomatically. The cough and dyspnoea improved, but never resolved completely. The patient also stated that he had picked up the use of electronic cigarettes (e-cigarettes) two months ago from his university mates.

His clinical condition deteriorated shortly after admission to the ward, with an arterial blood gas showing hypoxaemic respiratory failure, and a repeat CXR showing worsening bilateral infiltrates. He was intubated and transferred to the intensive care unit.

Further computed tomography of the chest showed bilateral diffuse consolidation with ground-glass changes. Additional lab tests revealed elevated C-reactive protein and a negative HIV test. He underwent a bronchoscopy with bronchoalveolar lavage (BAL) while intubated. The BAL fluid analysis was of neutrophilic predominance; of note, there were findings of lipid-laden macrophages on cytology. Evaluation of the BAL fluid by culture and polymerase chain reaction for bacterial, fungal and viral pathogens did not reveal any infection.

The patient was commenced on intravenous steroids, and his condition improved over the subsequent week. He was extubated, tapered down on the steroid dose, and weaned off oxygen supplementation before being discharged home three weeks after the initial presentation.

### THE CASE FOR ELECTRONIC NICOTINE DELIVERY SYSTEMS

Electronic Nicotine Delivery Systems, colloquially known as e-cigarettes, are battery-operated devices that serve as alternative, non-combustible tobacco products. These devices heat a liquid containing nicotine and flavours, and deliver them in an aerosolized form to the user. It was initially thought to be a tool that would help smokers who are users of traditional combustible cigarettes to quit smoking.

The act of using e-cigarettes, also known as vaping, is now a multi-billion dollar industry that appeals to current smokers, former smokers, and young people who have never smoked. In the United States, 6.9 million people are current e-cigarette users. Rates of e-cigarette

REMARKABLY, E-CIGARETTES HAVE, OVER THE YEARS, REACHED THE MASS MARKET WITHOUT EITHER EXTENSIVE PRECLINICAL TOXICOLOGY TESTING OR LONG-TERM SAFETY TRIALS, LARGELY BECAUSE THEY ARE NOT CONSIDERED AS CONVENTIONAL MEDICAL THERAPEUTICS OR DEVICES.

use are higher in young people, and have accelerated recently. The high prevalence rates in the senior high school age group are of great concern.

Remarkably, e-cigarettes have, over the years, reached the mass market without either extensive preclinical toxicology testing or long-term safety trials, largely because they are not considered as conventional medical therapeutics or devices. By extension, their effectiveness in contributing to smoking cessation, impact at the population level, and health effects of exposure remain uncertain and highly controversial.

### THE RISE OF E-CIGARETTES

Since their introduction to the mass market about 15 years ago, e-cigarettes have undergone major revamps in design which allow the user greater control over the liquid composition, the nicotine concentration, and how it is aerosolized. Initially, most sales came from cigar-like products which resembled traditional combustible cigarettes. More recently however, modular systems containing batteries, liquid tanks of different flavours, and heating coils have allowed the users to select custom-made flavours and individualize the heating mechanisms.

Of note, newer pod devices like the JUUL e-cigarette system (first introduced in 2015) now hold a dominant market position for e-cigarette sales in the US. The device resembles a USB memory stick with cartridges that can be exchanged by the user for different-flavoured liquids. This device found a loyal following among the young, and currently accounts for 70% of e-cigarette sales in the US.

As recent as summer this year, the US Centers for Disease Control and Prevention (CDC) reported an emerging epidemic of acute pulmonary illness related to e-cigarette use (Figure 1). This was first reported in Illinois and Wisconsin, and subsequent surveillance using the proposed case definition revealed high incidences in California and New York as well. There have been as least 8 deaths in the US which have been attributed to the use of e-cigarettes.

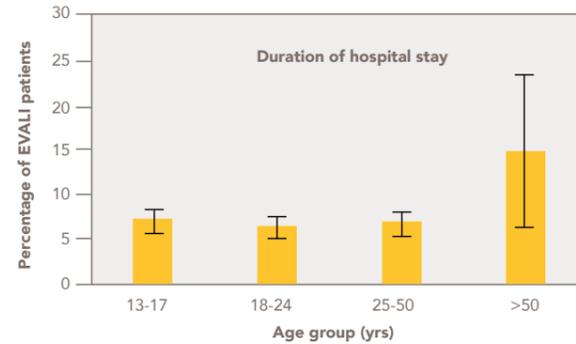
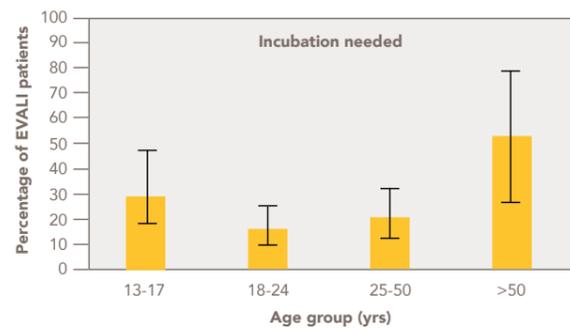


Figure 1. Proportion needing intubation (N = 338) and the duration of hospitalization (N = 242) among patients with e-cigarette or vaping product use-associated lung injury (EVALI), stratified by age, in the United States, February to October, 2019.

In Singapore, under section 16(2A) of the Tobacco (Control of Advertisements and Sale) Act, it is illegal to possess, purchase and use vaporisers in Singapore. This includes e-cigarettes, e-pipes and e-cigars. To date, the Health Sciences Authority (HSA) has prosecuted over 20 individuals for the illegal sales of e-cigarettes locally. Interestingly, the use of e-cigarettes remains legal in Malaysia despite calls for its use to be regulated or even banned, after multiple reports of lung diseases and at least six deaths related to its use.

#### ANATOMY AND PHYSIOLOGY OF THE HUMAN LUNG

Human lungs contain about 2000 km of capillaries which perform gas exchange in 300 million alveoli over a 70 m<sup>2</sup> surface area. With each breath, this organ is exposed to both infectious and inflammatory environmental stimuli.

Proximally, the airways function to conduct air to the deeper lung while protecting it from injurious toxicants and microorganisms. To this end, they have a complex structure with (i) cartilaginous elements anteriorly for structural support; (ii) a collapsing posterior wall to enable high airspeed velocity during coughing; (iii) nervous system innervation; (iv) a smooth muscle layer to facilitate bronchoconstriction; (v) glands and surface epithelia that produce a mucous layer that hydrates the underlying epithelium and traps microbes; (vi) cilia that transport mucus away from the alveolar space; and, (vii) extensive lymphatics. In contrast, the alveoli are delicate structures lined by thin alveolar type 1 epithelial cells and surfactant-producing alveolar type 2 cells, along with alveolar macrophages. A single, fused, basement membrane separates the alveolar epithelium and capillary endothelium, yielding a remarkably thin alveolar-capillary barrier of approximately 5 µm to facilitate gas diffusion.

A failure in any of these processes will lead to infection, inflammation, lung damage and impaired gas exchange.

#### EVALI: E-CIGARETTE OR VAPING PRODUCT USE-ASSOCIATED LUNG INJURY

E-cigarette aerosol exposes users to substances known

to have adverse health effects, including ultra-fine particles, heavy metals, volatile organic compounds, and other harmful ingredients. E-cigarettes are commonly used to inhale nicotine, but can also be used to deliver substances such as tetrahydrocannabinol (THC), cannabidiol (CBD), and butane hash oils.

Depending on the type of chemical agent and the amount of material inhaled, patients may experience a range of symptoms:

- Minor respiratory tract discomfort
- Acute airway injury and damage to the parenchyma with pneumonitis
- Alveolar oedema
- Respiratory failure
- Death

A common pathophysiological pathway includes inflammation, oedema of airways with epithelial sloughing, alveolar inflammation, and oedema with hypoxemia.

About 80% of persons who vaped and became ill reported having used both nicotine products and THC or CBD products. Acute toxic lung injury, instead of active infection, seems to explain the clinical presentation. Mixing of multiple ingredients with primary compounds and potential contaminants may result in *in vitro* (or even, *in vivo*) production of new agents that may be toxic. E-cigarette fluids have been shown to contain at least six groups of potentially toxic compounds:

- (i) Nicotine
- (ii) Carbonyls
- (iii) Volatile organic compounds (e.g. benzene and toluene)
- (iv) Particles
- (v) Trace metal elements according to flavour
- (vi) Bacterial endotoxins and fungal glucans

The CDC has given this novel vaping-associated illness an official name: e-cigarette or vaping product use-associated lung injury (EVALI). Whether EVALI is specifically caused by propylene glycol/vegetable glycerin and nicotine-containing e-cigarettes, or tetrahydrocannabinols and/or associated solvents and adulterants, remains to be determined. Similar cases

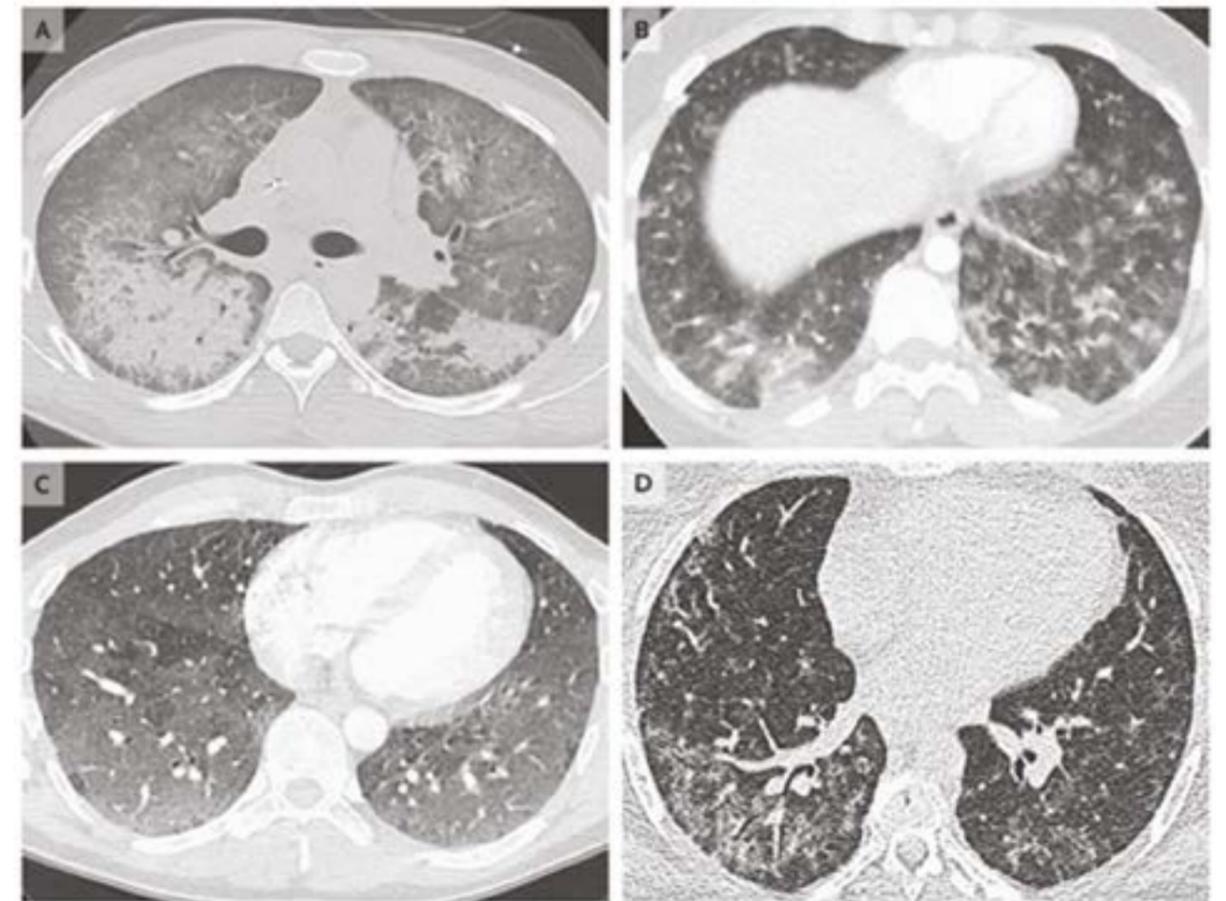


Figure 2. Computed Tomographic (CT) scans of the chest obtained from patients with vaping-associated lung injury.

Panel (A): An image obtained from a 20 year old man with diffuse alveolar damage shows dependent consolidation and diffuse ground-glass opacity, with some areas of bronchial dilatation typical of diffuse alveolar damage. The patient underwent intubation on hospital day 2, but eventually recovered after receiving glucocorticoid therapy. Panel (B): An image obtained from a 19 year old woman with acute eosinophilic pneumonia shows diffuse nodular areas of consolidation and ground-glass opacity, with mild septal thickening and a small right pleural effusion. The findings cleared within days after the administration of glucocorticoids. Panel (C): An image obtained from a 35 year old man with a pattern of hypersensitivity pneumonitis shows extensive centri-lobular ground-glass attenuation nodules, especially in the anterior region, and more confluent ground-glass opacity in the dependent lungs, with lobules of mosaic attenuation. The patient's symptoms improved after cessation of vaping. Panel (D): An image obtained from a 49 year old woman with giant-cell interstitial pneumonia, which was diagnosed on the basis of surgical biopsy findings of the lung and attributed to cobalt in her vape pen, shows fibrosis characterized by peripheral reticulation, ground-glass opacity, and mild traction bronchiectasis. The patient's symptoms improved after cessation of vaping.

have been found in the UK and Japan, suggesting that this has the potential to be a more widespread phenomenon, although country-to-country variations in prevalence have yet to be determined.

#### IMAGING AND PATHOLOGICAL FEATURES OF EVALI

Four imaging patterns have been found to generally correlate with pathological findings attributable to vaping, including (i) acute eosinophilic pneumonia, (ii) diffuse alveolar damage, (iii) organizing pneumonia, and (iv) lipoid pneumonia (Figure 2). Through clinical and pathological investigations, patterns of giant-cell interstitial pneumonia, hypersensitivity pneumonitis, and diffuse alveolar haemorrhage have been identified.

Although the variety of imaging patterns suggests different mechanisms of injury, most of the patterns have basilar-predominant consolidation and ground-glass opacity, often with areas of lobular or sub-pleural sparing. Rapidly developing acute lung injuries, in the setting of *acute eosinophilic pneumonia* and *diffuse*

*alveolar damage*, are associated with inhalational injuries. Such injuries have overlapping pathological and imaging findings, and are reported to occur with vaping. *Hypersensitivity pneumonitis* is an immune response to an environmental antigen, but the antigens related to vaping are unknown. *Lipoid pneumonia* is an inflammatory response to the presence of lipids within the alveolar space, and typically results from aspiration of hydrocarbons or oil-based products. However, it is now seen with vaping. CT finding of fat attenuation in the lung, which is a hallmark of lipoid pneumonia, has not been observed in these cases of EVALI though.

Not all cases are acute - *Organizing pneumonia* often develops sub-acute, over a period of days to weeks. There has even been a case report of giant-cell interstitial pneumonia (a rare fibrosing interstitial lung disease) that developed over a period of 6 months; this was correlated with hard metals in the e-cigarette device.

In the 4 patients with EVALI described in Figure 2, histopathological findings showed patterns of acute lung

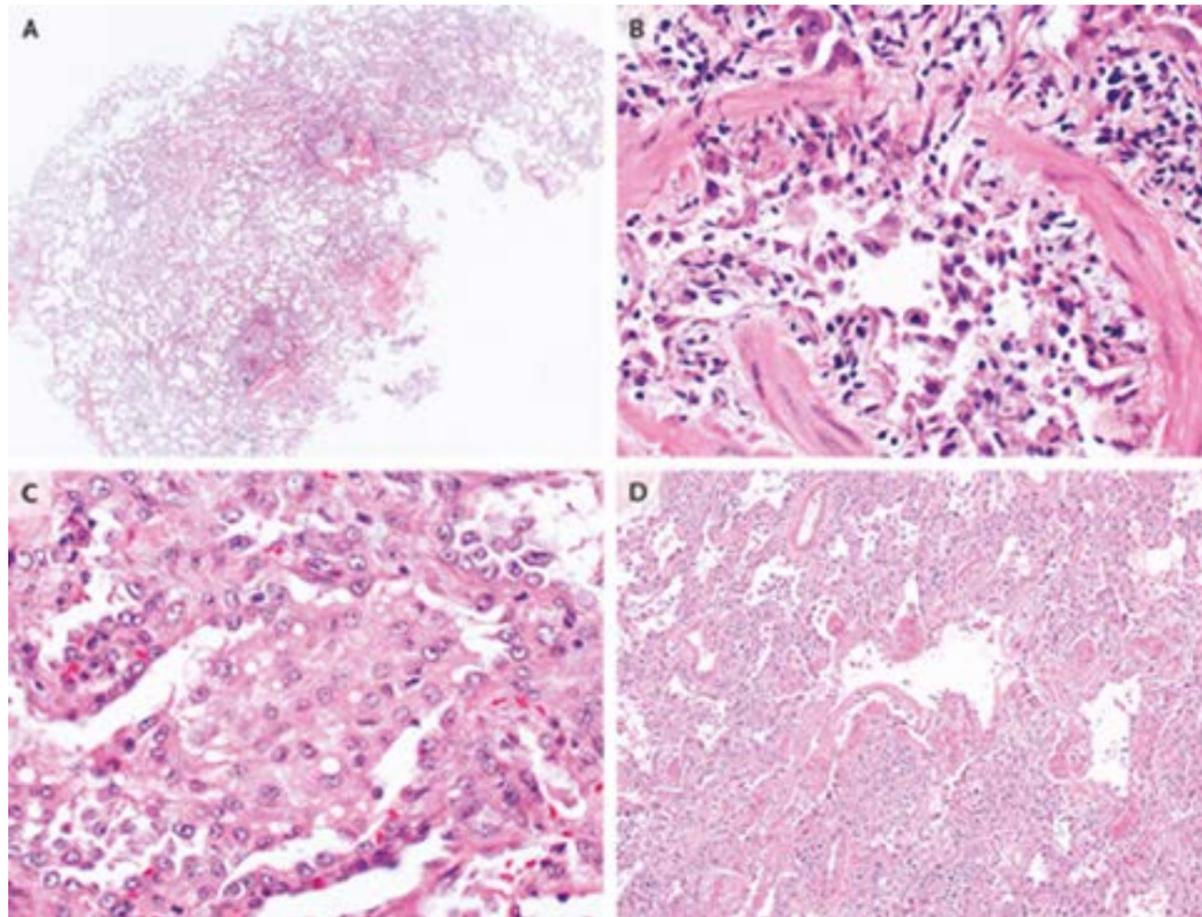


Figure 3. Histopathology of Acute Lung Injury Associated with Vaping.

Most cases showed airway-centered acute lung injury (Panel A), often with severe bronchiolitis accompanied by marked mucosal edema, sloughing of bronchiolar epithelium, and peribronchiolar organization (Panel B). All cases showed accumulation of foamy or vacuolated macrophages in peribronchiolar airspaces with pneumocyte vacuolization (Panel C). Four cases showed severe injury, with diffuse alveolar damage and hyaline membranes (Panel D); two of these patients died.

injury (including diffuse alveolar damage), or organizing pneumonia (usually bronchiolo-centric and accompanied by bronchiolitis). No histologic findings were specific, but foamy macrophages and pneumocyte vacuolization were seen in all cases; these may be useful diagnostic clues in an appropriate clinical context. Pigmented macrophages were sometimes present, but were never a dominant feature. Neutrophils were often prominent, but eosinophils were rare and granulomas were not seen. In some cases, BAL fluid contained abundant foamy macrophages.

To date, only a few reports of EVALI have included histopathological findings (Figure 3). Recent attention has been given to the possibility that vaping-

associated lung injury may represent exogenous lipoid pneumonia. Identification of lipid-laden macrophages or performing oil red O staining on BAL fluid as a marker of vaping-associated lung injury has been proposed, but even this remains a non-specific finding for EVALI, hence limiting its diagnostic utility. Until more data is available, this finding should be interpreted with caution, as it may simply be a marker of exposure instead of being a marker of toxicity. Although it is difficult to discount the potential role of lipids, the histologic changes suggest that vaping-associated lung injury represents a form of airway-centered chemical pneumonitis from one or more inhaled toxic substances, rather than

exogenous lipoid pneumonia. However, the agents responsible remain unknown.

#### CLINICAL EVALUATION AND MANAGEMENT OF PATIENTS WITH SUSPECTED EVALI

EVALI is considered a diagnosis of exclusion because, at present, no specific test or marker exists for its diagnosis. Healthcare providers should consider multiple aetiologies, including the possibility of EVALI and concomitant infection. In addition, healthcare providers should evaluate alternative diagnoses as suggested by clinical findings and medical history (e.g. cardiac, gastrointestinal, rheumatologic, and neoplastic processes; environmental or occupational exposures; or, causes of acute respiratory distress syndrome). An approach to the diagnosis of EVALI is summarized in Table 1.

#### History

- Ask about respiratory, gastrointestinal, and constitutional symptoms (e.g. cough, chest pain, shortness of breath, abdominal pain, nausea, vomiting, diarrhoea, and fever) for patients who report a history of use of e-cigarette/vaping products.
- Ask all patients about recent use of e-cigarette/vaping products.
  - ✓ Types of substances used (e.g., tetrahydrocannabinol [THC], cannabis [oil, dabs], nicotine, modified products or the addition of substances not intended by the manufacturer)
  - ✓ Product source
  - ✓ Specific product brand and name
  - ✓ Duration and frequency of use
  - ✓ Time of last use
  - ✓ Product delivery system
  - ✓ Method of use (aerosolization, dabbing, or dripping)

#### Physical exam

- Assess vital signs and O<sub>2</sub> saturation via pulse-oximetry.

#### Laboratory testing

- Infectious disease evaluation may include:
  - ✓ Respiratory viral panel including influenza testing during flu season
  - ✓ *Streptococcus pneumoniae*
  - ✓ *Legionella pneumophila*
  - ✓ *Mycoplasma pneumoniae*
  - ✓ Endemic mycoses
  - ✓ Opportunistic infections
- Initial laboratory evaluation
  - ✓ Consider complete blood count with differentials, liver transaminases, and inflammatory markers (e.g., erythrocyte sedimentation rate and C-reactive protein).
  - ✓ In all patients, consider conducting urine toxicology testing, including testing for THC.

#### Imaging

- Chest radiograph.
- Consider chest computed tomography for evaluation of severe or worsening disease, complications, other illnesses, or when chest x-ray result does not correlate with clinical findings.

#### Other considerations

- Further evaluation of patients meeting inpatient admission criteria might include:
  - ✓ Consultation with pulmonary, critical care, medical toxicology, infectious disease, psychology, psychiatry, and addiction medicine specialists.
  - ✓ Additional testing with bronchoalveolar lavage or lung biopsy as clinically indicated, in consultation with pulmonary specialists.

Table 1. Clinical evaluation for patients with recent history of e-cigarette/vaping product usage and suspected lung injury.

Healthcare providers should elicit a history of respiratory symptoms (e.g. cough, chest pain, and shortness of breath) and gastrointestinal symptoms (e.g., abdominal pain, nausea, vomiting, and diarrhoea). Gastrointestinal symptoms preceded respiratory symptoms in some patients. Respiratory or gastrointestinal symptoms were accompanied by constitutional symptoms such as fever, chills, and weight loss. Further history should include use of e-cigarette/vaping products, and ideally should ask about types of substances used (e.g. THC, cannabis, nicotine, modified products or the addition

of substances not intended by the manufacturer); product source, specific product brand and name; duration and frequency of use, time of last use; product delivery system, and method of use (aerosolization, dabbing, or dripping).

Physical examination should include vital signs and pulse-oximetry. About half of the patients reported tachycardia and tachypnoea, with pulse oximetry of < 95% at rest on room air (this emphasizes the need for routine pulse-oximetry). Among patients identified to date, pulmonary findings on auscultation exam

have often been unremarkable, even among patients with severe lung injury.

Laboratory testing should be guided by clinical findings. A respiratory virus panel, including influenza testing during influenza season, should be strongly considered. Additional testing should be based on published guidelines for evaluation of community-acquired pneumonia. Infectious diseases to consider include *Streptococcus pneumoniae*, *Legionella pneumophila*, *Mycoplasma pneumoniae*, possible mycoses, and opportunistic infections; the likelihood of

infection by any of these varies by geographic prevalence and patient medical history. Other abnormal laboratory tests reported in patients with EVALI include elevated white blood cell (WBC) count, serum inflammatory markers (C-reactive protein, erythrocyte sedimentation rate), and liver transaminases. However, at this point in time, these tests cannot be used to distinguish EVALI from infectious aetiologies. In all patients, healthcare providers should consider performing urine toxicology testing, including testing for THC.

Radiographic findings consistent with EVALI include pulmonary infiltrates on chest radiography and opacities on chest CT scan. A chest x-ray (CXR) should be obtained from all patients with a history of e-cigarette/vaping product use who have respiratory or gastrointestinal symptoms, particularly when accompanied by decreased O<sub>2</sub> saturation (< 95%). Chest CT might be useful when the CXR result does not correlate with clinical findings, or to evaluate severe or worsening disease, complications such as pneumothorax or pneumo-mediastinum, or other illnesses in the differential diagnosis (such as pneumonia or pulmonary embolism). In some cases, chest CT has demonstrated findings such as bilateral ground glass opacities, despite a normal or non-diagnostic CXR. Among patients with abnormal radiographic findings and a clinical picture consistent with EVALI, a chest CT scan may not be necessary for diagnosis. The decision to obtain a chest CT should be made on a case-by-case basis depending on the clinical circumstances.

#### MANAGEMENT OF PATIENTS WITH EVALI

Several factors should be considered when deciding whether to admit a patient with potential EVALI to the hospital (Table 2). Patients with suspected EVALI should be admitted if they have decreased O<sub>2</sub> saturation (< 95%) on room air, are in respiratory distress, or have comorbidities that compromise pulmonary reserve.

Outpatient management of suspected EVALI may be considered on a case-by-case basis for patients who are clinically stable, have less severe injury, and for whom follow-up within 24–48 hours of initial evaluation can be assured. Candidates for outpatient management should have normal O<sub>2</sub> saturation (≥ 95%), reliable access to care, and strong social support systems. For these patients, empiric use of antimicrobials, including antivirals if indicated, should be considered. Some patients who initially have mild symptoms may experience a rapid worsening of symptoms within 48 hours. Healthcare providers should instruct all patients to seek medical care promptly if respiratory symptoms worsen.

Corticosteroids might be helpful in managing EVALI. Several case reports describe improvement with corticosteroids, likely because of a blunting of the inflammatory response. However, the natural progression of this injury is not known, and it is possible that patients might recover even without corticosteroids,

or by avoiding the use of e-cigarette/vaping products. In some circumstances, it would be advisable to withhold corticosteroids while evaluating patients for infectious aetiologies (such as fungal pneumonia) that may worsen with corticosteroid treatment. Nevertheless, because the diagnosis remains one of exclusion, aggressive empiric therapy with corticosteroids, antimicrobial, and antiviral therapy may be warranted for patients with severe illness. Whenever possible, decisions regarding the use and dosing regimen of corticosteroids should be made in consultation with a pulmonologist.

Early initiation of antimicrobial treatment for community-acquired pneumonia in accordance with established guidelines should be strongly considered, given the overlapping signs and symptoms in these conditions. In addition, during influenza season, healthcare providers should consider influenza in all patients with suspected EVALI, and initiate antivirals with established guidelines. Decisions regarding initiation or discontinuation of treatment should be based on specific clinical features and, when appropriate, in consultation with specialists.

Patients discharged from hospital after inpatient treatment for EVALI should have a follow-up visit no later than 1–2 weeks post-discharge that includes pulse-oximetry. Clinicians should also consider repeating the CXR. Additional follow-up testing 1–2 months after discharge may include spirometry, diffusion capacity testing, and repeat CXR. Long-term effects and the risk of recurrence of EVALI currently remain unknown. While many patients' symptoms typically resolve, there have been reports that patients relapse during corticosteroid tapering post-hospitalization, underscoring the need for close follow-up. Some patients have persistent hypoxemia, requiring home oxygen at discharge, and may need ongoing pulmonary follow-up.

It is not known whether patients with a history of EVALI are at higher risk for severe complications of influenza (or, other respiratory viral infections) if they are infected simultaneously or after recovering from lung injury. Healthcare providers should emphasize the importance of annual influenza vaccination and pneumococcal vaccination, as per Ministry of Health (MOH) guidelines.

Advising patients to discontinue the use of e-cigarette/vaping products should be an integral part of the care approach during inpatient admission, and should be re-emphasized during outpatient follow-up. Cessation of e-cigarette/vaping products might speed up recovery from this injury; resuming the use of e-cigarette/vaping products has the potential to cause recurrence of symptoms and/or lung injury. Evidence-based tobacco product cessation strategies include behavioural counselling and approved cessation medications. For patients who have addiction to THC-containing or nicotine-containing products, cognitive-behaviour

therapy, contingency management, motivational enhancement therapy, and multidimensional family therapy have been shown to help. Consultation with addiction medicine services should also be considered.

#### CONCLUSION

While the use of e-cigarette/vaping products is illegal in Singapore, healthcare providers should have a high index of suspicion when patients present with non-specific respiratory and/or gastrointestinal symptoms

which cannot be accounted for by common diagnoses. Particular attention should be focused on taking an adequate exposure history to elucidate the use of non-combustible tobacco products, given the recent trends noted in other countries.

Rapid recognition of patients with EVALI, and an increased understanding of treatment considerations, could reduce morbidity and mortality associated with this injury.

#### Admission criteria and outpatient management

- Strongly consider admitting patients with:
  - ✓ Potential lung injury, especially if respiratory distress present
  - ✓ Comorbidities that compromise pulmonary reserve
  - ✓ Decreased (< 95%) O<sub>2</sub> saturation (consider modifying factors such as altitude to guide interpretation)
- Outpatient management for patients with suspected lung injury who have less severe injury might be considered on a case-by-case basis.

#### Medical treatment

- Consider initiation of corticosteroids.
- Early initiation of antimicrobial coverage for community-acquired pneumonia should be strongly considered in accordance with established guidelines.
- Consider influenza antivirals.

#### Patients not admitted to hospital

- Recommend follow-up within 24–48 hours to assess and manage possible worsening lung injury.
- Outpatients should have normal O<sub>2</sub> saturation, reliable access to care and social support systems, and be instructed to promptly seek medical care if respiratory symptoms worsen.
- Consider empiric use of antimicrobials and antivirals.

#### Post-hospital discharge follow-up

- Schedule follow-up visit no later than 1–2 weeks after discharge that includes pulse-oximetry testing. Consider repeating chest radiograph.
- Consider additional follow-up testing including spirometry and diffusion capacity testing, and consider repeating chest radiograph in 1–2 months.
- Consider endocrinology consultation for patients treated with high-dose corticosteroids.

#### Cessation services and preventive care

- Strongly advise patients to discontinue use of e-cigarette/vaping products.
- Provide education and cessation assistance for patients with nicotine addiction, and treatment or referral for patients with other addiction issues.
- Emphasize importance of routine influenza vaccination, and consider pneumococcal vaccine as per MOH guidelines.

Table 2. Management of patients with suspected EVALI.



DR LIM LIAN KIAT is a registrar in the Department of Respiratory & Critical Care Medicine, Tan Tock Seng Hospital.

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SINGAPORE HEALTH & BIOMEDICAL CONGRESS 2019

# MEDICAL HUMANITIES EXHIBITION

Organised by the National Healthcare Group (NHG), the Singapore Health & Biomedical Congress (SHBC) 2019 was held from 10th to 12th October 2019 at the MAX Atria, Singapore EXPO. The theme for this year's congress was "Sustainable Healthcare through Innovation". Over 3,000 local, regional and international delegates attended the annual congress, which serves as a vital platform for healthcare professionals, research scientists, academics, industry experts and key stakeholders to share and discuss ideas and breakthrough strategies with the ultimate goal of advancing healthcare to the next level.

On the sidelines of SHBC 2019, the 7th run of the Medical Humanities Exhibition (sponsored by NTU's LKCMedicine) highlighted the link between art and medicine. Centred on the theme of "Compassion" this year, the exhibition received over 60 remarkable artwork submissions from clinicians, medical students as well as independent artists.

In this issue of Medical Digest, we bring to you some of these thought-provoking and poignant artworks.

## THE ANAESTHETIST'S SOLILOQUY



**DR DAVID MATHEW**

Dr Mathew is a Resident in the Department of Anaesthesiology, Intensive Care & Pain Medicine, Tan Tock Seng Hospital.

*"This poem was written based on a real life event. The words of the poem were cathartic as they expressed my emotions. My ultimate goal was for the words to translate my feelings, and share them with the rest of the community. Words might never be able to replicate feelings, but sometimes when pieced together they can come close to striking a chord in the readers' emotions."*

To the boy whose life slipped out of my hands

*I taste*  
Sorrow as my heart bleeds tears of pain  
Each time my eyes reignite  
The burning memory of your voice  
From the ashes of my suffering.

*I saw*  
Hands deliver the drugs  
Meant to keep you asleep  
No longer than the moon's  
Rule over the night sky,  
Yet you never awoke  
To see another sunrise.

*I felt*  
The red wheals over your skin  
The antibiotic wreaking anarchy  
Your puffy eyes, swollen windpipe  
Lungs screaming for oxygen  
As they silently suffocated.

*I heard*

The screams of your parents  
Echo deep into the caves of my emotions  
When they realized you were now  
Afloat in a river far away from  
Their worldly reaches.

*I smell*

The shackles of death  
Pound my body for your freedom,  
Each night I lay to rest  
My heart bounces incessantly  
With guilt trapped endlessly below  
The ribs of my conscience.

To the boy whose life slipped out of my hands

Adrenaline could not save you,  
Yet it keeps my heart throbbing  
With your memories.  
It squeezes my veins so tight  
They bleed a teardrop from -

My five senses.

COMPASSION – TOUCH OF GENTLENESS



MR LIM MIN-CHIEH STANLEY

Mr Lim is a member of the Mouth and Foot Painting Association (MFPA).

“Dandelion is a gentle little flower but has the ability to thrive even in the most challenging circumstances. The future of the girl may be uncertain but like the dandelion, she will thrive wherever she goes.”



ENABLE ME

A/PROFESSOR UMAPATHI N THIRUGNAMAM

A/Prof Uma is a Senior Consultant in the Department of Neurology, National Neuroscience Institute.

“A poem inspired by my patient Mr. William Ngo, a jewellery technician, who after losing his hand dexterity became a mouth harmonica performer; and then when his breathing became laboured, a professional mouth painter.”



If I can fly,  
Why settle for walking.  
If I can see the rainbow,  
Why shroud me in grey.  
If I can hear the birdsong,  
Why leave me with a lifeless ring.  
If I can read the Iliad,  
Why give me a picture book.

My physician,  
As you heal my pain away,  
Talk not just of what I can't do,  
Tell me what I can.  
My glass half empty,  
Is also half full.

Leave me not disabled;  
When I can be enabled.  
I have but this life.

COMPASSION BLOOM

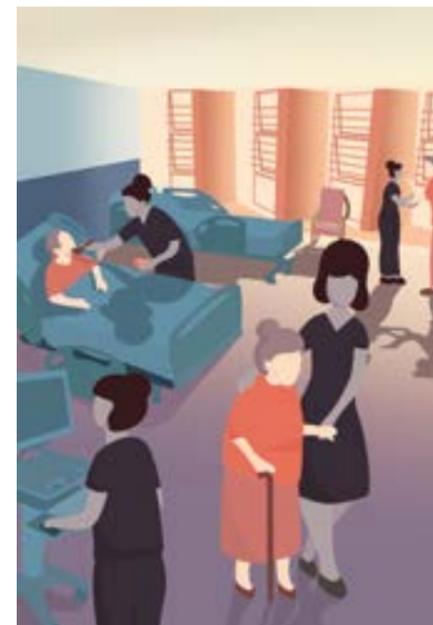


DR THIO SI MIN

Dr Thio is a Family Medicine Resident at Yishun Polyclinic.

“This is a collection of 6 hand-painted digital illustrations, depicting native Singapore orchids sprouting and blooming from human organs and skeletal structures. They suggest values of compassion, kindness, gratitude, love, empathy and humanity in every one of us, and shows the essential role that each individual plays.”

IN THE DARK



MS LEE PING ZHENG

Ms Lee is an independent artist.

“This piece pays tribute to nurses who display compassionate care to patients and family members in the face of stress, multiple administrative and clinical responsibilities, and sometimes burn out. The nurses are coloured in darker shades representing the hidden everyday heroes whose compassionate care can often be taken-for-granted.”



Not *the* doctor that cared  
 Not *the* doctor that told him it was okay to falter  
 Not *the* doctor to even ask, how are you?

*She begs, please*

*Mdm*, we need to do insert something into your nose  
 She looked around her  
 Masks, gloves, machines stared back  
 Like lions in the savanna  
 Waiting  
 Waiting to pounce their attack on her if she slips through,  
 the embrace of what some called "Life"

The man by the next bay was connected to more tubes than  
 she could count at a glance  
 Machines beeped  
 Metronome like  
 He looks peaceful  
 His chest rising gentling with each breath

*Blop*  
 Another drop plopped on the already-forming puddle in the  
 kidney dish  
 Clots were forming over her lips and chin  
 She wanted her husband  
 She cried, screamed  
 Anything to bring the man she held so dear for the past 40  
 years

Everything around her was so.... bizarre  
 She craved familiarity

### MS GOH XIN RONG

Ms Goh is a Medical Student at the Lee Kong Chian School of Medicine, Nanyang Technological University.

*"All of the cases described above were based on true-life events, with some adaptations and dramatization to conceal the identity of the involving parties. Writing this series proved to be an immensely therapeutic experience for me. It provided me with a safe avenue to express my emotions and thoughts on the various incidents I had observed over the years.*

*As I segmented the cases into the three different phases of one's medical journey – I am. Only. Just Another. – I was able to take the time to reflect on my own journey and consider the path that I aim to forge for myself."*

Anything away from the melancholy she was in  
 She was not dying  
 No, she could not die just yet  
 She had to meet the wedding planner  
 The gown fitting was due in a week  
 The menu has yet to be decided  
 She had to see them walk down that aisle

So why was she here  
 Home she should be  
 Anywhere but here

*We will bring him over after we are done*  
 She felt her hands being picked up  
 A sudden warmth amidst the 2 am cold  
 I stared into her eyes  
 Fear and confusion reflected across the tears  
*We will be here for you*

Or am I *the* doctor  
*The* doctor that told her she was brave woman  
*The* doctor that stayed by her side in the wee hours of the  
 morning  
*The* doctor that gave her the strength she has been struggling  
 to find for years

I am. Only. Just another.  
 Or am I  
 Who am I

Jane Doe.

## ACROSS THE SEA

I don't know why your passing  
 affects me so; I must have seen so many go  
 before you at this point

perhaps it was the shock of suddenly seeing faces  
 from my other life – usually in careful stowage –  
 now sailing in, a sorrowful well-met

the faint recall of my mother telling me  
 you were the one she could have been  
 (and the one she could still someday be)

your family, keeping it together and quietly falling apart  
 the glint behind your brother's glasses  
 the women around the table, docked like ships at a port  
 swallowed tears and the brave realization of your  
 impending departure

I wondered if I ought to have pushed this hard  
 begged another gust of wind to rustle your sails  
 beating against the unceasing tide  
 for a precious farewell

I should've said goodbye myself  
 but I rushed through the manic night  
 and crept away in the light of day  
 I like to think I managed, in my own way;  
 behind the curtain, in the silence  
 a hulking grim figure in blue scrubs  
 holding your hand in the pale glow

In my memory,  
 your face is cast into stark relief  
 a Rembrandt, almost beatific  
 looking at me,  
 through me,  
 across the sea.



### DR CHIN HAN XIN

Dr Chin is an Associate Consultant in the Department of Endocrinology, Tan Tock Seng Hospital.

*"A poem written upon a patient's passing. Clinicians often face the challenge of compartmentalising their emotions in a bid to balance emotional investment and detachment while caring for patients. However, to grieve is to foster compassion and empathy, and it is paramount that we find time to process our own emotions."*

## LET IT BE

The doctors on the night shift  
 are a skeletal crew  
 haunting the wards looking  
 for the sick and dying  
 whose alarming vital signs and  
 distressing symptoms attract our eye.

By the end of the fifth night shift  
 I knew all the dying on my ward.  
 Each had a unique story and  
 with each, I travelled a different journey.  
 All ending in the same place,  
 a place we all must go.

For it does not matter if we are  
 clever or foolish, rich or poor,  
 alone or surrounded by loved ones.  
 Despite the medical advances,  
 there is no pill that stops the clock,  
 or lets the music go on and on.

Everything I did was in vain.  
 Interventions to address one issue  
 only caused their own complications.  
 I was playing a game of chess  
 where every move I made  
 was being thwarted by a cleverer opponent.

Fluids given to prop up blood pressure  
 drowned lungs.  
 Antibiotics given to treat infection  
 fried the liver and kidneys.  
 A tube inserted to feed  
 caused bloating and vomiting.

By the end of the week,  
 we were all worse for wear.  
 When the nurses called  
 to inform me yet again  
 about the deteriorating state  
 of one such patient



I replied, quoting Paul McCartney:  
'Let it be'  
Not because I was 'letting them go'  
but because  
there was nothing more to be 'done'.  
There was only 'being' left.

Being with,  
Being there for,  
Being loved,  
Being held  
Being present  
Letting be.

#### DR ANNE TAN

Dr Tan is a Medical Officer in SingHealth.

*"This poem was inspired by real conversations while I was working a week of night shifts."*

## A COMPASSIONATE HEART IS AN OCEAN

If the earth could feel my wrath  
It would swiftly catch aflame  
Eating at its very source  
Withering.  
Still I've ground beneath my feet  
Cause you take heed.

The knowing gaze of yours  
Reflecting the stories in my eyes  
Gives repose to a vagrant soul.

A compassionate heart is an ocean  
Letting one's dark thoughts roam free  
Without the fear of scorn  
Washing out in endless surf  
As we await the breaking of dawn.

If the sky could feel my grief  
It would crystallise into a million shards  
Lodging in the windpipe  
Suffocating.

But my breath still flows like air  
Because you care.

"You won't walk alone." A sacred promise  
You silently conveyed in listening  
For a moment in time, for a lifetime.

A compassionate heart is an ocean  
Catching the meandering rivers  
Of tears un-shed but frozen  
Where strength and pride lie  
Atop many a frost-bound mountain.

When people come on their last legs  
On the worst days of their lives  
To weather their storms that last  
Is the burden of a heart so vast.

A compassionate heart is an ocean  
Uniting islets and continents  
Through outpouring of woes  
Quenched by the serenity  
Of kindness that overflows.

#### MS CLAIRE CHOW

Ms Chow is a Medical Student at the Lee Kong Chian School of Medicine, Nanyang Technological University.

*"The poem captures the feeling of being shown compassion during emotionally difficult times. It is written from the perspective of a patient who's grateful to be cared about and listened to. I chose the ocean metaphor as, like compassion, it is fundamental in life, connects people and creates positive feelings."*



## REMEMBER

I remember  
That awesome night when she nodded  
"Be my girlfriend"  
We held hands.

I remember  
That sweet moment when I whispered  
"Be my partner"  
We held hands.

I remember  
Those hard hours as she laboured  
"Our first child"  
We held hands.

I remember  
That long aisle when daughter wedded  
"Gave her away"  
We held hands.

I remember  
The years together now faded  
"Sickness and health"  
We hold hands.

I remember  
This last moment  
"I'll see you on the other side"  
We hold hands.

#### ASSOCIATE PROFESSOR KENNY TAN

A/Prof Tan is the Chief Executive Officer of St Luke's ElderCare Ltd.

*"This poem draws on the motif of holding hands as the expression of relationship that lasts through the different seasons of life. As our years slow us down and ebb away, what remain are the memories of life lived together."*

## DUSK TO DAWN

Meet Carteciano, Marion Christine Caraon - a passionate, fun-loving and optimistic Filipina who cannot see herself working anywhere other than in the Emergency Department (ED).

The 40-year-old Doctor at the National University Hospital ED came to Singapore nine years ago, in hopes of giving her daughter, Meeka, a better life.

Marion describes her time at the ED as one that is constantly filled with excitement and fulfilment. The process of saving lives of patients from the initial chaotic state never fails to leave her feeling satisfied.

However, like many other medical shift-workers, Marion finds it challenging to strike a work-life balance.

Her recent promotion from Senior Resident Physician to the department's Ambulatory Medical Director has also added on to this difficulty.

But the real challenge came when her daughter Meeka was diagnosed with Mitochondrial Myopathy in 2014, a condition that causes severe muscular problems and seizures due to damaged mitochondria in the body.

The intensive care required by Meeka posed a real challenge to Marion, especially in 2017, when Meeka started going in and out of the hospital almost on a weekly basis.

Whilst her mother flew to Singapore to help look after Meeka, Marion often found herself struggling emotionally - as a mother, she wanted to be around Meeka, but as a doctor, her duties were calling for her.

Her daughter has always been her motivation to work, to care for others like how she cares for her own. But when Meeka passed on in March at the tender age of 16, Marion felt like she suddenly lost all her purpose, and considered quitting and returning to the Philippines.

But she was reminded of why she started in the first place: to alleviate the pain of the injured and the sick. Her passion made her decide to stay in Singapore, and remain in the ED.

Marion is not alone in this struggle.

Many medical shift-workers are just like her, having to work odd hours and sacrifice their time with family and friends.

Her story kickstarts the series, titled 'Dusk to Dawn', which aims to explore the lives of medical shift-workers and shed light on their unseen struggles that comes with their unpredictable work lives, and hopefully prompt the general public to appreciate them more.

**C**  
COLLEAGUES-TURNED-FAMILY



All alone in a foreign country, Marion knew no one when she first arrived and struggled to adapt to cultural differences and expectations here.

But she soon found a home at NUH ED.

"They are my family," Marion smiled as she spoke fondly of her colleagues. "They were really welcoming and helpful, which made adjusting to the culture here so much easier."

When Meeka's condition took a turn for the worse, Marion described the period as a 'rollercoaster ride'.

With tears in her eyes, she recalled the days when she had to rush to and fro the hospital to take care of her daughter.

"But they (her colleagues) were very supportive," she said. "They offered to take over my shifts, and so many of them took turns to drive me home after work, and picked me up when it was time for my shift."

**O**  
OPTIMISM



Working at the ED means dealing with death on a daily basis.

"The losses will always be etched in your mind," Marion said as she recalled her first encounter with death at the hospital. "But they toughen you up."

To Marion, learning to deal with loss is important at the ED. It helps one to move on and be more efficient when tending to other patients.

"The experience (at the ED) has helped me develop a character that moves on from loss," she said. "But the tough part about being here is handling the families of the deceased."

**M**  
MANAGING FAMILIES



Most of the time, managing the families of demised patients can be tricky.

The sometimes sudden and unexpected nature of death sends family members into a state of panic and distress.

Regarding this, Marion has a tried-and-tested tip: hear them out.

"At times like this, good communication is key," she said. "Being direct and sincere gives families confidence when it is most needed."

**P**  
PASSION



One year into medical school, Marion's father asked her to reconsider her decision to pursue Medicine and urged her to be a Biologist instead.

But Marion was determined.

Her dream to become a doctor started way back when her mother, then a midwife, brought Marion with her to work.

"I would follow my mum to work and see the doctors donned in their white coats, looking so respectable. Being a child, I thought that looked really cool and immediately decided I wanted to be like that."

What started as an innocent admiration grew to become Marion's passion.

"Growing up, I realised my strong desire to alleviate the pain of others," she said excitedly. "And that passion made me determined to complete medical school."

**A**  
ADJUSTMENT



Adjusting her body clock is one of the many challenges Marion faces working in the ED.

"It's very tiring. It requires you to constantly adapt, and it gets a lot harder as you age."

However, it's not all bad, Marion assures. There are perks to shift-work.

For example, whenever Marion is on her favourite afternoon shift (4pm-11pm), she gets to stay in bed till 2pm before getting ready for work, something only shift-work could afford.

Night shifts (10pm-8pm) are the toughest, so Marion makes sure to have a cup of coffee by her side to keep her awake throughout the night.

**S**  
SACRIFICE



Before Marion entered medical school, she was already aware of how demanding it would be.

Like many others in healthcare, public holidays and family time are some of the sacrifices she has to make.

But Marion never complains.

With a beaming smile, she said, "Being a doctor has always been my dream, and I know that these are necessary sacrifices. So I was prepared, right from the start."

Going without food, water and ignoring nature's call for extended hours are also normal for the shift-workers at the ED.

Even so, Marion said without hesitation that she would pick working at the ED over any other department anytime.

**S**  
(ALL) SMILES



Marion's colleagues describe her with phrases like 'out of this world', because she is always seen with a smile on her face.

Even when Meeka's condition was critical, Marion was still strong and available for her colleagues and patients in need.

"She is a great confidant, who actively listens and helps even though her own struggles are greater," a colleague said of her.

**I**  
INDEPENDENCE



As a single mother and the sole breadwinner of her family, Marion is the definition of an 'independent woman'.

But the 40-year-old is still hopeful for a partner, and often jokingly gets 'engaged' to her colleagues.

"I call off the 'engagement' once they find themselves a girlfriend," she laughed.

**O**  
OVERTIME



With every shift filled with uncertainties, the timing of it is also more of an estimate than a fixed one.

Patients can come in at the last minute before the shift ends and the hustle begins all over again.

Even when it's over, it may not mean the end of the day for the shift-workers.

Attending meetings is just one of the many tasks that keep Marion busy even after work.

**N**  
NURTURE



"God has a purpose for our suffering," Marion reflected.

Throughout Meeka's crisis, the mother-daughter pair remained joyful and content.

This is her greatest lesson from Meeka's life, and one that she brings with her to the ED.

"This is my calling," Marion said about her work. "Dealing with suffering is the way I can pay Meeka's and my lessons forward to others who have need."

**MS OLYVIA LIM**

Ms Olyvia Lim is a 3rd year student at the Wee Kim Wee School of Communication and Information, Nanyang Technological University.

*"In an attempt to raise awareness of the lifestyle of medical shift workers, I followed one of them to gain a better understanding of her job's demands. Many people take the medical workers for granted and are unaware of the sacrifices they have to make in taking care of people like me. This series, titled 'Dusk to Dawn', will explore the lives of these unsung heroes and shed light on their unseen struggles with their unpredictable work lives, and hopefully prompt the general public to appreciate them more."*

**FEATURE**

**PROBABILISTIC THINKING IN MEDICINE**

I'd like to discuss a way of thinking in medical decision-making that I do not commonly see in doctors. If we want to practise in a complex world, if we want to manage the most difficult cases, if we want to know how to proceed in the face of uncertainty, we have to adopt some form of probabilistic thinking.

On the first day in office as Secretary of the Treasury, Robert Rubin convinced Bill Clinton to loan \$25 billion to Mexico to bail its floundering economy.<sup>1</sup> Most people would balk at making decisions of such magnitude. History bears witness to the wisdom of the action however, as it averted a crisis potentially of global proportions.



**MEDICINE HAS BECOME MORE COMPLEX BECAUSE OF THE ABILITY TO PERFORM MORE INVESTIGATIONS, MANY OF WHICH PRODUCE RICH, SOPHISTICATED AND SPECIFIC INFORMATION; THE AVAILABILITY OF PROFUSE PATIENT DATA FROM COMPUTERISED RECORDS; AND, THE BURGEONING MEDICAL LITERATURE.**

'A probabilistic approach is far from unusual and, at some level, merely describes what most people do, or think they are doing, when they describe weighing the pros and cons of an issue. But somehow or other, the discussion in Jacob's New York Times Magazine piece<sup>2</sup> resonated, and since then people in all kinds of circumstances have told me how it affected them ... The best explanation I can offer for why this discussion drew the response it did is something Larry Summers once suggested when we were both at the Treasury Department: that while a great many people accept the concept of probabilistic decision making and even think of themselves as practitioners, very few have internalized the mind-set. For me, probabilistic thinking has long been a highly conscious process. I imagine the mind as a virtual legal pad, with the factors involved in a decision gathered, weighed, and totalled up. To describe probabilistic thinking this way does not,

however, however mean that it can be reduced to a mathematical formula, with the best decision automatically jumping off a legal pad. Sound decisions are based on identifying relevant variables and attaching probabilities to each of them. That's an analytic process but also involves subjective judgments. The ultimate decision then reflects all of this input, but also instinct, experience and "feel" ... And once you enter the realm of probabilities, nothing is ever simple again. A truly probabilistic view of life quickly leads to the recognition that almost all significant issues are enormously complex and demand that one delve into these complexities to identify the relevant considerations and the inevitable trade-offs. Some people I've encountered in various phases of my career seem more certain about everything than I am about anything. That kind of certainty isn't just a personality trait I lack. It's an attitude that seems to me to misunderstand the very nature of reality – its complexity and ambiguity – and thereby provide a rather poor basis for working through decisions in a way that is likely to lead to the best results.'

I'll start with a simple clinical example. Recently, I saw a 47-year-old patient with antiphospholipid syndrome in the inpatient ward. She developed deep vein thrombosis 13 years ago, and superficial vein thrombosis 5 years ago. She had been anticoagulated since the first episode. She became prematurely menopausal 2 years ago. She had now developed post-menopausal bleeding. Of course, the warfarin was discontinued. When the flow decreased, low molecular heparin was initiated, which resulted in substantial vaginal haemorrhage. The gynaecologist opined that it was not possible to biopsy the endometrium until the bleeding had stopped, and suggested a one-week review. In the lead-up to the review appointment, we deliberated on whether to restart anticoagulation (with the attendant risk of a re-bleed) or withhold anticoagulation (with the danger of thrombosis). Weighing the probabilities led to the decision that not anticoagulating for a week or two was the better option. We considered the risk of thrombosis to be present but not high. The patient developed a venous clot, not arterial. There had been no potentially dangerous thrombotic events for 13 years. On the other hand, she bled immediately when heparin was administered. It was pertinent to exclude the diagnosis of endometrial cancer, and we did not want to delay this by exposing her to the likelihood of continual bleeding.

#### **MEDICAL PRACTICE IS BECOMING MORE DIFFICULT**

Medicine has become more complex because of the ability to perform more investigations, many of which produce rich, sophisticated and specific information; the availability of profuse patient data from computerised records; and, the burgeoning medical

literature. Computers (data storage and retrieval, artificial intelligence) and the internet have profoundly changed the world. Medicine will not be spared, and we haven't seen even half the impact yet.

There are a couple of models of thinking in Medicine.<sup>3</sup> With the hypothetico-deductive method, we form theories and then set out to test them. With pattern recognition, we make conclusions based on forms we recognise. These methods only work for relatively simple clinical problems or patterns we have seen before. In my view, these methods are used consecutively. By recognising a pattern, we form differential diagnoses. We order investigations or other manoeuvres to test our hypotheses. But when there is a bewildering problem with no established way of making progress, probabilistic thinking comes to the fore because we do not need to start with pattern recognition.

The shining hour of the Kennedy presidency is his handling of the Cuban Missile Crisis of October 1962. We can frame his management of this emergency as a probabilistic thinking exercise. After the failed Bay of Pigs invasion of April 1961, Cuba turned to Russia to curb American aggression. Kennedy said this about the disaster: "How could I have been so far off base? All my life I've known better than to depend on the experts. How could I have been so stupid, to let them go ahead?"<sup>4</sup> During a vacation in the Crimea in the spring of 1962, President Nikita Khrushchev thought of a plan to set up nuclear-armed, medium- and intermediate-range ballistic missiles in Cuba capable of striking American cities (now, it is believed that it was right of him to do so to redress the nuclear situation). On 16 October, President Kennedy and his team learnt that installation had already begun. He examined the

options. He could order another attack on Cuba, at the risk of precipitating a nuclear war with Russia. He staunchly resisted this, though there were hawks in his committee. He could order a blockade of the seas around Cuba to prevent any more missile from Russia reaching the island. This he did, and it was fortunate that no Russian vessel challenged this, or else the escalating tension would have led to war (the blockade is now acknowledged to have been illegal by international law standards). There was an option of negotiating with Russia. He could not appear to be weak or else West Germany would be the next annexation target. He could not be too hard or else Khrushchev, who also had hawks in his team, would walk away. However, one of his advisors, Llewellyn E. Thompson Jr., who had just returned as US ambassador to Russia, gave him a better assessment of the probabilities. Khrushchev demanded in a letter that US pledged not to attack Cuba, and a second letter demanded that US dismantled their missiles in Turkey too. Thompson advised Kennedy just to respond to the first letter. He said, "Well, because he's already got this other {Cuban} proposal which he put forward. The important thing for Khrushchev, it seems to me, is to be able to say 'I saved Cuba, I stopped an invasion ...'".<sup>5</sup> Thompson helped Kennedy decide that he could give in to

one of the demands, and that Khrushchev was rational and would keep his end of the deal. And this precise assessment of probabilities led to the right decision and the resolution of the conflict. The Washington Post called Thompson's judgement a '... electric evidence of a rare and wonderful poise, gutsiness and independence'.<sup>5</sup>

#### **GETTING OUR THINKING STRAIGHT**

To utilise probabilistic thinking properly, a few habits have to be examined. If the thoughts supporting our creating of the mental probabilities are not right, the conclusion won't be.

#### **o Insist on seeing the whole picture**

I met an Orthopaedic Surgeon in the corridor a few years ago. We had just gone through another upgrade of the electronic medical record system and were now required to make our entries on the keyboard. He asked, "How can I configure the system so I only see the Orthopaedic record?" I was shocked but managed not to let it show.

It is not possible to practice safe medicine, let alone holistic medicine, without a grasp of the whole picture. Without knowing the complete



history and those findings that may impinge on what we plan to do, how can we assign probabilities to events that may result? And without knowledge of the risks, how can we select the best treatment among many tailored to our patient's particular set of circumstances?

My litany to junior colleagues is *"If it is not found in the electronic medical record, it does not mean that it does not exist"*. We can ask the patient, quiz his relatives, trace the paper records, telephone his family doctor, and ask a colleague in a different hospital to retrieve the information lodged there.

**o Appreciate that the origin of information is as important as the data itself**

In the practice of antique authentication, a rule to go by is that it is easy to fake an object, but it is almost impossible to falsify its provenance. Therefore, we not only need to know a 'fact', we also have to know how it came about.

For decades, we were taught not to infuse fresh frozen plasma (FFP) in a patient with hereditary angioedema (HAE) who is experiencing an attack. The argument is that the angioedema of HAE, which is due to a deficiency of C1 esterase inhibitor, results from the uninhibited action of the complement cascade. Though FFP contains C1 esterase inhibitor, it also has other components of the complement system, so infusing this is like adding fuel to fire. How did this truism arise? Were there many patients who developed worse disease after receiving FFP? Was there a clinical trial? First of all, we have no doubt that that FFP works in acute HAE episodes.<sup>3</sup>

The concern originated from these two pieces of writing by acknowledged experts (one of them discovered the pathogenesis of HAE):

The concern originated from these two pieces of writing by acknowledged experts (one of them discovered the pathogenesis of HAE):

- 1) 'Infusions of fresh normal plasma have in fact been tried. Further attempts in this direction must take into account not only the aforementioned logistic problem but also the dangers of supplying potential enzyme a harmful substrate. If plasma were given early in the course of an attack of angioedema, it is conceivable that the attack might be aggravated rather than ameliorated.'<sup>7</sup>
- 2) 'The appeal of intravenous

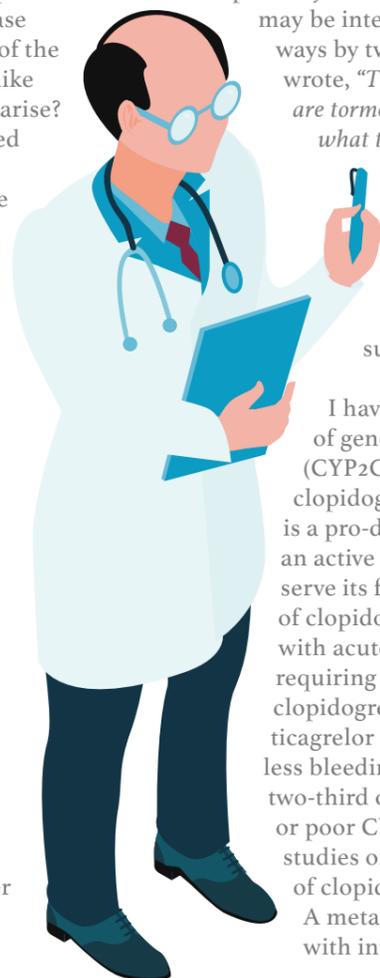
administration of unfractionated plasma to restore satisfactory levels of inhibitor of C1 esterase, as in the treatment of hereditary coagulation defects, is theoretically dangerous. Plasma may supply substrates for plasma enzymes active in forming permeability-increasing properties far in excess of inhibitor given, thus putting the patient at great risk.'<sup>8</sup>

Guidelines parrot this warning.<sup>9,10</sup> The expressed concern was an opinion, not grounded in fact. To test the veracity of the caution, a series of patients who received FFP were reviewed. Seventy-six out of 82 (93%) acute attacks of HAE improved with FFP administration, and there were no instances of adverse reactions.<sup>11</sup> Now, we know that angioedema is not caused by the terminal complement components, but from increased concentrations of bradykinin.<sup>12</sup> Though infusing FFP is not free from risks, exacerbating an attack of HAE is not one of them. This is one example in which erroneous pronouncements by influential people misled us for years. Let's find out the basis for platitudes before we embrace them.

**o Don't rely only on pre-digested views**

We should already know it, but the Trump presidency repeatedly teaches us that the same set of facts may be interpreted in diametrically opposite ways by two groups of people. Montaigne wrote, *"There is an old Greek saying that men are tormented not by things themselves but by what they think about them. If that assertion could be proved to be always true everywhere it would be an important point gained for the comforting of our wretched human condition"*.<sup>13</sup> It should not surprise us to learn that medical guideline writers suffer from the same problem.

I have been discussing the issue of genotyping for cytochrome 2C19 (CYP2C19) status when prescribing clopidogrel with my colleagues. As this is a pro-drug, it needs to be converted to an active form by cytochrome before it can serve its function. The antiplatelet effect of clopidogrel is most needed in patients with acute coronary events and those requiring angioplasty and stenting. Presently, clopidogrel, being generic, is cheaper than ticagrelor or prasugrel, and it probably causes less bleeding in Asians than others. About two-third of our population are intermediate or poor CYP2C19 metabolisers. Clinical studies on the efficacy and cost-effectiveness of clopidogrel show a mixed picture. A meta-analysis showed that patients with intermediate or poorly functioning



CYP2C19 have higher risk of major acute coronary events (MACE) or stent thrombosis.<sup>14</sup> Another review did not show any benefit with testing.<sup>15</sup> A 2019 clinical trial compared two arms, clopidogrel plus CYP2C19 genotyping versus standard prasugrel or ticagrelor. The findings were that both arms were equivalent in cardiovascular outcomes, but there was more bleeding in the standard prasugrel or ticagrelor group.<sup>16</sup>

On 12 March 2010, FDA felt compelled to order that a black box warning be placed in the clopidogrel prescribing information sheet.<sup>17</sup> The ACCF and AHA responded by interpreting the intention of FDA: *"In the current warning, the moderate position of the FDA does not appear merely to be a reluctance to make strong recommendations about genetic testing, but rather to reflect an attempt to weigh the evidence and to give the prescriber more information"*.<sup>18</sup> The 2016 guidelines maintained the same position: *"The role of platelet function testing and genetic testing in patients treated with DAPT is addressed in the 2011 ACCF/AHA/SCAI PCI guideline and the 2014 ACC/AHA NSTEMI-ACS guideline. To date, no RCT has demonstrated that routine platelet function testing or genetic testing to guide P2Y12 inhibitor therapy improves outcome; thus, the routine use of platelet function and genetic testing is not recommended (Class III: No Benefit)"*.<sup>19</sup> The 2019 consensus statement, not equivalent to guidelines, seems to moving towards the support of genotyping in patients with acute coronary syndrome: *"CYP2C19 genotyping in patients on clopidogrel may provide useful prognostic data for cardiovascular risk prediction (for both bleeding and ischemic events) after PCI for ACS"*.<sup>20</sup> In contrast, the Clinical Pharmacogenetics Implementation Consortium Guidelines fully support genotyping.<sup>21</sup>

My colleagues who opposed the testing base their argument on

the 2016 guidelines. I think that the situation is more nuanced now, and new insights have been gleaned after the guidelines were published. In my opinion, it would have been better to discuss the original studies than the recommendations of guidelines.

room doctor, without critically studying the particulars of the case themselves. I argue that the electronic medical record reinforces this problem: it is tempting to copy-and-paste what was written by the previous doctor in this age of time pressure and



... THERE IS A COGNITIVE ERROR, COMMON IN MEDICINE, KNOWN AS CASCADE THINKING OR DIAGNOSIS MOMENTUM. THIS HAPPENS WHEN DOCTORS ACCEPT THE CONCLUSION OF THE PRECEDING HEALTH CARE PROVIDERS, SUCH AS THEIR CONSULTANT OR THE EMERGENCY ROOM DOCTOR, WITHOUT CRITICALLY STUDYING THE PARTICULARS OF THE CASE THEMSELVES. I ARGUE THAT THE ELECTRONIC MEDICAL RECORD REINFORCES THIS PROBLEM ...

Anyway, the dialogue continues – watch this space.

On a different but related note, there is a cognitive error, common in Medicine, known as cascade thinking or diagnosis momentum. This happens when doctors accept the conclusion of the preceding health care providers, such as their consultant or the emergency

information overload. The perfect storm is brewing, and we must consciously steer our dinghy away from the gathering dark clouds.

I enjoin all clinicians to apply elbow grease to understand the complexity of the issues pertinent to their patients, and never to place their faith solely on other people's conclusions.



## PEOPLE ALWAYS CHOOSE THE OPTION THAT SEEMS TO EXPOSE THEM TO THE SMALLEST LOSS, WHICH IS OUT OF PROPORTION TO THE POTENTIAL GAIN. DOCTORS WILL PRACTICE IN A RISK-AVERSE WAY IF THEY ARE UNSURE.



### o Don't put excessive emphasis in test results

There are three sources of information that we use in clinical practice: (i) we obtain the patient's history and perceptions; (ii) we examine the patient carefully to elicit the signs, even the well-hidden or the obscure ones; and finally, (iii) the investigations, always ordered with the guidance of history and physical findings, confirm or quantify our prior conclusions. I am in charge of a clinical service laboratory, but I think that we should not over-order tests or over-interpret the results.

I have written previously that there are two types of blood tests, the physiological (examples are serum sodium, potassium, calcium, creatinine) and the diagnostic (such as prostate-specific antigen, rheumatoid factor, antinuclear antibody, food allergy IgE concentration). The second type are always interpreted in the context of the patient's condition – they are meaningless in isolation. I have observed doctors, both juniors and senior consultants, diagnose patients based on the second type of test results alone, sometimes with tragic outcomes. And this habit shows no signs of abating.

### o Know that the fear of loss is a powerful drive

Many years ago, there was a discussion in my hospital about the management of patients with penicillin allergy. One of the emergency department doctors said, "We'll use erythromycin in all penicillin-allergic patients, even if they have meningitis." This would be an excellent idea if all infections can be treated with erythromycin. Unfortunately, gram-negative septicaemia or urinary tract infection cannot be treated by erythromycin. This problem is amenable to probabilistic thinking. If we do not treat the serious infectious with the appropriate antibiotic, the patient is likely to die. For the penicillin-allergic patient, we need to determine the nature of the reaction. If the reaction was urticaria, angioedema or anaphylaxis, then the status of the allergy may be determined with a skin test. If negative, we are at least 97% certain that a course of antibiotic will not cause any problems. If we treat a penicillin-allergic patient who did not experience Stevens-Johnson syndrome, toxic epidermal necrolysis or anaphylaxis with cephalosporin without skin testing, the risk of reaction is very low. The risk of reaction in when carbapenem is used in this same group of patient is higher, perhaps 10%.<sup>18</sup> There is no simple answer for patients who developed severe reactions to penicillin and who now need gram-negative coverage. Though the monobactam is an option, it is good to discuss these patients with your friendly

Allergist. We need not quiver when we encounter risky situations. We can usually figure out the risks for every possible strategy and reason our way to a reasonable approach.

Risk aversion was studied by Kahneman and Tversky, and their work is summarised in the former's book.<sup>23</sup> Given a situation with an uncertain outcome, people always choose the option that seems to expose them to the smallest loss, which is out of proportion to the potential gain. Doctors will practice in a risk-averse way if they are unsure. Reporting on the reformation of the disciplinary process in Singapore, the Straits Times stated that: "One doctor practising at Mount Elizabeth Medical Centre openly admitted to presenting patients with 16-page consent forms ... Another makes patients watch a 10-minute video, no matter whether it made sense to them ... Yet others said they no longer dare to advise patients - instead, they would just lay out the options and let the patient decide."<sup>24</sup>

### GESTALT

I am not against intuition, except when it is used to the exclusion of everything else. Interestingly, probabilistic thinking and intuition do not produce the same conclusions.

Recently, a 60-year-old patient was admitted for uncontrolled hypertension and kidney failure. She was diagnosed with overlap connective tissue disease two years ago (manifested by puffy fingers and antinuclear antibody). She was also suffering from hypertension and diabetes mellitus. She developed heart failure despite our efforts to prevent it.



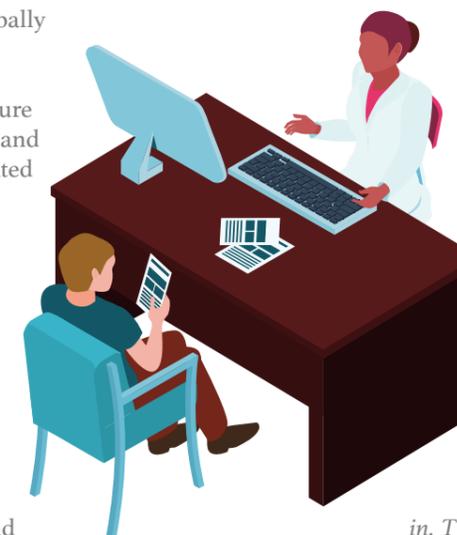
2D-echocardiography showed globally dysfunctional myocardium with 20% ejection fraction. Were these hypertensive crisis and kidney failure due to uncontrolled hypertension and diabetes mellitus, or due to untreated autoimmune disease? The kidney biopsy showed mostly sclerosed glomeruli, and the one that was spared did not show antibody staining. There were changes demonstrating hypertension in the vessels. The pathologist opined that it was not possible to offer a pathogenetic mechanism because of the late-stage findings. Some of my colleagues wanted to administer high-dose steroid and cytotoxic agents.

Their argument was that the patient had been diagnosed to have some form of autoimmune disease (and now could have the devastating scleroderma renal crisis), the antinuclear antibody was positive, and the heart failure was due to cardiomyopathy. That would be the intuitive conclusion.

However, the weighing of probabilities led to a different viewpoint. Was the patient suffering from scleroderma renal crisis? It was unlikely because there was no clinical scleroderma at present. Of course, there is a version of systemic sclerosis that doesn't have scleroderma, but it is rare (perhaps 100 cases reported in the world literature). Scleroderma renal crisis, itself an unusual occurrence (0.5 to 0.6% in patients with limited scleroderma), in a patient with systemic sclerosis sine scleroderma (a form of limited scleroderma), must be rare. Anyway, the histology did not support this diagnosis. Did the patient have lupus? Lupus can cause kidney failure, but signs of the disease such as photosensitivity, mouth ulcers, arthritis, haemolysis, cytopaenia and hypocomplementaemia were absent. This means that uncontrolled hypertension and diabetes, leading to ischaemic damage to the glomeruli, remained the more likely diagnosis.

### THE NATURE OF AI

A whimsical definition of artificial intelligence (AI) is '... the study of how to make computers do things at which, at the moment, people are better' (by Elaine Rich).<sup>25</sup> I think that AI is superb and will profoundly change Medicine before long.<sup>26</sup> AI works best in selecting the best answer among a known number of identified possibilities. It is better than clinicians in deciding if a patient with chest pain is suffering from myocardial infarction, if a nodule in the chest film is due to malignancy, and in predicting the risk of a patient collapsing within the next hour. However, simple problems for humans can mislead or flummox AI, so doctors still need to think for themselves, at least for now.<sup>27</sup>



When we confront AI, we are forced to think probabilistically because AI assigns probabilities to each outcome. AlphaZero is a computer chess program that learnt how to play the game itself after being taught the rules of the game and simply by playing millions of games against itself. One of its developers, Thore Graepel, talked about its evaluative capability: "This is where AlphaZero's neural network – a computer system loosely modelled on the connections and neurons in the brain – comes in. The neural network takes the current

game position as its input, and returns move probabilities for each possible move to be the strongest move (this is sometimes called the 'policy network'), along with a value estimate for the current position (sometimes called the 'value network'). This output guides the Monte Carlo tree search towards the most promising segments of the game tree".<sup>28</sup> Interestingly, AI utilises probability in the same way as our advocated approach for humans to tackle tough clinical decisions.

### THE PROBLEM WITH GROUP PREDICTION

The stress on evidence-based medicine over the past 15 years has caused us to view clinical trials as the ultimate source of knowledge. But clinical trials only provide grouped data. I saw a patient who works as an actuary. Since there are tables that we can look up, I asked him if he calculates the risks for individual clients. He admits that it is impossible to predict the outcome for a given person. He did not tell me what he did exactly, but I suppose that he calculated the risks for new insurance-linked instruments for his bank. When applied to individual patients, we are left with probabilities.

### KNOW THE LAY OF THE LAND

How do we navigate this complicated landscape? We first have to identify the problem, which in most situations should be obvious. It may be solved by pattern recognition, if not by ourselves, then by a colleague more familiar with these kinds of situations. If we are still stuck, we have to start gathering the information to determine probabilities. We need to list all the diagnoses or all the strategies we are contemplating, not only those we can think of immediately, but also those that arise through discussion and internet searches. Then we assign probabilities to each, preferably using data from published reports, failing which we exercise judgement. Remember that there is no need to decide if there is time. Robert Rubin again: One thing Summers says he has learned from Rubin is the value of not always choosing among the available options.

"Rubin ends half the meetings with -- 'So we don't have to make a decision on this today, do we?' Summers says. New information will evolve."<sup>2</sup> Test your decision, if possible, with a therapeutic trial. Always keep an open mind after your decision because 'the wheel's still in spin' (misquoting Bob Dylan).

#### CONCLUSION

One of the most unsettling movie endings I know comes from 1998's *Pleasantville*. Two teenagers were transported to a TV world where everything is black-and-white, and there is certainty. The two brought complexity and moral ambiguity into that perfect world. In the end, everything was in full colour, but the future was uncertain and uneasy. Well, that's exactly the world we inhabit, and our thinking must conform to the perplexity and unpredictability that characterises it.

WE NEED TO LIST ALL THE DIAGNOSES OR ALL THE STRATEGIES WE ARE CONTEMPLATING, NOT ONLY THOSE WE CAN THINK OF IMMEDIATELY, BUT ALSO THOSE THAT ARISE THROUGH DISCUSSION AND INTERNET SEARCHES. THEN WE ASSIGN PROBABILITIES TO EACH, PREFERABLY USING DATA FROM PUBLISHED REPORTS, FAILING WHICH WE EXERCISE JUDGEMENT.

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## PHARMACY

# THE ROLE OF HOSPITAL PHARMACISTS AND THEIR IMPACT ON PATIENT CARE FROM ADMISSION TO OUTPATIENT FOLLOW-UP

Working together with doctors, nurses and other healthcare professionals, pharmacists strive to provide quality care for all patients in the hospital. From admission to outpatient follow-up, pharmacists are part of the multidisciplinary team providing holistic care for patients by ensuring safe and effective medication use. But what exactly do pharmacists do? This article will delve into the various roles pharmacists perform throughout a patient's stay in a hospital and beyond.

**(A) MEDICATION RECONCILIATION**

**What is medication reconciliation and why is it important?**

Upon admission, it is crucial to obtain a comprehensive medical history from patients. Pharmacists carry out medication reconciliation as an integral part of history-taking to obtain the most precise patient medication list, which is essential for ensuring continuity of care.

IN A STUDY CONDUCTED BY TAN TOCK SENG HOSPITAL (TTSH) ON PHARMACIST-LED MEDICATION RECONCILIATION SERVICES, THERE WAS AN INCREASE IN MEDICATION ERRORS DETECTED, FROM 348 TO 925 PER MONTH, IN THE 12 MONTHS AFTER THE INITIATION OF THIS SERVICE.

The term medication reconciliation is defined by the Singapore Ministry of Health (MOH) as the “structured and explicit process of creating the most accurate list possible of all medications a patient is taking”, with the aim of ensuring accurate and complete medication information transfer during the transition of care, thereby reducing medication errors and preventable adverse drug events (ADEs).<sup>1</sup>

According to the World Health Organization (WHO), many ADEs occur due to a lapse in communication between healthcare professionals and patients and/or carers during transition of care. It has been reported that up to 67% of patients' prescription medication histories recorded on admission to hospital have one or more errors, and up to 46% of medication errors occur when new orders are written on admission or discharge.<sup>2</sup>

In a study conducted by Tan Tock Seng Hospital (TTSH) on pharmacist-led medication reconciliation services, there was an increase in medication errors detected, from 348 to 925 per month, in the 12 months after the initiation of this service. The most common error reported was transcription mistakes, followed by incomplete medication history.<sup>3</sup> These findings demonstrate that medication reconciliation can help to reduce medication errors, and improve the quality of care when conducted well.

In TTSH's setting, instances where pharmacist medication reconciliation is performed include:

- a) Within 48 hours of inpatient admission
- b) Before discharge from acute care
- c) During visits to outpatient care (e.g. Specialist Outpatient Clinic)

**How is medication reconciliation carried out?**

In a nutshell, medication reconciliation is a systematic process involving 3 Cs - Collection, Checking, and Communication (Figure 1).

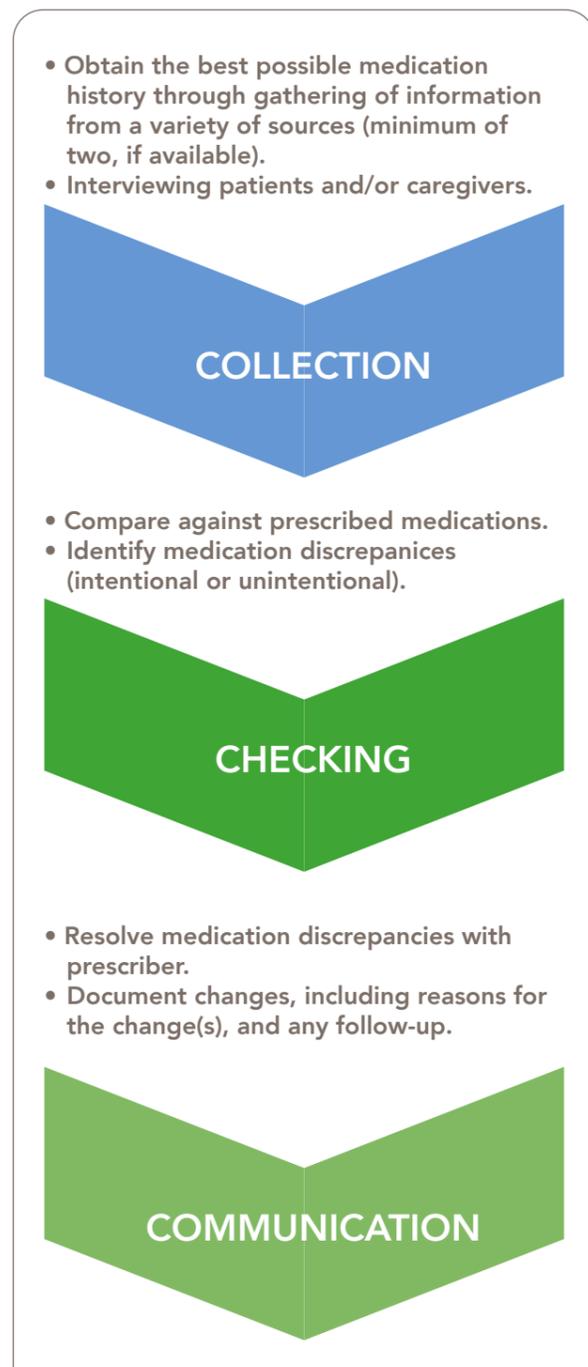


Figure 1. The 3 Cs of Medication Reconciliation.

**Collection**

To obtain the best possible medication history, the patient's medication information is gathered from a variety of sources. The information is then cross-checked and verified with a minimum of two sources, if available. Sources of information include:

- Electronic databases e.g. National Electronic Health Record (NEHR)
- Medication lists or charts from long-term care facilities
- Discharge/transfer information
- General practitioners/specialists in private practice
- Interviews with patient and/or caregivers
- Inspection of home medications



An electronic platform that is frequently utilised to retrieve medication history is the National Electronic Health Record (NEHR) – a secure system that consolidates patient health records across different healthcare providers such as General Practitioner (GP) clinics, polyclinics, specialist clinics, therapy centres, and hospitals.

Although NEHR is a valuable and holistic platform, information gaps may still exist. For example, for patients residing in long-term care facilities (e.g. nursing homes, community hospitals, etc.), medications may be actively titrated and adjusted during their stay, but this may not be documented on NEHR via electronic prescriptions. In such cases, medication charts or lists from these facilities would be more accurate when compiling a patient's medication list.

Other than official medication records, patient and/or caregiver interviews are one of the most valuable sources of information during medication reconciliation, as medication compliance can also be assessed during such interviews. Information regarding medication

side effects, efficacy, as well as the patient's use of supplements and traditional medications, can be obtained through such interviews.

**Checking**

Upon obtaining the most accurate medication history possible, the list of medications is compared against medications prescribed on admission in order to identify discrepancies.

Examples of discrepancies include:

- *Omission* – Absence of drug from the list of medication that the patient is currently taking.
- *Commission* – Presence of a drug on patient's medication list that the patient is no longer taking, or with no clinical explanation to support the commission.
- *Incorrect or missing details about a medication* – E.g. dosage form, dose, route or frequency.

**Communication**

Upon identification of a discrepancy, pharmacists will investigate the cause of the problem and engage the prescriber on the next course of action.

Some potential causes of medication discrepancies include:

- *Lack of knowledge on medication use* – i.e. the patient does not understand how to take the prescribed medication properly.
- *Medication compliance* – i.e. medications are intentionally taken differently than what was prescribed, either because of side effects or personal beliefs.
- *Transcribing error* – i.e. clerical error while ordering medications.
- *Incomplete medication history due to information gaps*

Once the discrepancies have been resolved, the best possible medication list is updated with the current regime and reasons for any changes. This will form the reconciled list, which represents the most up-to-date and accurate version of the patient's medication list.

**(B) MEDICATION REVIEW**

**Identifying and managing drug-related problems**

Medication review is defined as a structured, critical examination of a patient's medications with the objective of reaching an agreement with the patient about treatment, optimising the impact of medicines, minimising the number of drug-related problems (DRPs) and reducing waste.<sup>4</sup> Throughout a patient's admission, pharmacists identify, resolve and document any DRPs in a patient's medication list during medication reviews through pharmacist interventions. Examples of DRPs are shown in Table 1. If no DRPs are present, pharmacists will then focus on ensuring that the goals of medication therapy are met without compromising patient safety.

CATEGORY	DRUG-RELATED PROBLEMS (DRPS)	DEFINITION
Indication	Omission of drug therapy/Untreated Indication	<ul style="list-style-type: none"> <li>• Patient has a medical problem that requires drug therapy, but is not receiving a drug for that indication, or is not adequately controlled with drugs at optimal doses, and requires additional drugs.</li> </ul>
	No indication for drug ordered	<ul style="list-style-type: none"> <li>• Patient is taking a drug without a medically valid indication.</li> </ul>
	Therapeutic duplication	<ul style="list-style-type: none"> <li>• Patient is taking more drugs than required, usually from the same therapeutic class, for the same indication.</li> </ul>
Drug Selection	Ineffective drug	<ul style="list-style-type: none"> <li>• Patient has a drug indication but is taking an inappropriate drug, e.g. drug contraindication, drug unable to reach target site, inadequate response to the drug at optimal dose and require switch to alternative drug or evidence to support use of one drug over another.</li> <li>• Includes cost issues and drug unavailability, IV to PO switch, inappropriate formulation/dosage form, inappropriate change in brand.</li> </ul>
	Contraindication	
	More affordable drug available	
	Inappropriate drug formulation/dosage form	
	Inappropriate change in brand	
Dosing Regimen	Dosage too low	<ul style="list-style-type: none"> <li>• Patient has a medical problem that is not treated with an optimal regimen of the correct drug, e.g. disease state not responding or experiencing signs of toxicity, low or elevated serum drug level, inadequate or excessive duration of therapy, and patient with unusual dosage requirements.</li> <li>• Includes dosage adjustments for renal and hepatic failure.</li> <li>• Patient is on a drug that is no longer available and has to be substituted.</li> </ul>
	Dosage too high	
	Inappropriate frequency/route/site (without change in daily dose)	
	Duration too short	
	Duration too long	
	Therapeutic Substitution	
Adherence	Drug administration issues	<ul style="list-style-type: none"> <li>• Patient does not follow the recommendations for prescribed treatments, and reasons for deviating from the (agreed) treatment plan may be intentional or unintentional. It includes using/ taking more or less than the prescribed treatment or using drug at the wrong time.</li> <li>• Patient may face problems in administering drug e.g. inappropriate crushing of tablets, wrong insulin injection technique, difficulty in swallowing tablet/capsule.</li> <li>• Patient may decide not to fill his/her prescriptions in the pharmacy and not start treatment at all.</li> <li>• Patient may also discontinue treatment prematurely.</li> </ul>
	Cannot afford drug	
	Forgets to take	
	Prefers not to take as instructed	
	Lacks understanding/awareness of drug use	
Adverse Drug Reaction	Adverse drug event	<ul style="list-style-type: none"> <li>• Patient may have a medical problem that is the result of an adverse drug event, which can be an extension of the drug's pharmacological effects or an allergic/idiopathic reaction.</li> </ul>
Drug Interactions	Drug-drug	<ul style="list-style-type: none"> <li>• Patient may have or potentially have a medical problem that is the result of a drug-drug, drug-food, drug-laboratory or drug-disease interaction.</li> </ul>
	Drug-food	
	Drug-lab	
	Drug-disease	
Monitoring	Monitoring parameters required	<ul style="list-style-type: none"> <li>• There is an issue relating to investigations or parameters for monitoring therapeutic or adverse effects of drug therapy.</li> </ul>
Storage	Inappropriate storage conditions	<ul style="list-style-type: none"> <li>• Patient may face problems in proper storage of drugs, or taking drugs beyond expiry date.</li> </ul>
	Expired medications	

Table 1. Drug-Related Problems (DRP) Categories and Definitions from MOH Pharmaceutical Care Services Guidelines 2019.<sup>4</sup>

Having pharmacists participate in daily ward rounds with clinicians can improve medication appropriateness through timely recommendations made at the point of prescribing, rather than retrospectively. This has potential patient safety benefits since there are no delays in correcting any erroneous prescriptions.

The recommendations are likely to be more appropriate and relevant as pharmacists gain a better sense of the patients' current medical problems through discussion during rounds. In addition, participation in ward rounds enables pharmacists to share their knowledge on drug-related issues with other members of the medical team. This can positively influence prescribing practice in the long run, as well as improve the communication within the multi-disciplinary team.

Benefits of having pharmacists participate in ward rounds:

1. Drug therapy is optimised upstream (at the point of prescribing) to avoid "near-misses" related to medications.
2. Timely and comprehensive medication reconciliation is carried out.
3. Drug-related issues are brought up to the medical team to discuss and act upon prospectively.
4. Improvements in the appropriateness of medications ordered and administered.
5. Through frequent pharmacists' participation, skills and knowledge may be imparted to junior doctors to improve overall medication use.

**(C) BEDSIDE DISPENSING**

To ensure smooth transition of care, pharmacists in TTSH perform bedside dispensing for patients before their discharge. In bedside dispensing, pharmacists counsel the patients on the safe and effective use of medications, focusing on newly initiated medications and medication regime changes. Pharmacists can also reassess medication administration techniques as well as reinforce medication compliance through patient education. Bedside dispensing can also be used to educate patients on non-pharmacological techniques to aid in the management of their condition, answer questions regarding medication therapy, and empower patients to take charge of their own health.

**(D) POST-DISCHARGE PHARMACIST-LED MEDICATION REVIEW**

With a rapidly ageing population and rising incidence of chronic diseases in Singapore, polypharmacy is a prevalent and pressing problem. There is a growing need for effective medication management services to optimise medication use and health outcomes. Medication therapy management has been shown to be effective in lowering systolic and diastolic blood pressure; lowering LDL cholesterol and other health indicators (e.g. HbA1c); and, increasing patient knowledge on their health condition and medications. In addition, it improves the safe and effective use of

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medications, including reducing therapeutic duplication, decreasing total medications prescribed, and increasing adherence for therapeutic care.

A comprehensive medication review is especially important for patients with (i) multiple chronic conditions, (ii) different prescribers, and (iii) complex medication therapies, as these increase the risk of medication errors, resulting in poorer health outcomes. An example of a medication review clinic led by pharmacists in TTSH is the General Medicine Medication Review (GMMR) clinic.

**Pharmacist-led GMMR Clinic**

The GMMR clinic started out as a pilot service in October 2015 in collaboration with the General Medicine (GM) Department. At these medication review sessions, pharmacists perform the following through a shared-decision making process with patients and their clinicians:

- Medication reconciliation
- Optimizing medication therapy through (i) monitoring for efficacy and side effects of medications, (ii) titration of doses according to disease states, and (iii) appropriate de-prescribing
- Assess and address medication adherence
- Provide in-depth medication-related education
- Offer relevant and appropriate lifestyle and diet modification counselling
- Screening and recommending influenza and pneumococcal vaccination

The service offered by the GMMR clinic complements the current GM complex care (GMCC) programme

in TTSH, which aims to provide coordinated and consolidated care management for patients with multiple chronic conditions and physicians' follow-up, thus reducing confusion and improving care.

Benefits of pharmacist-led GMMR Clinic:

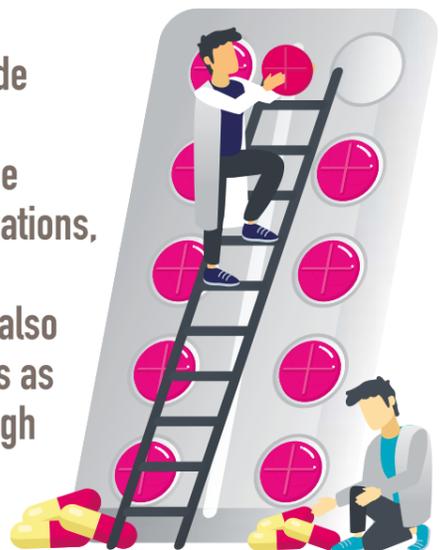
1. Improve the quality of patient care and outcomes (e.g. disease and/or symptom improvement/resolution).
2. Reduce health care expenditures (e.g. reduction in expenses associated with emergency care visits and hospitalizations).
3. Reduce medication-related adverse events (e.g. improved patient safety).
4. Empower patients to take charge of their health and maintain their medication list (e.g. improved adherence, increased understanding of their health conditions and medications).
5. Improved efficiency of doctors' consultation with patients.
6. Collaborate with the patient, physician, and other healthcare providers to develop and achieve optimal goals of medication therapy.

Other than medication reviews with the GM department, TTSH pharmacists also run services with the Endocrinology department, working closely together with clinicians to support the care plans of patients with diabetes. Outside of the hospital, TTSH pharmacists are part of the multi-disciplinary teams which reach out to patients in the community. Through close interactions at patients' homes, pharmacists educate them on the proper use of medications to improve adherence, prevent readmissions and reduce unnecessary emergency department visits.

CONCLUSION

Pharmacists play an integral role in the care management of patients. From admission to post-discharge, pharmacists work together with multi-disciplinary teams to provide holistic care for patients through (a) medication reconciliation, (b) medication review, (c) bedside dispensing and, (d) post-discharge pharmacist-led medication review. All these are carried out with the aim of optimising medication use to ensure patients' safe and effective consumption of medications.

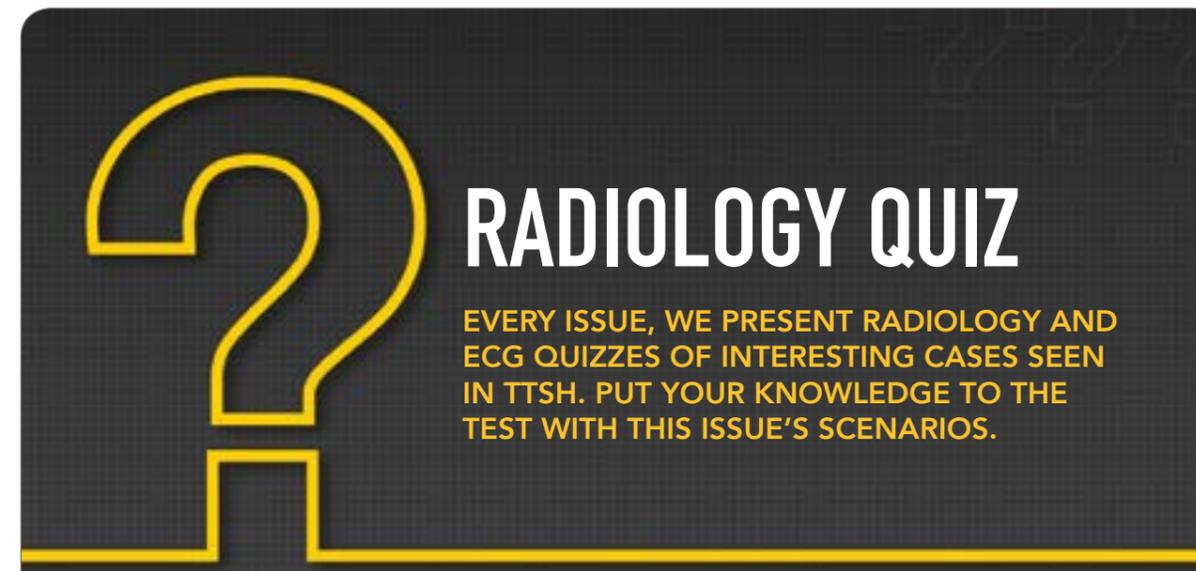
**To ensure smooth transition of care, pharmacists in TTSH perform bedside dispensing for patients before their discharge. In bedside dispensing, pharmacists counsel the patients on the safe and effective use of medications, focusing on newly initiated medications and medication regime changes. Pharmacists can also reassess medication administration techniques as well as reinforce medication compliance through patient education.**



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A previously well 57-year-old Malay gentleman presented to the Emergency Department for left thigh swelling. His vital signs were stable, and examination revealed an erythematous, warm and non-fluctuant

induration on the left upper thigh.

An X-ray of the femur was ordered to rule out osteomyelitis (Figure 1).

QUESTION

What does the X-ray in Figure 1 show? What are the possible differential diagnoses?



Figure 1. X-ray of the left femur.

ANSWER

The X-ray shows an incidental finding of a solitary lytic lesion, eccentrically located in the metaphyseal/ epiphyseal region of the distal femur. It has sclerotic margins and is slightly expansile, without any other obvious periosteal reaction.

Based on the location (metaphyseal/epiphyseal), the most likely diagnoses of a solitary lytic lesion are aneurysmal bone cyst (ABC), chondromyxoid fibroma (CMF), giant cell tumour (GCT), infection, or geode. Chondroblastoma would also be a consideration in a younger patient, and enchondroma or chondrosarcoma may be considered if the lesion is centrally located.

**QUESTION**

What investigations would you order next?

**ANSWER**

CT/ MRI (see Figures 2a to c).



Figure 2a. Two sagittal sections of the left lower thigh (CT images).



Figure 2b. Sagittal section of the left lower thigh (MRI T1 image on the left and T2 image right).

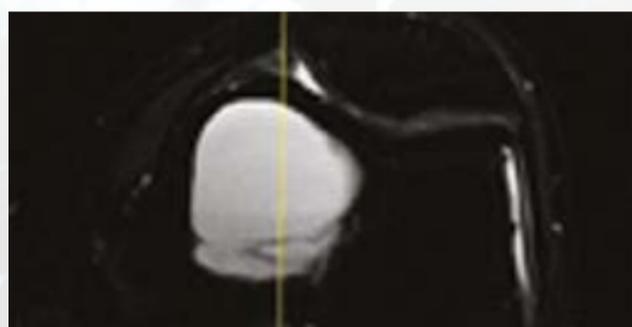


Figure 2c. Transverse section of the left lower thigh (MRI).

**QUESTION**

What additional information do the CT and MRI provide? What is now the most likely differential?

**ANSWER**

Cross-sectional imaging reveals a predominantly cystic lesion, with T1 low signal and T2 high signal on MRI. Because of this, CMF is a less likely diagnosis due to the lack of a chondroid matrix. The lesion is not quite abutting the articular surface, making GCT less likely as well. The lesion has a well-defined, sclerotic margin, which is not typical of infections. The remaining considerations are ABC and geode. A fluid track was seen originating near an area of cartilage wear at the articular surface, and extending to the lesion, consistent with a geode.

Subsequently, a bone scan showed photopaenia on both the delayed and blood pool images, further strengthening the argument that geode is the most likely diagnosis.

**DISCUSSION**

The term geode is taken from geology, where it refers to a small, gas-filled space in a rock. It is also known as a subchondral cyst, but this is a misnomer as a geode is not a true cyst.

A geode appears as a well-defined lytic lesion with sclerotic margins, generally located at the periarticular surfaces or epiphysis. The geode in this case is slightly atypical, being large and located a distance away from the articular surface. The histology of a typical geode is a cavity, surrounded by layer of fibrous connective tissue with adipocytes and osteoblasts, containing necrotic bone fragments and denuclearised cells.

They are commonly associated with osteoarthritis, rheumatoid arthritis, osteonecrosis, and calcium

pyrophosphate deposition disease (CPPD), and generally found in older patients (above the age of 40).

There are two theories to explain their formation:

- *Synovial fluid intrusion theory* - Elevated intra-articular pressure causes intrusion of joint fluid into the subchondral bone and secondary resorption of bone
- *Bone contusion theory* - Impact of two opposing articular surfaces causes traumatic bone necrosis

Geodes are benign lesions that do not intrinsically cause problems. Instead, symptoms associated with geodes often arise from the underlying disease process. However, large or atypical geodes may cause pathological fractures, thus necessitating intervention.



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The histology of a typical geode is a cavity, surrounded by layer of fibrous connective tissue with adipocytes and osteoblasts, containing necrotic bone fragments and denuclearised cells.

# ECG QUIZ

A 78-year-old lady presented to the polyclinic for a short episode of 'pulling' chest pain that started the day before. She was pain-free when she saw the polyclinic doctor. Apart from hypertension, she had no significant past medical history. A resting 12-lead electrocardiogram (ECG) was performed in the polyclinic (Figure 1).

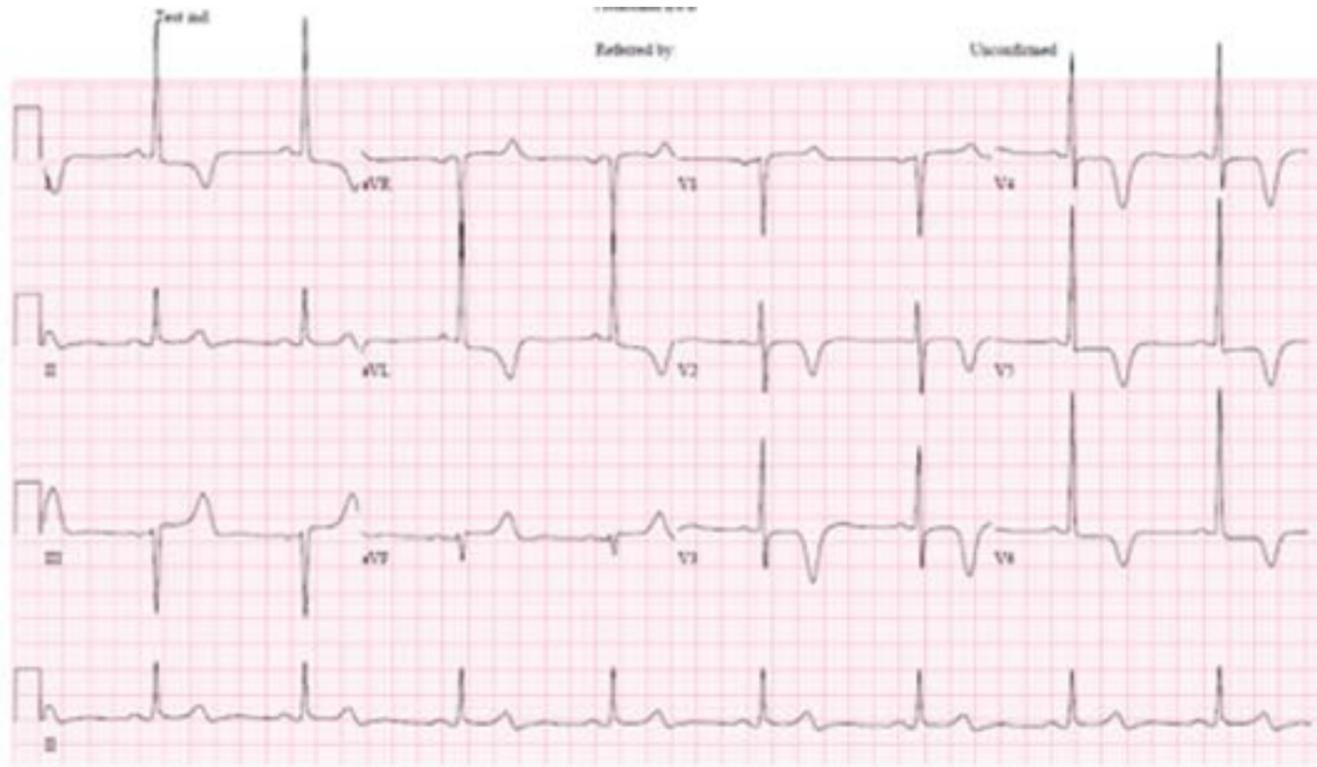


Figure 1. Chest X-ray performed in the polyclinic 2 weeks prior to hospital presentation.

In view of the ECG abnormalities, she was rushed to the Emergency Department. Serial cardiac troponins were normal. There were no dynamic ECG changes seen on subsequent ECGs performed in the hospital.

## QUESTION

What is the most likely diagnosis?

## ANSWER

Hypertrophic cardiomyopathy.

### DISCUSSION

The ECG demonstrates left ventricular hypertrophy (LVH) based on voltage criteria (*Sokolow criteria, defined by  $S V_1 + R V_5 > 35mm$* ), in association with prominent, symmetrical T inversions over the precordial leads. This pattern is suggestive of hypertrophic cardiomyopathy (HCM), particularly apical HCM. A transthoracic echocardiogram performed on this patient confirmed the diagnosis. Coronary artery disease was also excluded with non-invasive testing.

HCM is defined as LVH in the absence of a secondary cause (such as hypertension, valvular disease, etc). Many morphological variants of HCM exist, with asymmetric septal hypertrophy being the most common and classical form. The apical variant, however, is seen more frequently in the Asian population than in the western world. Apical HCM was first described in Japan by Sakamoto, who reported a novel cardiac condition characterized by a spade-like left ventricular cavity, apical hypertrophy,

and giant negative T waves on the ECG. Contemporary data from Asian cohorts now suggest that apical HCM constitutes 25 – 38% of the total HCM population, and is not uncommon in our local practice.

Echocardiography is the first-line investigation for further evaluation. Cardiac magnetic resonance imaging

is also particularly useful in diagnosing cases of apical HCM. As with all HCM cases, apical HCM patients are at risk of sudden cardiac death (SCD). Although apical HCM is generally associated with a lower risk of SCD when compared to other forms of HCM, this does not preclude the need for apical HCM patients to undergo a comprehensive risk evaluation by a cardiologist.



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