

# MEDICAL DIGEST



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We all segue inexorably through the Seven Ages of Man. As doctors, we are reminded of mortality everyday, and that not everyone enjoys all Seven Ages.

This piece is inspired by the recent passing of two doctors in the prime of their lives. Until we figure out how we can delay or do away our end (not as hopeless as we think, see Fahy GM, et al. Reversal of epigenetic aging and immunosenescent trends in humans. Aging Cell 2019:e13028), we should spare a thought about how we should live.

The events recounted by Dr. Paul Kalanithi, a neurosurgeon who died of metastatic lung cancer at age 37, resonated with many readers (When Breath Becomes Air, Random House 2016). For me, the most striking lesson was his oncologist's constant refusal to say how much time he had left. Instead, she told him to find his values. That's the approach the protagonist Kanji Watanabe took in Akira Kurosawa's Ikiru.

I think there are two main ways doctors can leave a mark. One is to train the next generation; the other is to improve the way things are perceived or are carried out, through administrative leadership or scientific discovery. However, it would be quite something if our accomplishments could persist longer than the cave drawings at Font-de-Gaume.

Let's not make too much of a fuss about ourselves. Montaigne wrote 'And so it follows that we reckon our death to be a great event, something which does not happen lightly nor without solemn consultations among the heavenly bodies ... And the higher we rate our worth the more we think that way' (Screech's translation, Penguin, 1987). Henning Mankell was diagnosed with cancer in January 2014 and died October 2015; in this period, he wrote a book (Quicksand, Harvill Secker 2014). Besides recording myriad small observations he made throughout life, he was concerned that the longest standing human building Hagar Qim existed only for 6,000 years, while the nuclear waste we accumulate will last much longer.

We cannot better what Horace has written: 'Ah, Postumus! they fleet away, Our years, nor piety one hour; Can win from wrinkles and decay, And Death's indomitable power ... Your land, your house, your lovely bride; Must lose you; of your cherish'd trees; None to its fleeting master's side; Will cleave, but those sad cypresses. Your heir, a larger soul, will drain; The hundred-padlock'd Caecuban, And richer spilt the pavement stain; Than e'er at pontiff's supper ran.' (Odes book 2, 14).

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 select a few reports and asked one of the authors of each to summarise and discuss the clinical relevance of their research.



## OLDER PATIENTS' PARTICIPATION IN PHYSICAL ACTIVITY DURING HOSPITALIZATION: A QUALITATIVE STUDY OF WARD NURSES' PERCEPTIONS IN AN ASIAN CONTEXT

Chan EY, Hong LI, Tan YHG & Chua WL. *Geriatric Nursing* 2019;40(1):91-98. doi:10.1016/j.gerinurse.2018.07.002.

Maximising the functional ability of older adults during hospitalisation is critical to preventing functional decline (i.e. loss of ability to perform activities of daily living, such as grooming, dressing, showering, eating, and using the bathroom). This qualitative study explored the perceptions of nurses on the facilitators and barriers of hospitalised older patients' participation in physical activities. Semi-structured focus group interviews were conducted with 30 registered and enrolled nurses via purposive sampling. Facilitators included seeing physical activity engagement as a fundamental facet of nursing, drawing social contracts and motivating patients, and engaging a multidisciplinary team approach. Barriers included psychological factors, falls culture, nurses' heavy workload and language impediment. Barriers more unique to the Asian culture were patients' adoption of sick-role behaviour, reliance on domestic helpers and, social suppositions on paid service.

*This summary was prepared by DR CHAN EE YUEE, Assistant Director of Nursing in the Department of Nursing Services, Tan Tock Seng Hospital.*

### IMPORTANCE IN CLINICAL PRACTICE

Functional decline is commonly experienced by approximately a third of hospitalized older adults. The onset of functional decline often precedes hospitalization, and potentially worsens through the course of hospitalization. Care settings that have adopted a philosophy of care whereby older patients are engaged at their highest level of ability to optimize function and physical independence, have reported many benefits including larger improvements in activities of daily living and function, greater physical resilience, less fears in falling and fewer readmissions. The findings from this study on the facilitators and barriers can be used to develop culturally appropriate interventions to promote physical activity participation for hospitalized older patients in an Asian context. To cultivate such an environment, all key stakeholders including nursing leaders, ward nurses, therapists, medical practitioners, patients, and families, must recognize the importance of physical activity participation, and work together towards achieving this goal.

### IMPORTANCE IN CLINICAL PRACTICE

This study makes clear the profile of the PMD accident victim, the types of injuries sustained and the location of greatest danger. The impact of the accidents includes not just health-related morbidities, but the loss of productive years, long-term cost of caregiving, and opportunity cost to the economy. Protective headwear must be made compulsory for PMD users. The debate about legislation and choice continues, but society and PMD users in particular must think of safety first of all.

Electronic bicycles and scooters, also known as personal mobility devices (PMDs), are commonly encountered in public roads and walkways in Singapore. The number of reports of accidents involving PMDs has been rising over the past few years. The authors retrospectively reviewed the types of injuries related to PMD accidents which occurred during the period January 2014 - November 2017. There were 22 patients with an injury severity score (ISS) of at least 9. The typical patient is a 40-year-old man. 77% of the patients suffered injuries to the head and neck, 50% to the limbs and 36% to the chest. There were three deaths, all due to head and neck injuries in riders not wearing protective helmets. The mean ISS score was higher in accidents that occurred on roads and involved other vehicles.

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



## ELECTRONIC BICYCLES AND SCOOTERS: CONVENIENCE AT THE EXPENSE OF DANGER?

Goh SNS, Leong XY, Cheng YWJ and Teo LT. *Ann Acad Med Singapore*. 2019; 48(4):125-128.



## THE PATTERN OF USE AND SURVIVAL OUTCOMES OF A DEDICATED ADULT HOME VENTILATION AND RESPIRATORY SUPPORT SERVICE IN SINGAPORE: A 7-YEAR RETROSPECTIVE OBSERVATIONAL COHORT STUDY

Tan GP, Soon LHY, Ni B, Cheng H, Kok HTA, Kor AC, Chan Y. J Thorac Dis. 2019;11(3):795-804.

Home mechanical ventilation (HMV) is used to support patients with chronic ventilatory insufficiency such as amyotrophic lateral sclerosis (ALS), congenital muscular dystrophy and spinal cord injury (SCI), so as to allow them to return to their own home with all the attendant benefits such as interaction with loved ones and familiar surroundings. However, HMV is a heavy commitment and imposes significant care and financial burden on affected individuals, family members and the healthcare system. The Home Ventilation and Respiratory Support Service (HVRSS) at Tan Tock Seng Hospital was set up in 2009 to enable patients requiring mechanical ventilation to go home.

This was a retrospective study of all individuals referred for HMV consideration from 1 January 2009 to 31 December 2015. 155 patients were assessed, and 112 were found suitable for HMV. The ventilator-assisted individuals (VAIs) were mostly male aged 40-70 years. The monthly per capita household income was below S\$1,000 in about half of the VAIs. Seventy-four (66%) individuals were prescribed non-invasive ventilation, and 15, mostly sufferers of ALS, subsequently transitioned to invasive ventilation. For analysis, the VAIs were divided into 4 groups based on the reason for mechanical ventilation: ALS; other neuromuscular and chest wall diseases (NMCW); SCI; and complex intensive care unit (ICU) conditions. The median (95% CI) survival was 1.8 (0.6-5.7), 2.6 (0.8-4.8), 4.2 (2.1-7.6) and 6.7 (4.5-10.7) years for ALS, complex ICU, SCI and NMCW groups, respectively.

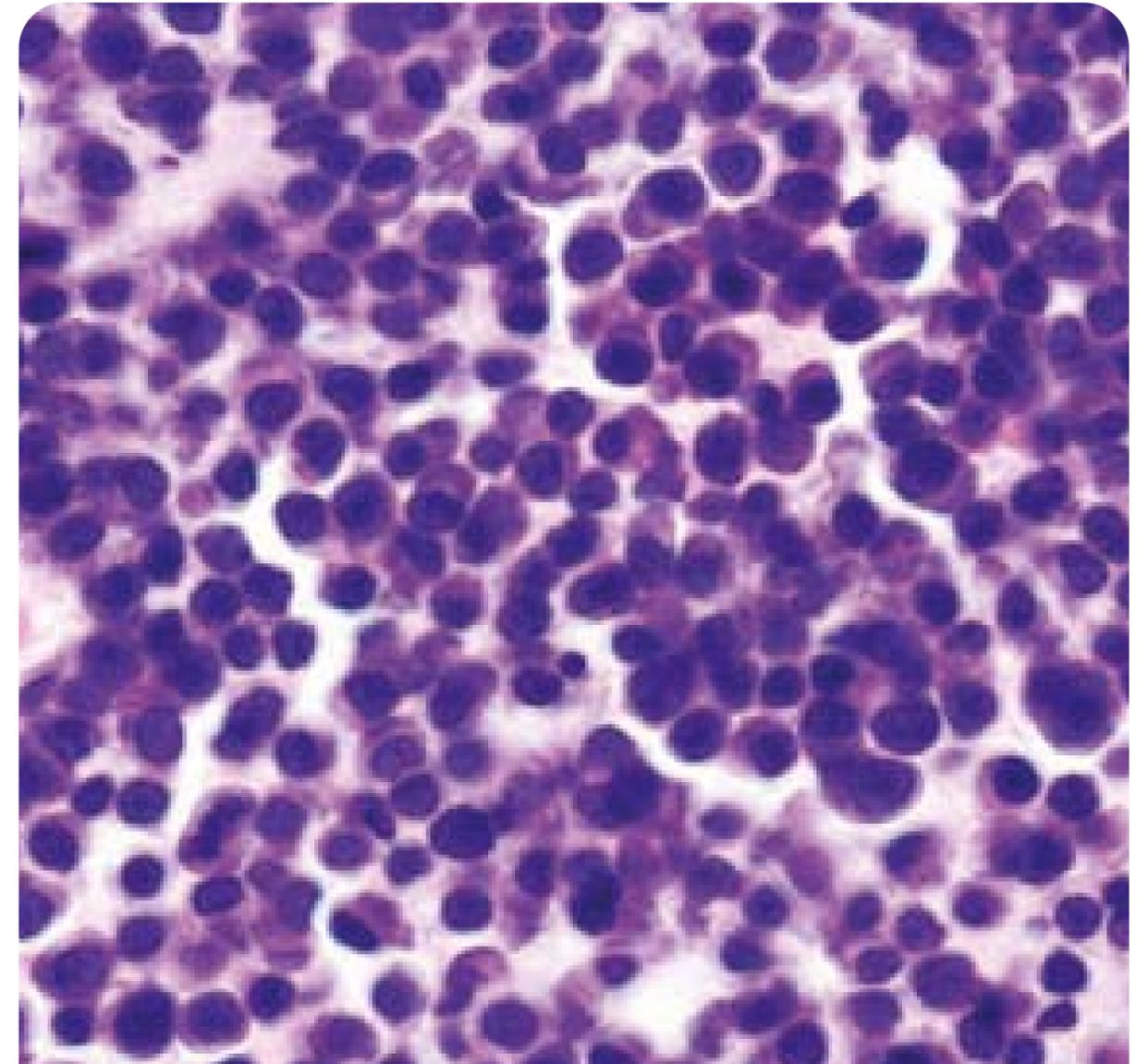
*This summary was prepared by the editorial team of Medical Digest.*

### IMPORTANCE IN CLINICAL PRACTICE

The HVRSS is the only national adult multidisciplinary service in Singapore. The number of referrals to HVRSS has increased over the years. Patients in the NMCW group were the longest survivors and many in the SCI group were eventually weaned off ventilatory support. This study shows that though the responsibility is very heavy for the caregivers and healthcare providers of patients who depend on ventilatory support, this is better than the alternative of long-term institutionalisation.



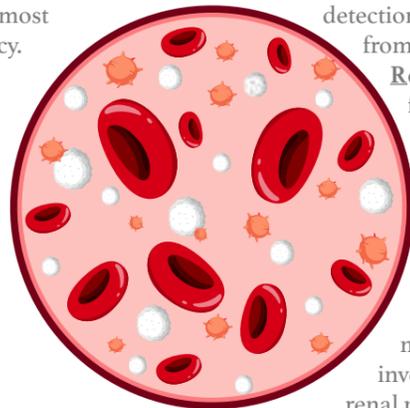
TTSH Research News is curated and edited by DR MELISSA TIEN, consultant in the Department of Ophthalmology, Tan Tock Seng Hospital.



## FEATURE

# A STEP TOWARDS MAKING MULTIPLE MYELOMA A CHRONIC DISEASE

Cancer is currently the leading cause of death in Singapore, accounting for 29.7% of deaths in 2015.<sup>1</sup> Multiple myeloma accounts for approximately 1% of all cancers, and is the second most common haematological malignancy. An estimated 159,985 new cases of myeloma were diagnosed in 2018 worldwide.<sup>2</sup> The incidence of myeloma in Singapore is estimated to be over 100 cases per year, and rising year on year. The precise cause of the increasing incidence is unknown, but is likely to be contributed by earlier detection, increasing affluence and life expectancy.



Plasma cell dyscrasias range from the clinically silent pre-malignant MGUS (monoclonal gammopathy of uncertain significance) and Smoldering Myeloma (SMM), to Multiple Myeloma (MM) and Plasma Cell Leukaemia. Each year, ~1% of patients with MGUS and ~10% of patients with SMM progress to Multiple Myeloma.<sup>3,5</sup> Apart from the classical type of Myeloma where an M (monoclonal)-band can be detected by serum electrophoresis, ~15% patients have light chain Myeloma where the plasma cells only secrete light chains (Bence-Jones protein) and are usually detected by serum free light chain (SFLC) analysis. 1-2% of patients have non-secretory Myeloma where the diagnosis can only be confirmed with a bone marrow biopsy.

**PRESENTATION AND REFERRALS**

In the UK between 2012 and 2013, while one-third of patients with an eventual diagnosis of myeloma were picked up after presenting to the emergency

department, approximately 53% of cases were referred to haematologists by general practitioners, demonstrating the importance and significance of early detection by primary care physicians.<sup>6,7</sup> Apart from exhibiting “CRAB” (elevated Calcium, Renal failure, Anaemia, Bone lesions) features, patients may also present with symptoms such as pathological fractures, weight loss, recurrent infections from immunoparesis, hyperviscosity, neuropathies secondary to plasmacytomas, and complications of an associated condition, Amyloidosis. Patients with suspected myeloma should have the following investigations performed: full blood count, renal panel, calcium, myeloma panel (including immunoglobulins, serum and urine electrophoresis and immunofixation), serum free light chains (SFLC) analysis and, a skeletal survey for assessment of lytic bone lesions. Symptoms suggestive of cord compression warrant urgent admission and imaging with MRI. Any patient with an abnormal M (monoclonal)-band should be referred for further evaluation and follow-up; those with CRAB features or myeloma-related complications should be referred urgently.

**DIAGNOSIS, STAGING AND RISK STRATIFICATION**

With better understanding of the biology, molecular and pathogenesis of myeloma over the last few decades, the International Myeloma Working Group (IMWG) revised the diagnostic criteria (table 1) in 2014 incorporating the use of specific disease-defining biomarkers and imaging tools (such as MRI, low dose CT and PET CT), in addition to the classical CRAB features.<sup>8</sup> The staging of myeloma has also moved away

**BOTH CRITERIA MUST BE MET:**

1. Clonal bone marrow plasma cells >10% or biopsy-proven bony or extramedullary plasmacytoma
2. Any one or more of the following myeloma defining events:
  - a) Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
    - i) Hypercalcemia: serum calcium > 0.25mmol/L (> 1mg/dL) higher than the upper limit of normal or > 2.75 mmol/L (> 11 mg/dL)
    - ii) Renal insufficiency: creatinine clearance < 40mL/min or serum creatinine > 177mmol/L (> 2mg/dL)
    - iii) Anaemia: Hb > 2 g/dL below the lower limit of normal, or Hb < 10 g/dL
    - iv) Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT
  - b) Clonal bone marrow plasma cell percentage > 60%
  - c) Involved: uninvolved serum free light chain (FLC) ratio ≥100 (involved FLC level must be ≥100 mg/L)
  - d) > 1 focal lesion on MRI studies (at least 5 mm in size)

Table 1. IMWG diagnostic criteria for multiple myeloma and related plasma cell disorders.<sup>8</sup>

R-ISS Stage	5-year OS	Median OS	5-year PFS	Median PFS
I	82%	Not reached	55%	66 months
II	62%	83 months	36%	42 months
III	40%	43 months	24%	29 months

Table 2. Revised ISS for multiple myeloma – Overall Survival (OS) and Progression-free Survival (PFS).<sup>7</sup>

from the well-recognised Salmon / Durie system established in 1975, to the latest R-ISS (Revised ISS) staging system published by the IMWG in 2015 (table 2). By incorporating prognostic information such as serum lactate dehydrogenase (LDH) and high-risk chromosomal abnormalities detected by interphase fluorescent in situ hybridization (iFISH), the R-ISS stratifies patients with myeloma more effectively with respect to their risk of survival.<sup>7</sup>

**TREATMENT**

The treatment of myeloma involves a holistic approach, from the management of emergency complications (e.g. dialysis, plasmapheresis, surgery, radiotherapy), symptomatic management (e.g. pain control) and supportive treatment (e.g. bisphosphonates, anti-virals, thromboprophylaxis), to definitive treatment regimes.

The treatment options for myeloma have recently undergone major transformation (figure 1).<sup>9</sup> From chemotherapy-based drugs in the 1960s and thalidomide in the 1990s, the breakthrough came around the turn of the millennium with the first-generation proteasome inhibitor (PI), *Bortezomib*, and the immunomodulatory

drug (IMiD), *Lenalidomide*. Since then, we have newer PIs (*Carfilzomib*, *Ixazomib*) and IMiDs (*Pomalidomide*) providing more convenient and/or effective treatment options, especially for patients in the relapsed/refractory setting.

In 2015, three novel myeloma agents were approved by the U.S. Food and Drug Administration (FDA): a) *Daratumumab*, an anti-CD38 monoclonal antibody; b) *Elotuzumab*, an anti-SLAMF7 monoclonal antibody; and, c) *Panobinostat*, a HDAC inhibitor.

In July 2019, *Selinexor*, the first in the SINE (selective inhibitors of nuclear export) class of drugs that blocks Exportin-1 (XPO1), was approved by the FDA, giving yet more treatment options for patients who fail earlier lines of therapy. More recently, some of these novel agents have moved from the treatment of relapsed/refractory patients to the front-line treatment setting, with the aim of obtaining deeper responses (e.g. MRD (minimal residual disease) negativity), leading to longer progression-free survival (PFS) and potentially, longer overall survival (OS).

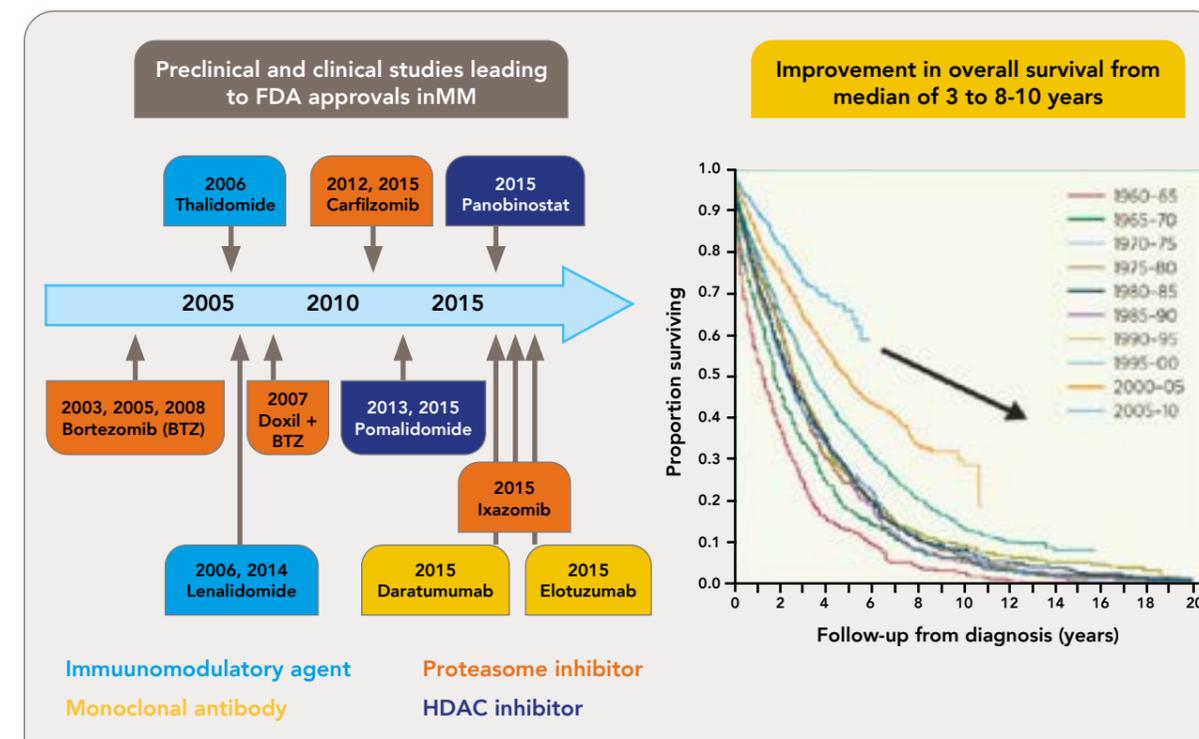


Figure 1. Treatment options for myeloma over time (Anderson KC, 2016).<sup>9</sup>

Novel myeloma therapies in clinical trials include the following, to name a few:

- a) Next generation PIs e.g. *Oprozomib*;
- b) BCL-2 inhibitor e.g. *Venetoclax*;
- c) Dendritic Cell / Tumour Fusion vaccines;
- d) Anti-CD138 antibody e.g. *Indatuximab Ravtansine*;
- e) New anti-CD38 monoclonal antibody e.g. *Isatuximab*; and,
- f) Immunotherapy e.g. Chimeric Antigen Receptor (CAR) T-Cell Therapy, Antibody-Drug Conjugates (ADCs) and Bispecific T-cell Engager (BiTE®) antibodies.

Of course, autologous stem cell transplant remains one of the most effective treatment modality and should be offered to all eligible patients. With so many available treatment options, the Singapore Myeloma Study Group published a set of Consensus Guidelines in 2017 to guide the selection of myeloma therapies.<sup>10</sup>

Apart from the very young and fit who may be eligible for an allogenic stem cell transplantation, there is no cure for multiple myeloma as it is generally a disease of the elderly. Myeloma cells are immortal, continually undergoing clonal competition, evolution and replication. With each relapse and attempt to control the disease using a new line of therapy, the progression-free survival (PFS) becomes shorter and shorter until the myeloma clones become refractory to available agents, or the patient simply becomes too frail to tolerate further treatment (figure 2).<sup>11</sup>

Fortunately, the plethora of treatment options have been able to improve the prognosis of most of our

APART FROM THE VERY YOUNG AND FIT WHO MAY BE ELIGIBLE FOR AN ALLOGENIC STEM CELL TRANSPLANTATION, THERE IS NO CURE FOR MULTIPLE MYELOMA AS IT IS GENERALLY A DISEASE OF THE ELDERLY.

myeloma patients, increasing the overall survival (OS) by an impressive 300% since the 1990s – The median OS increased from 2.5 years in 1997 to >10 years in 2012 (figure 3).<sup>12</sup> This has effectively transformed myeloma from an atrocious disease with little treatment options and an truncated lifespan to what is considered by some as a form of ‘chronic disease’. The holistic management of myeloma is incomplete without the involvement of our palliative care specialists, who are integral, indispensable, and should be introduced as early as possible after diagnosis.

**ACCESS TO MYELOMA THERAPIES**

The transformation of myeloma into a form of chronic disease depends, in part, on the access to novel and often costly medicines. Access to new cancer drugs is often a highly emotional issue, and is one of the most complex and vexing problems that stands in the way of better health. Although affordability is the cornerstone of access, many other factors also determine whether patients get the medicines they need. Gaps in the health system and infrastructures, procurement

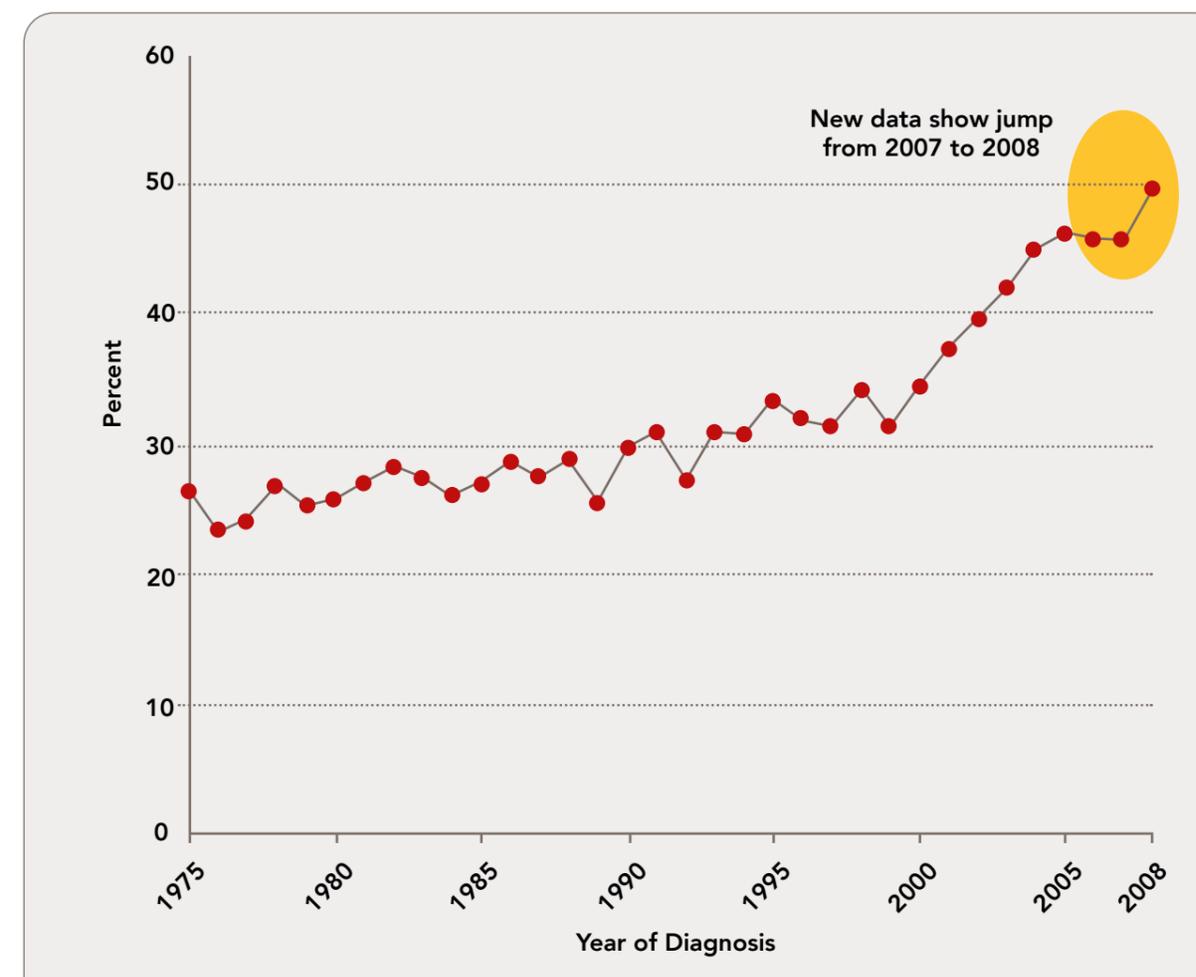


Figure 3. Five-Year Relative Survival (percent) of multiple myeloma patients by Year of diagnosis (National Institutes of Health USA, 2016).<sup>12</sup>

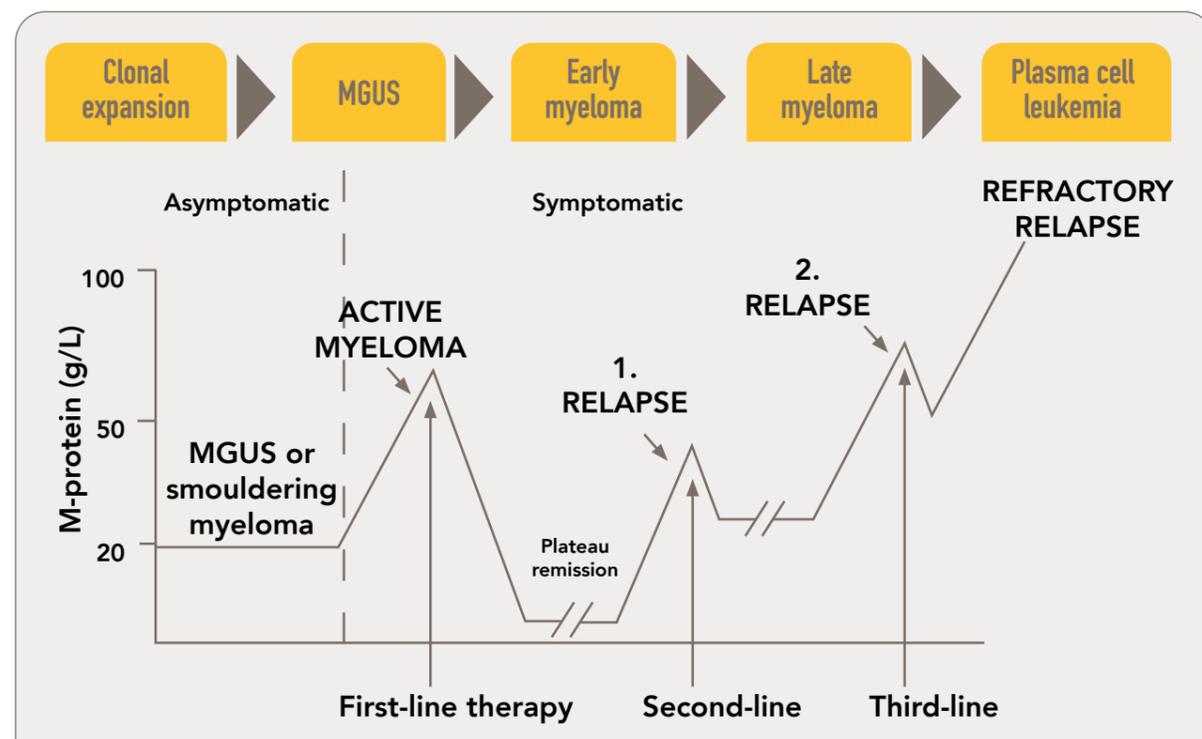


Figure 2. Natural history of multiple myeloma (Hajek R, 2013).<sup>11</sup>

POSSIBLE SOLUTIONS TO ADDRESS THIS ISSUE MAY INCLUDE ENGAGEMENT, COLLABORATION AND PARTNERSHIPS BETWEEN STAKEHOLDERS (SUCH AS GOVERNMENT, PHARMACEUTICAL COMPANIES, CLINICIANS, PATIENT-ADVOCACY GROUPS, AND NON-GOVERNMENTAL ORGANISATIONS) TO IMPLEMENT STRATEGIES FOR IMPROVED AND SUSTAINED ACCESS TO MEDICINES.

practices, availability of insurances, subsidies, pricing, tax and tariff policies, as well as mark-ups along the supply chain all play an important role.<sup>13</sup> Possible solutions to address this issue may include engagement, collaboration and partnerships between stakeholders (such as government, pharmaceutical companies, clinicians, patient-advocacy groups, and non-governmental organisations) to implement strategies for improved and sustained access to medicines. Examples include the following:

- A ‘differential’ or ‘tiered’ pricing system for select (and often patented) medicines tagged to the purchasing power of consumers across different socio-economic groups;
- ‘Patient Access Programs’ that provide free, or heavily discounted, medicines to targeted patient populations (e.g. subsidised patients);
- ‘Value-Based Pricing’ whereby pricing is based on the benefits perceived by the consumer, instead of the cost of product development.

However, it is important to note that the above mentioned tiered pricing system and access programs neither guarantee affordability nor imply cost-effectiveness. The Agency for Care Effectiveness (ACE), the national health technology assessment (HTA) agency in Singapore, issues evidence-based guidances on clinically-effective and cost-effective drug technologies to better inform clinical decision-making, thus enabling optimization of health benefits and sustainability of finite resources.

The birth of the Asian Myeloma Network (AMN; established by the International Myeloma Foundation in 2011) was very timely in improving the access to drugs for myeloma patients. Apart from publishing

resource-stratified clinical guidances for the management of Asian myeloma patients and offering physician education and patient support, it also enables Asian patients to gain access to novel (and often, unaffordable) myeloma therapies through clinical trials.<sup>14</sup> Many of our Singaporean patients have participated in, and benefited from, multiple AMN-initiated trials since 2011.

**CONCLUSION**

Our increased understanding of the biology of myeloma has led to the development of multiple novel therapies. While the prognosis for the majority of myeloma patients has significantly improved, there are still many unmet needs, especially from high-risk patients with poor cytogenetic and FISH abnormalities. To be one step closer towards making multiple myeloma a chronic disease, we need more cross-institutional collaborations, establishment of a Singapore-wide myeloma registry, improved access to novel therapies, conduct of more phase III clinical trials in Singapore and, active participation in clinical research.

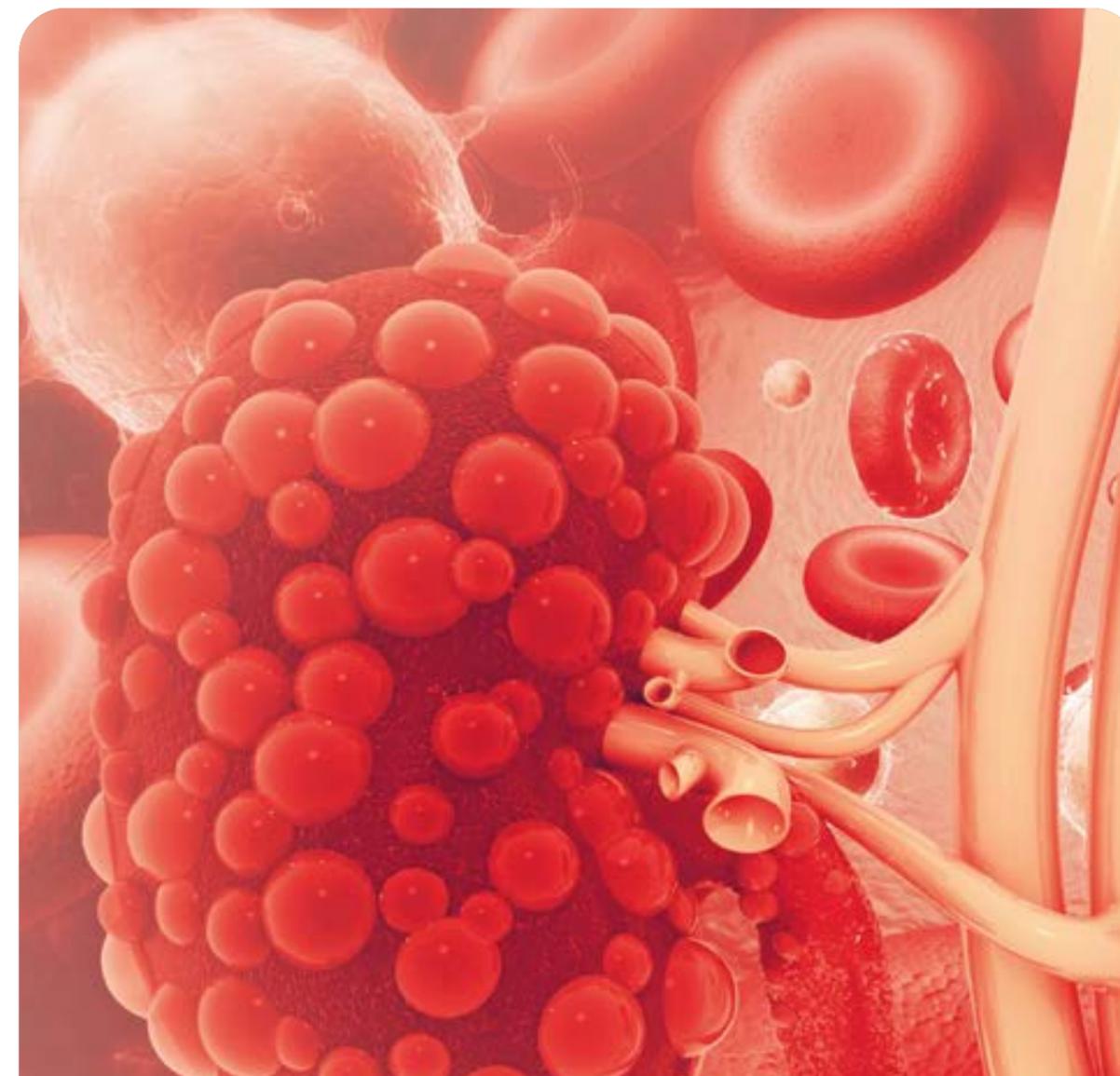
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TO BE ONE STEP CLOSER TOWARDS MAKING MULTIPLE MYELOMA A CHRONIC DISEASE, WE NEED MORE CROSS-INSTITUTIONAL COLLABORATIONS, ESTABLISHMENT OF A SINGAPORE-WIDE MYELOMA REGISTRY, IMPROVED ACCESS TO NOVEL THERAPIES, CONDUCT OF MORE PHASE III CLINICAL TRIALS IN SINGAPORE AND, ACTIVE PARTICIPATION IN CLINICAL RESEARCH.



FEATURE

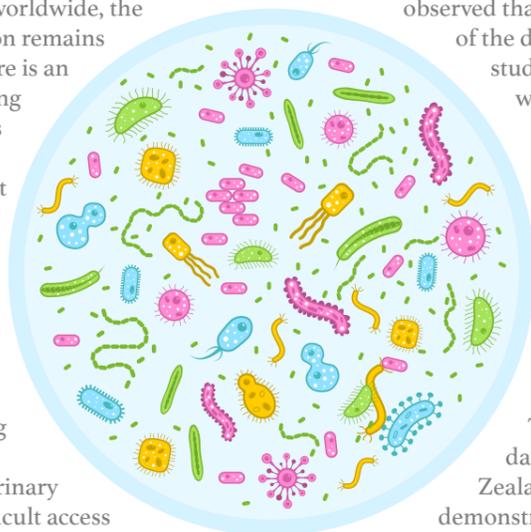
**IMMUNOGLOBULIN A NEPHROPATHY – A COMMON ENIGMA**

Immunoglobulin A nephropathy (Ig AN) was first described by Berger and Hinglais in 1968. It was defined as a kidney disease with the dominance or codominance of diffuse mesangial deposition of Ig A in a biopsy. Five decades have passed and though it is the most common glomerular disease worldwide, the understanding of this condition remains elementary, and its exact nature is an enigma that is only slowly being unravelled. This slow progress in the understanding of Ig AN can be ascribed to the indolent nature of the disease where majority of the patients are asymptomatic.

As a kidney biopsy is paramount to the diagnosis of Ig AN, the true prevalence is difficult to ascertain. Varying health screening practices, differing referral criteria for urinary abnormalities, sometimes difficult access to a kidney biopsy, and inconsistent clinical thresholds for kidney biopsy among nephrologists all have an impact on the detection rate of the disease. Singapore does not have nationwide screening for urinary abnormalities. In a local study examining the prevalence of glomerular diseases over three

decades spanning 1976 to 2008, Ig AN accounted for approximately 40% of all glomerular diagnoses on biopsy.

A decade after Ig AN was first described, it was observed that there was a familial clustering of the disease. As the tools of genetic studies became more sophisticated with the use of linkage mapping and population-based genome-wide association studies (GWAS), differences in the disease observed at various geographical locations have become more apparent. There appears to be a higher burden of disease in East and Pacific Asian countries such as Japan, China and Singapore. This is further supported by data registries in Australia, New Zealand and North America, which demonstrated a higher incidence of Ig AN and progression to end stage renal disease in immigrants from Asian countries. Some researchers suggest that Ig AN may be a complex disorder with a common histopathological phenotype, but disparate in terms of pathogenesis, genetics, triggers and clinical course.



The pathogenesis of Ig AN is thought to be a multi-hit process, with an interplay of genetic and environmental factors and/or triggers (figure 1). There are four main processes which culminate in the tissue injury seen in the kidney. First, there is aberrant glycosylation of Ig A1, followed by the synthesis of antibodies directed against abnormal Ig A1. These then form immune complexes that accumulate and cause inflammation in the kidney. Ig A is produced mainly in mucosal-associated lymphoid tissue (MALT) that is present in the nose, pharynx, tonsils and the gut. Acute infections such as tonsillitis or acute diarrhoea have been shown to increase the levels of Ig A1 immune complexes in patients with Ig AN. These synpharyngitic infections are associated with episodes of gross haematuria. It has also been reported that there is a higher frequency of Ig AN in patients with inflammatory bowel disease and celiac disease. There has been increasing interest in examining

associated with Ig AN, and are classified as secondary Ig AN. There is limited data on the clinical significance, prognosis and treatment response due to the heterogeneity of the underlying diseases. Ig A mediated small vessel vasculitis is termed Henoch Schonlein purpura (HSP). It is a systemic disease that affects mainly the joints, kidney, gut and skin. This occurs more frequently in the paediatric population, and they tend to have a better prognosis compared to adults.

The clinical presentation of Ig AN is variable. Patients can present at any age, but the peak incidence is in the second and third decade of life. There are three main clinical presentations:

**1. Asymptomatic microscopic haematuria with or without proteinuria**  
Most patients with Ig AN will present with this clinical syndrome. The microscopic

glomerular disease or basement membrane abnormalities (such as Alport syndrome or thin basement membrane disease).

**2. Nephrotic syndrome**  
Fewer than 10% of patients with Ig AN develop nephrotic syndrome. In some reports, the clinical course and treatment is similar to that of minimal change disease.

**3. Rapidly progressive glomerulonephritis**  
This is an uncommon clinical presentation of Ig AN. An early renal biopsy is important to confirm the diagnosis and start appropriate treatment for maximum salvage of kidney tissue.

Although Ig AN is a common disease, current evidence-based treatment options are limited. Clinical trials that examine hard outcomes, such as renal survival, would be very expensive to conduct due to the slowly progressive nature of the disease. Furthermore, many patients remain asymptomatic until they have advanced renal impairment, by which time there is little reversibility. Recently, risk prediction scores have been developed combining clinical and histopathological data to predict the renal prognosis, and these are currently being validated in different ethnic populations. Clinical parameters that can affect renal prognosis include time-average proteinuria, blood pressure control and the degree of renal impairment at diagnosis.

Renin-angiotensin-aldosterone system (RAAS) blockade with an angiotensin-converting-enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) is the cornerstone of treatment of Ig AN. Supportive treatment with an ACE inhibitor or ARB should be optimised to reduce proteinuria to the lowest level possible. In the STOP IG AN trial, 34% of the patients were ineligible for randomisation for the next phase

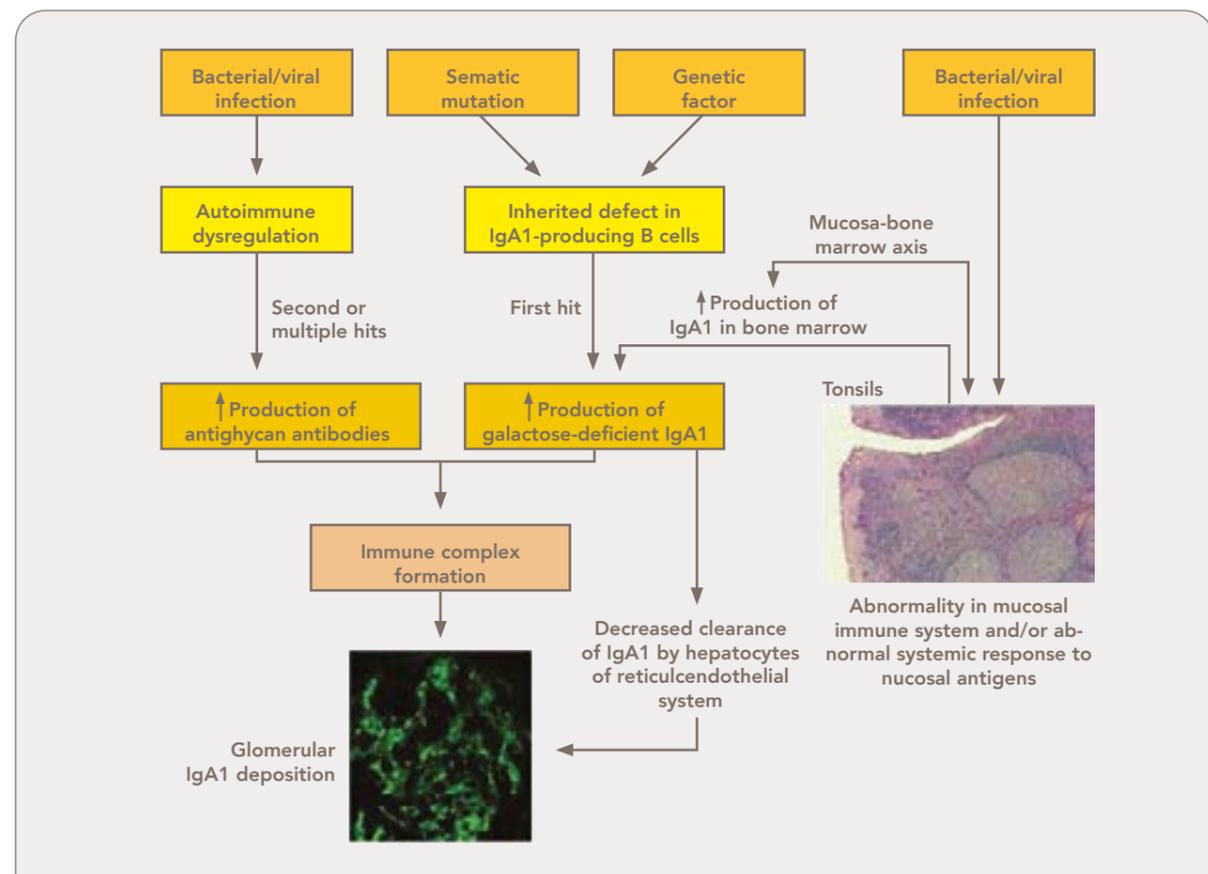


Figure 1. The proposed multi-hit process underlying the pathogenesis of Ig AN (Lai KN, 2012).4

IMMUNOGLOBULIN A NEPHROPATHY (Ig AN) WAS FIRST DESCRIBED BY BERGER AND HINGLAIS IN 1968. IT WAS DEFINED AS A KIDNEY DISEASE WITH THE DOMINANCE OR CODOMINANCE OF DIFFUSE MESANGIAL DEPOSITION OF Ig A IN A BIOPSY.

the association between the gut microbiome and Ig AN. It remains to be proven definitively if gut health or dietary influences will exert any significant effect on the disease course of Ig AN.

Ig AN can be primary or secondary. Chronic liver disease, autoimmune disease and infection have been

haematuria may be persistent or intermittent, together with low-grade proteinuria and normal renal function, reflecting the indolent nature of the disease. These patients may not undergo renal biopsy, and therefore remain undiagnosed. The differential diagnoses include urological causes, other types of

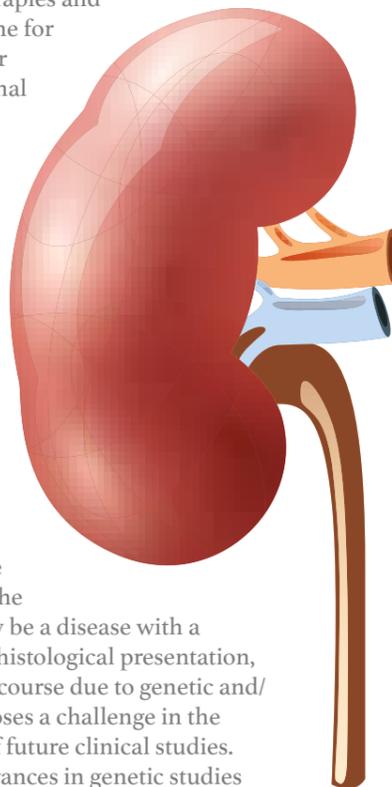
of the trial after the initial run-in period to optimise supportive treatment with ACE inhibitors or ARBs. Older meta-analyses have also shown that RAAS blockade has a reno-protective effect in addition to the proteinuria reduction. In patients with proteinuria lower than 0.3 g/day, target blood pressure should be below 130/80 mmHg, and for patients with proteinuria more than 1 g/day, target blood pressure should be below 125/75 mmHg.

The current choice of immunosuppression in patients with active Ig AN is corticosteroids. The 2012 KDIGO guidelines recommend that patients with proteinuria greater than 1 g/day, despite 3 to 6 months of optimised supportive care (including ACE inhibitors or ARBs, and blood pressure control), and a GFR greater than 50ml/min/1.73m<sup>2</sup>, receive a 6-month course of corticosteroid therapy. Use of cyclophosphamide or azathioprine (except in crescentic Ig AN) is not recommended. Mycophenolate mofetil in combination with corticosteroids has demonstrated promising results mainly in Chinese patients. However, its efficacy in the Caucasian population has not been proven.

Tonsillectomy as a treatment modality for Ig AN is not widely accepted, except in Japan where it is practised in combination with the use of corticosteroids. Modified release oral budesonide targeted at the enteric lymphoid tissue has shown promising results, and a larger scale study is being planned to evaluate this.

There are many novel therapies and clinical trials in the pipeline for the treatment of Ig AN. For patients with advanced renal impairment, there is a clearly defined “point of no return” where the risks of immunosuppressive therapy will outweigh the benefits of renal salvage. However, for patients with slowly progressively disease, the optimal time to initiate treatment as well as the duration of treatment remain unknown.

There remains much to be discovered about Ig AN. The hypothesis that Ig AN may be a disease with a homogenous clinical and histological presentation, but heterogenous clinical course due to genetic and/or environment factors, poses a challenge in the execution and planning of future clinical studies. Nevertheless, with the advances in genetic studies and pharmacogenomics, the practice of personalised medicine looks set to become a reality for many diseases, including Ig AN.



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**THERE ARE MANY NOVEL THERAPIES AND CLINICAL TRIALS IN THE PIPELINE FOR THE TREATMENT OF IG AN. FOR PATIENTS WITH ADVANCED RENAL IMPAIRMENT, THERE IS A CLEARLY DEFINED “POINT OF NO RETURN” WHERE THE RISKS OF IMMUNOSUPPRESSIVE THERAPY WILL OUTWEIGH THE BENEFITS OF RENAL SALVAGE.**



#### FEATURE

## PHARMACOLOGICAL THERAPY IN STABLE CHRONIC OBSTRUCTIVE PULMONARY DISEASE – APPLICATION OF GOLD 2019

Mr Tan, a 68-year-old man, presents to your clinic for 6 months' duration of shortness of breath on exertion. He used to be able to brisk walk 2-3 kilometres in 30 minutes daily, but now finds that he can only complete half his normal routine. He also has intermittent productive cough with whitish sputum. There is no chest pain on exertion, orthopnea, paroxysmal nocturnal dyspnea or lower limb swelling. His significant past medical history includes hypertension and hyperlipidemia, and he is a chronic smoker of 40 pack-years. Physical examination of the respiratory and cardiovascular system is otherwise unremarkable.

You suspect that Mr Tan has chronic obstructive pulmonary disease (COPD). What would you do next?

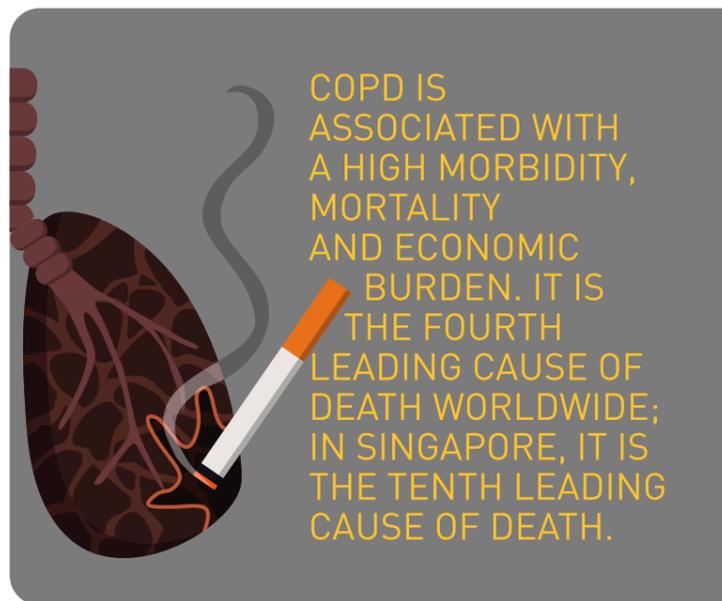
- A) Chest X ray
- B) Electrocardiogram
- C) Full blood count
- D) Spirometry

To evaluate a patient who presents with shortness of breath on exertion, all of the above investigations are relevant. In particular, spirometry is required to establish a diagnosis of COPD. Mr Tan's chest X-ray shows lung hyperinflation with flattened hemidiaphragms; otherwise no consolidation or masses. His electrocardiogram shows normal sinus rhythm with no acute ischemic changes, and his full blood count shows haemoglobin level of 13 g/dL (no anemia or polycythemia). Spirometry reveals an obstructive ventilatory defect - Forced expiratory volume in 1 second/ Forced vital capacity (FEV<sub>1</sub>/FVC) ratio of 57 %, FEV<sub>1</sub> of 1.81 L (58 % of predicted), FVC of 3.17 L (85 % of predicted), and the maximum expiratory flow volume curve is concave. There is no significant bronchodilator response.

Mr Tan is diagnosed with COPD. According to the Global Initiative for Chronic Lung Disease (GOLD) 2019 guidelines, COPD is defined as "a common, preventable and treatable disease that is characterised by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases".<sup>1</sup> COPD is associated with a high morbidity, mortality and economic burden. It is the fourth leading cause of death worldwide;<sup>2</sup> in Singapore, it is the tenth leading cause of death.<sup>3</sup>

The main goals of treatment are:

- (1) To reduce symptoms of COPD, thereby improving exercise tolerance and health status; and,
- (2) To reduce the frequency and severity of COPD exacerbations.<sup>1</sup>



These goals can be achieved via non-pharmacological and pharmacological therapies. Non-pharmacological therapies include the following:

- Smoking cessation
- Vaccination (influenza and pneumococcal)
- Pulmonary rehabilitation
- Nutritional support

As for pharmacological therapies, the mainstay of COPD treatment are inhaled bronchodilators.

Besides advising Mr Tan to quit smoking and get vaccinated, which of the following pharmacological treatment would you start?

- A) SABA/SAMA
- B) LAMA
- C) LABA
- D) LABA/LAMA
- E) LABA/ICS

SABA, short-acting  $\beta_2$ -agonist; SAMA, short-acting muscarinic antagonist; LAMA, long-acting muscarinic antagonist; LABA, long-acting  $\beta_2$ -agonist; ICS, inhaled corticosteroids.

Before initiating pharmacological treatment, the symptoms and exacerbation risk using the revised ABCD assessment tool in GOLD 2019 (figure 1) have to be assessed and scored. Mr Tan is found to have a modified Medical Research Council (mMRC) Dyspnea Scale score of 1, and a COPD Assessment Test (CAT) score of 8. He has never had any COPD exacerbations. This would place him in Group A, and the recommended initial pharmacological treatment is a bronchodilator (either a short or long-acting bronchodilator).<sup>1</sup>

Since 2017, the spirometric grade (range: 1 – 4; indicates severity of airflow limitation) has been separated from group A to D (indicating symptom burden and risk of exacerbation). This refined ABCD assessment tool acknowledges that although FEV<sub>1</sub> is an important parameter to predict prognosis at the population level, FEV<sub>1</sub> loses precision at the individual patient level. Hence, patient symptoms and exacerbation risks are more vital in guiding COPD therapy.<sup>1</sup>

Inhaled bronchodilators are central to the pharmacological treatment of COPD. They act by altering airway smooth muscle tone, thereby reducing dynamic hyperinflation at rest and during exercise, making it easier for patients to breathe. There are 2 main classes of inhaled bronchodilators -  $\beta_2$ -agonists and muscarinic antagonists - which can be short-acting (4-8 hours) or long-acting (12-24 hours).<sup>1</sup>  $\beta_2$ -agonists stimulate  $\beta_2$ -adrenergic receptors, thus increasing cyclic adenosine monophosphate and causing direct relaxation of airway smooth muscle. On the other hand, muscarinic antagonists inhibit M<sub>3</sub> muscarinic receptors, thus blocking the bronchoconstrictor effects of acetylcholine and resulting in indirect smooth muscle relaxation.

SABAs (short-acting  $\beta_2$ -agonists) and SAMAs (short-acting muscarinic antagonists), when used regularly

and as-needed, improves FEV<sub>1</sub> and COPD symptoms.<sup>5</sup> The combination of SABA with SAMA is superior to either medication alone.<sup>6</sup> For patients with relatively few symptoms and low risk of exacerbations, these short-acting bronchodilators are an option. However, most COPD patients have significant breathlessness and require a more intensive treatment with long-acting bronchodilators. LABAs (long-acting  $\beta_2$ -agonists) and LAMAs (long-acting muscarinic antagonists) significantly improve lung function, dyspnea and health status, and reduce exacerbation rates.<sup>7,8</sup>

In Mr Tan's case of COPD scored as GOLD grade 2, group A, it is reasonable to start with either a short-acting or long-acting bronchodilator. Is there evidence that one is better than the other in early COPD? This question remained unanswered for a long time as most studies were done in patients with severe COPD. In 2017 however, a clinical trial on patients with COPD of GOLD stage 1 (mild) or 2 (moderate) who had minimal or no respiratory symptoms found that tiotropium, a long-acting bronchodilator, resulted in a higher FEV<sub>1</sub> than placebo at 24 months, and ameliorated the annual decline in post-bronchodilator FEV<sub>1</sub>.<sup>9</sup>

Why is this important? Contrary to conventional thinking, patients with early stage/mild COPD can remain asymptomatic even though they experience the greatest decline in FEV<sub>1</sub>. This decline in FEV<sub>1</sub> is approximately 50 ml/year in GOLD stage 2, compared to an estimated 30 ml/year in GOLD stage 4, as observed in the TORCH and UPLIFT studies.<sup>7,8</sup> Given that a large number of patients constitute early stage/mild COPD, it provides a window of opportunity for early intervention to prevent progressive functional deterioration, and to maintain lung function at a higher level. However, further studies are needed to conclude whether early intervention with a long-acting bronchodilator alters the long-term course of COPD.

	GROUP C	GROUP D
<b>≥2 moderate exacerbations or ≥1 leading to hospitalisation</b>	LAMA	LAMA or LAMA + LABA* or ICS + LABA**
		* Consider it highly symptomatic (e.g. CAT >20) ** Consider if eos ≥300
	GROUP A	GROUP B
<b>0 or 1 moderate exacerbations (not leading to hospital admission)</b>	A bronchodilator	A long-acting bronchodilator (LABA or LAMA)
	mMRC 0-1 CAT <10	mMRC ≥ CAT ≥10

LAMA= long-acting muscarinic receptor antagonists; LABA= long-acting beta agonist; ICS= inhaled corticosteroids; CAT= COPD assessment test; COPD= chronic obstructive pulmonary disease; eos= blood eosinophil count in cells per microfire; mMRC= modified Medical Research Council dyspnoea questionnaire.

Figure 1. Algorithm for initial pharmacological treatment for COPD based on GOLD guidelines (Guidelines, 2019).<sup>4</sup>

You decide to start Mr Tan on a long-acting bronchodilator. Which LAMA inhaler would you choose?

\*LABA monotherapy is currently unavailable in Singapore.

- A) Tiotropium DPI or SMI
- B) Umeclidinium DPI
- C) Glycopyrronium bromide DPI
- D) Acclidinium bromide DPI or MDI

DPI, dry powder inhaler; SMI, soft mist inhaler; MDI, metered dose inhaler.

All the above LAMA formulations have been used for COPD, of which Tiotropium SMI (Spiriva(R) Respimat) and Umeclidinium DPI (Incruse® Ellipta®) are available in the Tan Tock Seng Hospital (TTSH) drug formulary.

There are few head-to-head comparison studies between the different LAMAs.<sup>10,11</sup> Indirect comparisons of LAMAs have been made by comparing the relative effects of treatments against a common comparator, or by combining a variety of comparisons- also known as mixed treatment comparison or network meta-analysis. These analyses have not shown any significant differences in preventing COPD exacerbations among LAMAs.<sup>12</sup> There are also similar improvements in lung function, health-related quality of life and dyspnea.<sup>13</sup>

According to GOLD 2019, “each pharmacologic treatment regimen should be individualised and guided by the severity of symptoms, risk of exacerbations, side-effects, comorbidities, drug availability and cost, and the

patient’s response, preference and ability to use various drug delivery devices”.<sup>1</sup>

DPI is easy to load, but requires sufficient inspiratory effort by the patient.<sup>14</sup> SMI has a more complex loading, which may be challenging for elderly patients with arthritis; however, it is able to generate slow-moving mist that allows patients to take slow deep breaths, as well as fine aerosol droplets that facilitate increased lung deposition. It can also be used with a spacer.<sup>15</sup> MDI is widely prescribed and relatively inexpensive. However, MDI drug delivery is highly dependent on the patient’s inhalation technique; it requires correct actuation and inhalation coordination, which can be difficult for elderly patients, thus necessitating the use of a spacer.<sup>16</sup>

Adverse effects of LAMAs are uncommon as the inhaled drugs are poorly absorbed into the systemic circulation. The main side effect is mouth dryness. Occasional urinary symptoms have been reported.<sup>17</sup>

**According to GOLD 2019, “each pharmacologic treatment regimen should be individualised and guided by the severity of symptoms, risk of exacerbations, side-effects, comorbidities, drug availability and cost, and the patient’s response, preference and ability to use various drug delivery devices”.**

Mr Tan is started on Umeclidinium DPI (Incruse® Ellipta®). He also decides to quit smoking. You review him in clinic 3 months later. His symptoms of dyspnea is better, and he is able to complete his daily brisk walking routine again.

To summarise the model for initiation of pharmacotherapy based on the ABCD assessment scheme (figure 1) in GOLD 2019:

- Group A patients: A bronchodilator (either short- or long-acting) can be started.<sup>1</sup>
- Group B patients: The initial therapy should consist of a long-acting bronchodilator (LABA or LAMA) as it is superior to short-acting bronchodilator when taken as needed.<sup>18,19</sup>

- Group C patients: LAMA is recommended as the initial therapy as it is superior to LABA for exacerbation prevention.<sup>10-12</sup>
- Group D patients: The initial therapy includes LAMA, or LABA/LAMA combination in highly symptomatic patients (e.g. CAT > 20), or LABA/ICS combination if blood eosinophil counts ≥ 300 cells/μL.<sup>20-24</sup>

You continue to follow up with Mr Tan’s COPD. One year later, Mr Tan complains of progressive breathlessness on exertion despite being compliant to his inhalers with good inhaler technique. Your assessment does not reveal other comorbidities that could be contributing to his worsening symptoms. Specifically, you screen for lung cancer, cardiovascular disease, anxiety/depression, gastroesophageal reflux disease, osteoporosis and sleep-disordered breathing. The GOLD 2019 guidelines emphasize the importance of identifying and treating comorbidities that can coexist with COPD and significantly impact prognosis.<sup>1</sup>

You think that his symptoms are due to COPD progression. What would you do next with regards to his inhalers?

- A) Switch to LABA/LAMA
- B) Switch to LABA/ICS
- C) Switch to LABA/LAMA/ICS

SABA, short-acting β<sub>2</sub>-agonist; SAMA, short-acting muscarinic antagonist; LAMA, long-acting muscarinic antagonist; LABA, long-acting β<sub>2</sub>-agonist; ICS, inhaled corticosteroids.

According to the GOLD guidelines, follow-up pharmacological management should be guided by the principles of first review and assess, then adjust if needed (figure 2):

(1) Review symptoms (dyspnea) and exacerbation risk;

(2) Assess inhaler technique and adherence, and the role of non-pharmacological approaches; and,  
 (3) Adjust pharmacological treatment, including escalation or de-escalation.

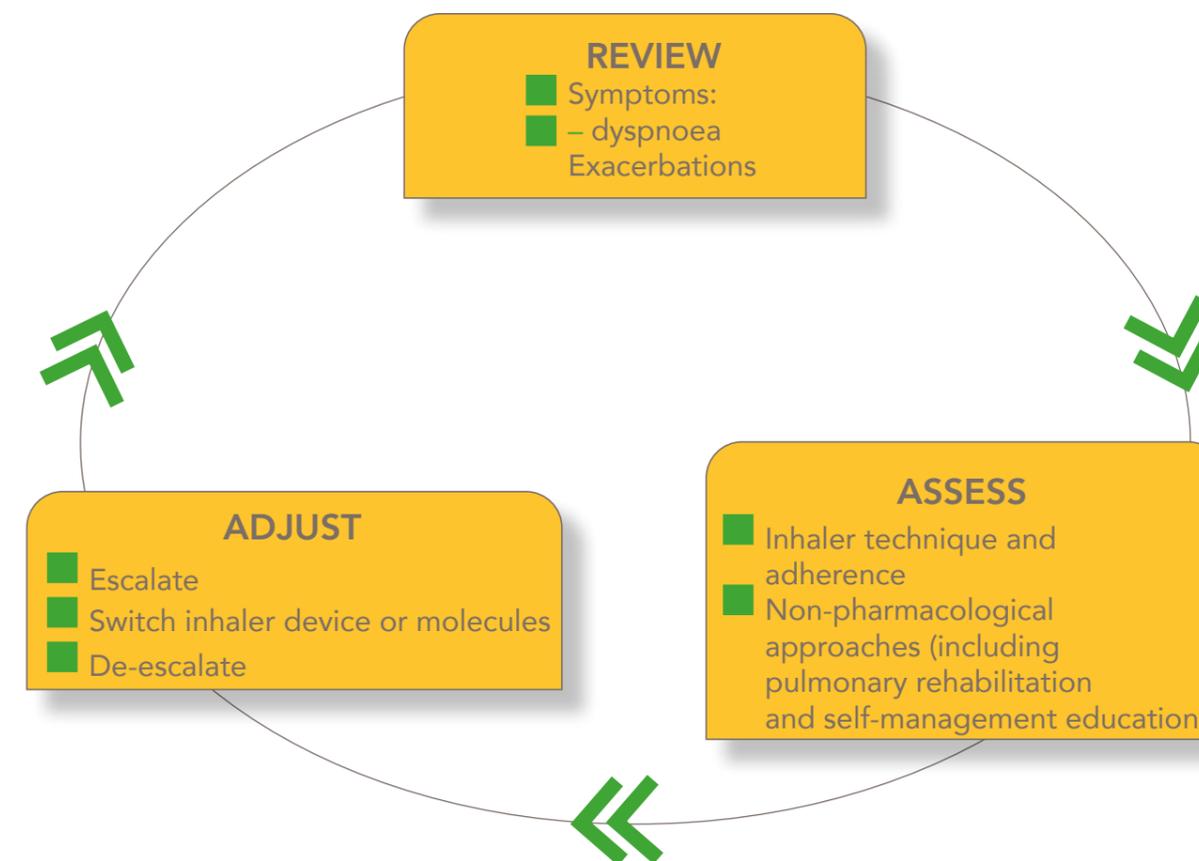


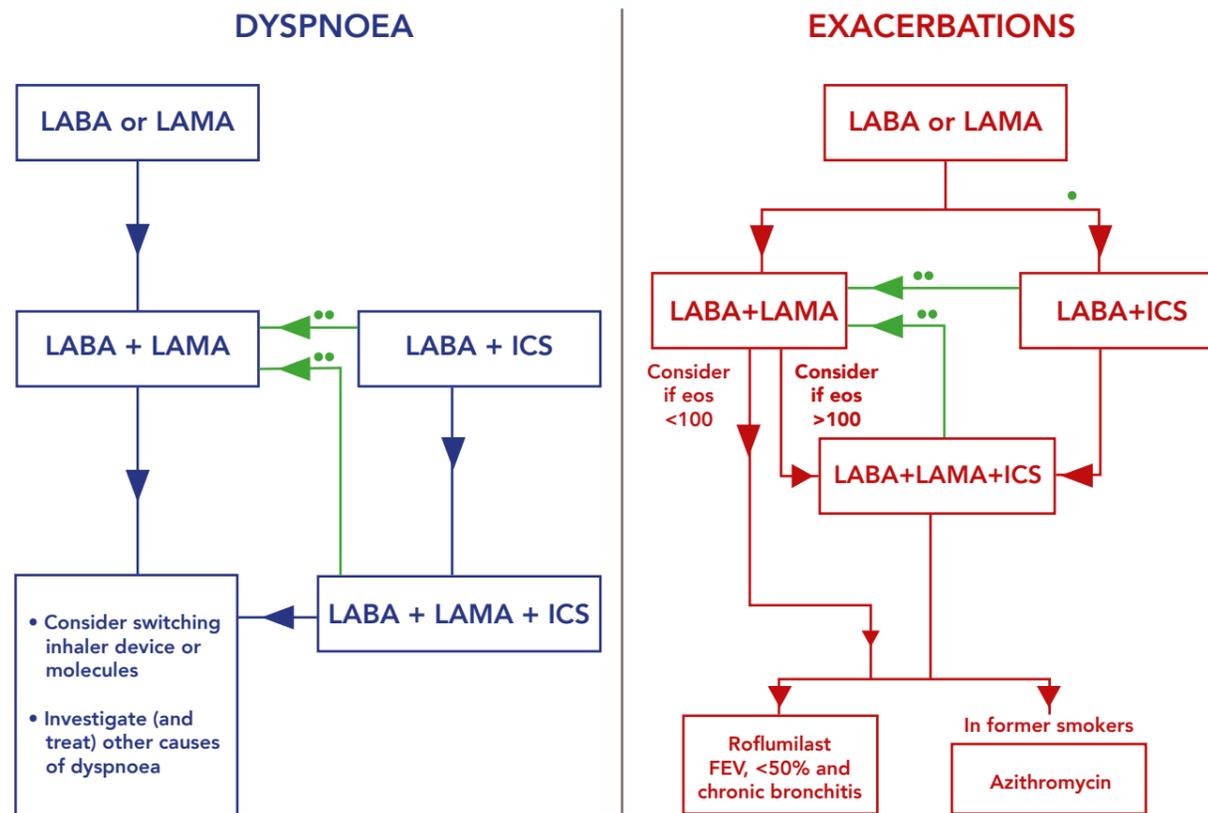
Figure 2. COPD management cycle based on GOLD guidelines (Guidelines, 2019).<sup>4</sup>

In the latest 2019 revision, these recommendations no longer depend on the GOLD group ABCD allocation at treatment initiation. Instead, a separate algorithm is provided for follow-up treatment where the management is divided into treating patients with persistent dyspnea or exacerbations.<sup>1</sup>

As Mr Tan is experiencing persistent dyspnea on long-acting bronchodilator monotherapy, the use of dual bronchodilators is recommended (figure 3).<sup>1,20</sup> If the addition of a second long-acting bronchodilator does not improve symptoms, treatment could be stepped down again to monotherapy, or switched to another inhaler device or molecule.<sup>1</sup> It is also important to investigate and treat other causes of dyspnea.

If the addition of a second long-acting bronchodilator does not improve symptoms, treatment could be stepped down again to monotherapy, or switched to another inhaler device or molecule.<sup>1</sup> It is also important to investigate and treat other causes of dyspnea.

1. IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.
2. IF NOT:
  - ✓ Consider the predominant treatable trait to target (dyspnoea or exacerbations)
    - Use exacerbation pathway if both exacerbations and dyspnoea need to be targeted
  - ✓ Place patient in box corresponding to current treatment and follow indications
  - ✓ Assess response, adjust and review
  - ✓ These recommendations do not depend on the ABCD assessment at diagnosis



eos = blood eosinophil count (cells/ $\mu$ L)  
 • Consider if eos  $\geq 300$  or eos  $\geq 100$  AND  $\geq 2$  moderate exacerbations/1 hospitalisation  
 •• Consider de-escalation of ICS or switch if pneumonia, inappropriate original indication or lack of response to ICS.

Figure 3. Follow-up pharmacological treatment algorithm for COPD (Guidelines, 2019).<sup>4</sup>

You decide to switch Mr Tan's inhaler to a LABA/LAMA combination. Which LABA/LAMA inhaler would you choose?

- A) Vilanterol/Umeclidinium DPI
- B) Olodaterol/Tiotropium SMI
- C) Indacaterol/Glycopyrronium DPI
- D) Formoterol/Acclidinium DPI
- E) Formoterol/Glycopyrronium MDI

DPI, dry powder inhaler; SMI, soft mist inhaler; MDI, metered dose inhaler.

All the above LABA/LAMA formulations have been approved for use in COPD. Vilanterol/Umeclidinium DPI (Anoro™ Ellipta™), Olodaterol/Tiotropium SMI (Stiolto® Respimat®) and Indacaterol/Glycopyrronium DPI (Ultibro® Breezhaler®) are available in TTSH's drug formulary.

Again, there are limited head-to-head comparison studies between different LABA/LAMA combinations.<sup>25,26</sup> These studies, together with indirect evidence from

network meta-analyses, suggest that a potential efficacy gradient exists within the LABA/LAMA class, at least with regards to lung function - Vilanterol/Umeclidinium showed greater improvement in trough FEV<sub>1</sub> compared to Olodaterol/Tiotropium and Indacaterol/Glycopyrronium, although no clinically meaningful differences in symptomatic endpoint were seen.<sup>25-28</sup> However, further trials are needed to confirm these findings.

Mr Tan reports improvement in his symptoms with Vilanterol/Umeclidinium DPI (Anoro™ Ellipta™). You also refer him for pulmonary rehabilitation.

Two years later, Mr Tan is admitted to the hospital for COPD exacerbation. He comes to see you 2 months after discharge. In the clinic, Mr Tan complains of increasing cough, sputum production and sputum purulence in the last 3 days without fever. There is expiratory wheeze on auscultation. You think he has another exacerbation of COPD. You start him on nebulisation and prednisolone in the clinic. His wheezing improves. Besides giving him a course of prednisolone and antibiotics, what would you do?

According to GOLD 2019, patients who develop further COPD exacerbations on combination LABA/LAMA therapy are recommended for escalation to LABA/LAMA/ICS if blood eosinophils  $\geq 100$  cells/ $\mu$ L (figure 3). The higher the eosinophil count, the greater the beneficial response with ICS.<sup>23,24</sup> If blood eosinophils  $< 100$  cells/ $\mu$ L, or if patients treated with LABA/LAMA/ICS still have exacerbations, the following options may be considered (figure 3):

- (i) Adding roflumilast if FEV<sub>1</sub>  $< 50\%$  of predicted and chronic bronchitis;<sup>29</sup> or,
- (ii) Adding macrolide (e.g. azithromycin), especially for those who are not current smokers.<sup>30</sup>

De-escalation of ICS is recommended if there are adverse effects (such as pneumonia), inappropriate indication or, a reported lack of efficacy.<sup>31-33</sup>

Mr Tan's blood eosinophil counts are 380 cells/ $\mu$ L. You add ICS to his LABA/LAMA. You review him in clinic 3 and 6 months later - his symptoms remain controlled with no further COPD exacerbations.

**IN SUMMARY, WHAT'S NEW IN GOLD 2019?**

1. Initial treatment of COPD is separated from follow-up treatment. Initial treatment is based on the ABCD assessment tool, whereas follow-up treatment is based on dyspnea or exacerbation algorithms. If both dyspnea and exacerbation are present, the exacerbation algorithm is used.

2. Blood eosinophil count is incorporated as a biomarker to guide the use of ICS for exacerbation prevention.  
 3. The concept of treatment de-escalation is introduced, in which ICS is stopped if there is lack of clinical benefit and/or side effects occur.

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## FEATURE

# UNDERSTANDING DUAL-TASKING AND THE ROLE OF PHYSIOTHERAPY

In everyday life, people engage in dual-tasking, which is the concurrent processing of motor and cognitive tasks. Usually, healthy adults will not experience difficulties in dual-tasking; but many elderly people, individuals with impaired cognition, as well as individuals with neurological disorders, may experience difficulties.

**WHAT IS DUAL-TASKING?**

Dual-tasking is defined as the concurrent performance of two tasks that can be performed independently, and have distinct and separate goals. For example, being able to talk to a friend on the phone while crossing a busy street, or check the map while walking towards a destination. The concurrent practice of both motor and cognitive tasks may result in performance declining in at least one

of the tasks. This is termed “dual-task interference”. This arises because of competing demands for attentional resources needed for both tasks.<sup>1</sup> Dual-task interference has been associated with processing capacity and attention limitation, as described in the Capacity Sharing Model<sup>2</sup>; as well as delayed-response performance, as proposed in the Central Bottleneck Model.<sup>3</sup>

On the other hand, the **Central Bottleneck Theory** suggests that a “bottleneck” is created when two tasks are processed simultaneously by the same mental processing mechanisms or neural processor.<sup>3</sup> Broadbent described attention as a bottleneck, where we are able to pay attention to only one thing at a time.<sup>7</sup> A delay in the mental processing of the second task is experienced until the neural processor completes processing of the first task.<sup>3</sup>



**EACH INDIVIDUAL TASK IS SUGGESTED TO OCCUPY A PROPORTION OF THE PROCESSING CAPACITY WITHIN THE BRAIN- THE MORE DEMANDING THE TASK, THE GREATER THE PROPORTION OF PROCESSING CAPACITY REQUIRED.**

In the **Capacity Sharing Model**, dual-task interference is presumed to happen when two or more tasks are competing for attention resources and there is limited processing capacity within the brain.<sup>4,5</sup> Each individual task is suggested to occupy a proportion of the processing capacity within the brain- the more demanding the task, the greater the proportion of processing capacity required. This model assumes that individuals should allocate more attention to

**HOW DOES AGING AFFECT DUAL-TASKING?**

Dual-task interference has been shown to increase with ageing.<sup>8-12</sup> Specific cognitive abilities such as executive function have been associated with cognitive-motor dual-tasking, especially in older adults.<sup>13,14</sup>

Executive function (or executive control) is defined as “a family of top-down mental processes required when one has to concentrate or pay attention, where going on automatic or relying on instinct or intuition would be ill-advised, insufficient, or impossible”.<sup>15,16</sup>

Executive function is necessary to achieve an effective, goal-directed and independent management of daily activities and mobility.<sup>17</sup> Higher-level cognitive processes, such as executive function and attention, play a vital role in walking performance under dual-task conditions.<sup>13,14</sup>

Age-related changes in cognitive and motor systems could exert detrimental effects on cognitive-motor performance. Age has been found to be associated with reduced processing efficiency, i.e. nerve conduction speed and fluid intelligence in the central nervous system.<sup>18,19</sup> The prefrontal lobe and cingulate cortex play important roles in executive function. The frontal lobes are highly susceptible to age-related changes.<sup>20</sup> Studies have shown that atrophy of the frontal cortex on magnetic resonance imaging has been associated with reduced processing speed and a decline in cognitive function, particularly executive function.<sup>21,22</sup> Similarly, Beurskens and colleagues reported a substantial reduction in prefrontal cortex activation during dual-task walking incorporating a complex visual task in 10 older adults using functional Near-Infrared-Spectroscopy (fNIRS).<sup>23</sup> Additionally, age-related changes in musculoskeletal, somatosensory, vestibular and visual systems commonly affect older adults.<sup>24</sup> These changes could alter sensory input and feedback responses required in the coordination of postural control.<sup>25</sup> Consequently, this altered input from the peripheral somatosensory systems, together with declined cognitive function increase the attentional demands during dual-task walking or postural tasks, causing deterioration in the performance of one or both tasks.<sup>24</sup>

**WHAT ARE THE IMPLICATIONS OF DUAL-TASK INTERFERENCE?**

Dual-task interference may have detrimental effects on motor performance in older adults e.g. walking and postural control. This may increase with age. It is well documented that walking-related dual-task performance is a predictor of falls in older adults. A meta-analysis of 17 studies showed that impaired gait or attention-demanding task performance during dual-tasking significantly augmented the likelihood of falls.<sup>26</sup>

Another implication would be that dual-task interference during walking could serve as a clinical sign in identifying individuals with mild cognitive impairment at risk of progression to dementia. A recent prospective study revealed that in patients with mild cognitive impairment, poor dual-tasking ability during walking was associated with a 3 times increased risk of developing dementia.<sup>27</sup>

**HOW DO YOU IDENTIFY PATIENTS WITH REDUCED DUAL-TASK ABILITY?**

The most obvious sign of impairment in dual-tasking ability is having difficulty in performing (or, even being unable

to perform) cognitive and motor tasks simultaneously. For example, family members may notice that the patient walks unusually slowly, or shows signs of unsteadiness when talking.

One of the common tools used to identify reduced dual-tasking ability is the “*Stops walking when talking*” test. The patient is engaged in conversation when walking on a straight path. The test is considered positive if the patient stops walking for at least 1 second in order to engage in the conversation. In addition, walking tests in combination with cognitive tests (such as counting backwards, engaging in conversation,



**AGE-RELATED CHANGES IN COGNITIVE AND MOTOR SYSTEMS COULD EXERT DETRIMENTAL EFFECTS ON COGNITIVE-MOTOR PERFORMANCE. AGE HAS BEEN FOUND TO BE ASSOCIATED WITH REDUCED PROCESSING EFFICIENCY, I.E. NERVE CONDUCTION SPEED AND FLUID INTELLIGENCE IN THE CENTRAL NERVOUS SYSTEM.**



performing manual tasks and reciting letters) are commonly used to assess the level of dual-task ability in clinical settings.<sup>26,28</sup>

#### PHYSIOTHERAPY MANAGEMENT FOR INDIVIDUALS WITH REDUCED DUAL-TASKING ABILITY ASSESSMENT

When an individual with impaired dual-tasking ability is first referred to a physiotherapist, the physiotherapist begins by taking a collaborative case history from the individual and accompanying family members. Information such as cognitive ability, motor function, difficulties faced during dual-tasking, and fall history, is gathered. Formal assessments are carried out to evaluate cognition, motor function, balance, gait and dual-tasking ability. Results of the assessment allow the physiotherapist to diagnose if an individual has impaired dual-task ability. Following assessment, the therapist discusses possible treatment plans and goals with the individual and his or her family.

#### THERAPY AND MANAGEMENT

Dual-task training has been demonstrated to improve cognitive-motor dual-task performance in older adults.<sup>29,30</sup> Studies have shown that varied dual-task training could improve dual-task performance, compared to single-task training.<sup>30</sup> As the underlying cause of dual-task interference could be due to impaired cognitive function, aerobic training is also highly recommended. Aerobic training was found to have robust benefits for cognition, especially in the case of executive function.<sup>31</sup>

A local study (MINDVital) examined a programme which combined cognitive stimulation and physical

exercise. As part of the programme, participants performed aerobic, resistance training and Square Stepping exercises. The Square Stepping exercise involved cognitive-motor training, requiring participants to perform a specific stepping sequence across a gridded floor mat (figure 1). The training led to significant improvements in dual-task walking in individuals with early dementia.<sup>32</sup>

Individuals with Parkinson's disease, stroke and cognitive impairment (such as dementia) as well as those at high risk of falls, will benefit from specific physiotherapy training. Physiotherapy interventions, which include cognitive-motor dual-task training, gait training, balance and resistance exercises, aim to prevent falls and improve strength and balance.

Apart from physiotherapy interventions, healthy community-dwelling elderly are encouraged to participate in general exercise activities (e.g. dance and Zumba Gold), and activities involving cognitive-motor training organized by senior activity centres, in order to keep healthy and prevent falls. Where safe and able, they can also practise walking in different directions or engage in stair-climbing while performing cognitive tasks such as serial subtraction, calculation or naming objects (e.g. animals, countries, fruits) at the same time. The type of dual-task training should be selected based on pathology and the individual's cognitive capacity. For patients with gradual improvement in cognitive and motor function, such as patients recovering from stroke, dual-task training may be effective in improving community ambulation and preventing falls. In contrast, dual-task training in patients with degenerative conditions such as moderate dementia may not result in a sustained improvement in performance.<sup>34</sup>



Figure 1. Example of Square Stepping exercise (Shigematsu, 2008).<sup>33</sup>

#### PATIENT AND FAMILY EDUCATION

Apart from dual-task training, it is important to educate individuals with reduced dual-task ability and their family regarding safety during activities of daily living and functional mobility. Planning of activities or task prioritization strategies is important when performing cognitive-motor dual-tasks, especially in individuals with impaired cognition or motor deficits.

The home environment should also not be cluttered in order to reduce the cognitive demands and risk of falls during walking at home.

#### CONCLUSION

Cognitive-motor dual-task interference is common among older adults and people with neurological conditions. This could lead to gait instability and increase the risk of falls, which in turn significantly impacts quality of life.

Although there remains much to be done in developing training strategies to improve dual-tasking ability, there is emerging evidence that varied dual-task training can help to improve dual-tasking ability in the elderly. It is important for the healthcare professional to identify clients with early signs of impaired dual-tasking ability, and refer them to physiotherapists for assessment and intervention.

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DRUG UPDATE: TOUJEO®

Toujeo® U-300 insulin glargine (300 units/mL) is a long-acting basal insulin approved for use in Singapore by the Health Sciences Authority (HSA) in December 2016. It is indicated for use in adults with diabetes mellitus (DM) to improve glycaemic control. Similar to its predecessor Lantus®, Toujeo also contains insulin glargine. However, Toujeo is three times more concentrated than Lantus which is available as an injection dosage of 100 units/mL (i.e. Lantus® U-100).

Concentrated insulin is not new to the scene. Apart from Toujeo, there are currently 3 other concentrated insulin products on the market: Humalog® U-200 insulin lispro (200 units/mL), Humulin R® U-500 regular insulin (500 units/mL), and Tresiba® U-200 insulin degludec (200 units/mL). The growing interest in concentrated insulin products has primarily been driven by the increasing rates of obesity and insulin resistance, which can result in the requirement for very high total daily insulin doses (for instance, greater than 200 units/mL per day). Restricted by insulin pens' maximum individual doses (e.g. up to 80 units of insulin per dose for Lantus SoloSTAR® and U-100 glargine pen), some individuals may require more than one injection per dose of insulin. Concentrated insulin products were initially formulated to solve this problem- with smaller volumes to inject, insulin pens can now be dialled to greater maximum doses per injection (for example, up to 160 units of insulin per dose for U-200 insulin degludec), thus reducing the total number of injections required per day for some individuals. More interestingly, studies done with Toujeo have raised the possibility that smaller-volume basal insulin injections may produce more consistent release profiles, with less inter- and intra-patient variability in onset and duration.<sup>1</sup> This increased consistency in release profiles may lead to lower rates of hypoglycaemia.

In this review, we introduce Toujeo and its notable properties; review the studies backing the claims; and, give an overview on how to prescribe it safely.

TOUJEO IS AVAILABLE IN THE SAME SOLOSTAR PEN AS LANTUS, AND THUS EMPLOYS THE SAME INJECTION TECHNIQUE. THE PHARMACEUTICAL MANUFACTURER (SANOFI-AVENTIS) HAS TWEAKED THE TOUJEO PEN SUCH THAT ONE UNIT DIALLED ON THE TOUJEO PEN IS THE EQUIVALENT DOSE OF ONE UNIT DIALLED ON THE LANTUS PEN

WHAT IS TOUJEO®?

Toujeo contains the same type of insulin as Lantus – basal insulin glargine – but in a more concentrated form. In Toujeo, one millilitre of solution contains 300 units of insulin glargine (U-300); in Lantus, one millilitre of solution contains only 100 units of insulin glargine (U-100). Even though the two products consist of the same type of insulin, each dose of Toujeo is one-third the volume of the same dose of Lantus (figure 1).

Toujeo is available in the same SoloStar pen as Lantus, and thus employs the same injection technique. The pharmaceutical manufacturer (Sanofi-aventis) has tweaked the Toujeo pen such that one unit dialled on the Toujeo pen is the equivalent dose of one unit dialled on the Lantus pen (figure 2).<sup>3</sup>

WHAT IS SO SPECIAL ABOUT TOUJEO®?

According to Sanofi-aventis, Toujeo is a long-acting concentrated insulin which:

1. Has a slower onset (6 hours vs. 3-4 hours), and longer duration of action (> 24 hours vs. 10.8 to > 24 hours) when compared to insulin glargine U-100;<sup>3</sup>
2. Has a smaller volume per injection than insulin



Figure 1. Toujeo® is three times more concentrated than Lantus®.<sup>2</sup>

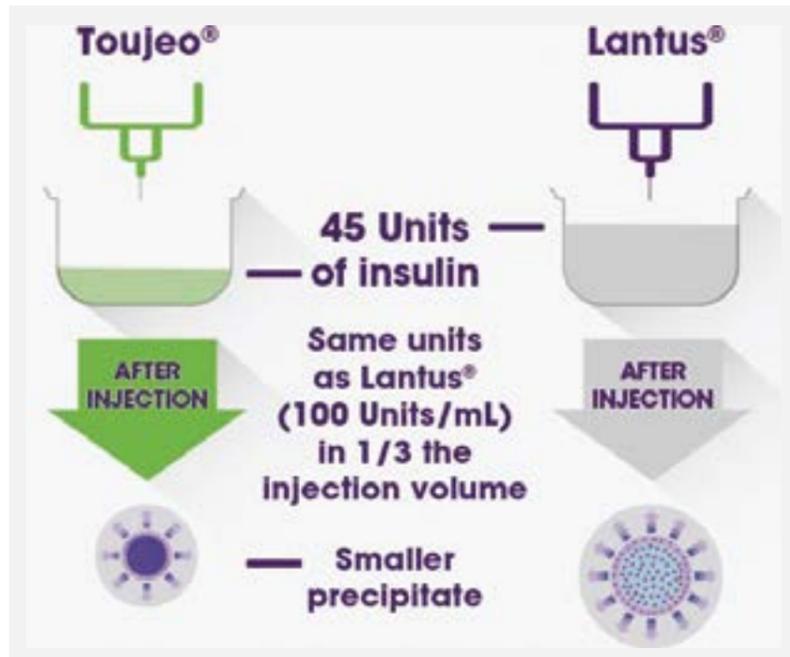


Figure 2. The pen for Toujeo® delivers a smaller volume of insulin at each click compared to the pen for Lantus®, even though the number of units on the pen dial is the same for both. This reduces the risk of administration error. Source: <https://www.healthline.com/diabetismine/ask-dmine-dose-disorientation-dilemmas>.<sup>4</sup>

glargine U-100. This has been postulated to result in less painful injections, especially for larger doses; and,

3. Potentially requires fewer injections. Some patients requiring twice-daily injections of Lantus (insulin glargine U-100), Basaglar® (biosimilar insulin glargine U-100) or Levemir® (insulin detemir U-100) may need only once-daily injections of Toujeo because of its longer duration of action (24 - 36 hours).

**HOW CAN A SIMPLE DIFFERENCE IN CONCENTRATION LEAD TO MORE CONSISTENT BASAL INSULIN ACTIVITY?**

Insulin glargine is formulated to be soluble only in an acidic solution. It precipitates at physiological pH, forming a subcutaneous depot. It is hypothesized that the size

	Lantus® (insulin glargine 300units/3mL)	Toujeo® (insulin glargine 450 units/1.5mL)
Concentration (units/mL)	1mL of Lantus contains 100 units	1mL of Toujeo contains 300 units
Total units in each pen	300 units	450 units
Priming	2 units	3 units  *TTSH in-house practice to standardise to prime 2 units when using 4-6 mm pen needles
Doses available	1 – 80 units (even units indicated by numbers, odd units indicated by lines)  Doses are prescribed in units for both products.	
Appearance	Purple and grey	Green and grey
Image		
Duration to hold down push button after administration of insulin	10 seconds	5 seconds

Table 1. Key differences between Lantus® and Toujeo®.

of this insulin depot affects the dissolution rate- the larger the depot, the greater the surface area exposed to the surrounding tissue, and the faster it dissolves and diffuses into the bloodstream.<sup>1</sup> Toujeo, with its smaller volume, forms a smaller depot with a smaller surface area, and thus takes a longer time to dissolve and be released into the bloodstream (figure 3):

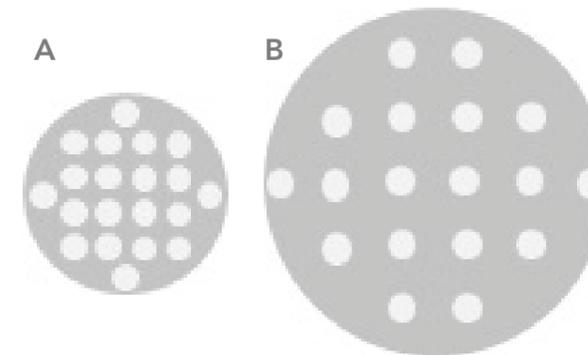


Figure 3. Due to its reduced volume, Toujeo® (A) is able to form a subcutaneous depot with a reduced surface area (A), compared to the depot formed by Lantus® (B) which has a larger surface area.

This slower release into the bloodstream theoretically leads to a more consistent level of insulin in the body. At steady state, Toujeo is claimed to have a prolonged duration of action of over 24 hours, and up to 36 hours, with no appreciable peak regardless of dose. In comparison, the duration of action of Lantus has been reported to vary from 10.8 hours to over 30 hours, while that for Levemir has been reported to be dose-dependent, ranging from 6 hours to 23 hours.<sup>5</sup>

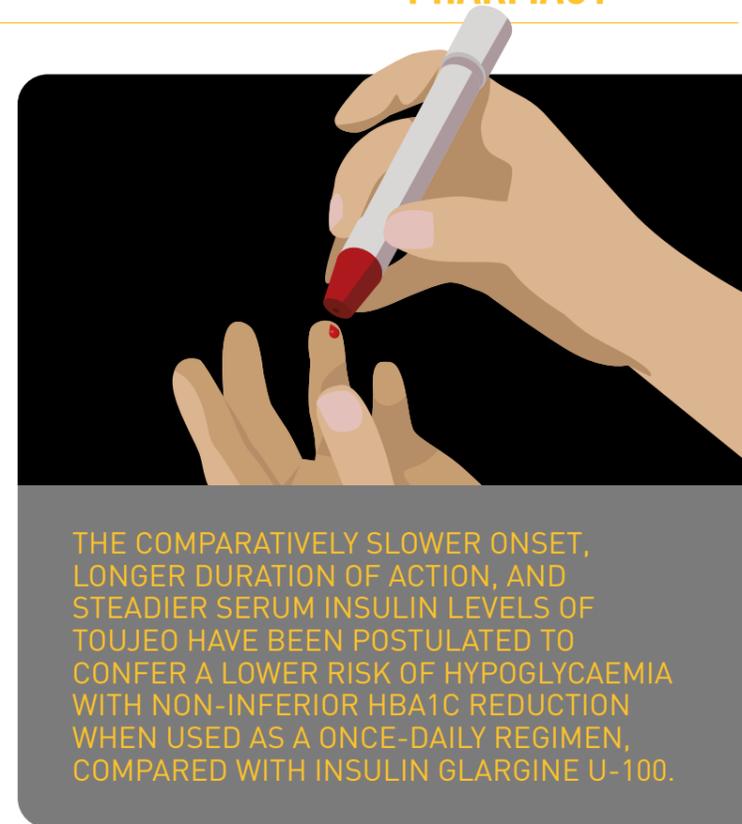
The comparatively slower onset, longer duration of action, and steadier serum insulin levels of Toujeo have been postulated to confer a lower risk of hypoglycaemia with non-inferior HbA1c reduction when used as a once-daily regimen, compared with insulin glargine U-100.

**WHAT DO RESEARCH STUDIES SHOW?**

Three randomised controlled trials (EDITION 1, EDITION 2 and EDITION 3), compared the efficacy and safety of Toujeo (insulin glargine U-300) versus insulin glargine U-100 in different Type 2 DM patient populations (table 2):

Clinical Trial	Patient Population	Clinical Trial
EDITION 1	Patients with Type 2 DM on basal insulin (≥ 42 units/day) plus mealtime insulin	Toujeo® vs. Insulin glargine U-100
EDITION 2	Patients with Type 2 DM using basal insulin (≥ 42 units/day) plus oral anti-hyperglycemic drugs	
EDITION 3	Insulin-naïve patients with Type 2 DM using oral glucose-lowering drugs	

Table 2. Different sub-populations of Type 2 DM patients were studied in each EDITION trial.<sup>6-9</sup>



THE COMPARATIVELY SLOWER ONSET, LONGER DURATION OF ACTION, AND STEADIER SERUM INSULIN LEVELS OF TOUJEO HAVE BEEN POSTULATED TO CONFER A LOWER RISK OF HYPOGLYCAEMIA WITH NON-INFERIOR HBA1C REDUCTION WHEN USED AS A ONCE-DAILY REGIMEN, COMPARED WITH INSULIN GLARGINE U-100.

The EDITION trials successfully demonstrated that Toujeo was non-inferior to insulin glargine U-100 in terms of HbA1c reduction (from baseline to 6 months post-trial initiation (table 3). A similar proportion of participants in both treatment groups in each of the 3 trials achieved HbA1c below 7% 6 months post-trial initiation.

The EDITION trials also hoped to demonstrate that, based on its pharmacodynamic and pharmacokinetic profiles, Toujeo would be associated with a lower risk of hypoglycaemia, which is the most common adverse reaction associated with any insulin treatment. With the exception of EDITION 3, non-insulin-naïve patients in EDITION 1 and 2 demonstrated statistically significant lower rates of nocturnal hypoglycemic events over the 6-month study period with Toujeo than insulin glargine U-100 (table 3). In EDITION 3, there was no statistically significant difference in the occurrence rate of nocturnal hypoglycaemic events between insulin-naïve patients

Clinical Trial	Difference in HbA1c reduction between treatment groups	Proportion of patients with ≥ 1 nocturnal confirmed or severe hypoglycemic events <sup>o</sup>
EDITION 1	- 0.00 % [95 % CI: -0.11 to 0.11]	Toujeo <sup>®</sup> : 36% vs. Insulin glargine U-100: 46% [RR 0.79; 95 % CI: 0.67 - 0.93, p=0.0045]
EDITION 2	- 0.01 % [95 % CI: -0.14 to 0.12]	Toujeo <sup>®</sup> : 22% vs. Insulin glargine U-100: 28% [RR 0.77; 95 % CI: 0.61 - 0.99, p=0.038]
EDITION 3	0.04 % [95 % CI: -0.09 to 0.17]	Toujeo <sup>®</sup> : 16% vs. Insulin glargine U-100: 17% [RR 0.89; 95 % CI: 0.66 - 1.20, p > 0.05]

Table 3. Difference between the treatment groups (Toujeo<sup>®</sup> vs. insulin glargine U-100) for the primary efficacy endpoint (change in HbA1c) and secondary efficacy endpoint (percentage of patients experiencing one or more nocturnal confirmed/severe hypoglycemic event).<sup>6-9</sup>

<sup>o</sup> Nocturnal (0000 – 0559 hours) confirmed hypoglycemic event was defined as a self-measured plasma glucose level ≤ 3.9 mmol/L. Nocturnal severe hypoglycemic event was defined as an event requiring assistance by another person to administer carbohydrate, glucagon, or other therapy. Nocturnal severe hypoglycaemic events were rare in all 3 trials, and too few for meaningful analysis in each trial.

receiving Toujeo or insulin glargine U-100 (table 3). A post-hoc meta-analysis of the three EDITION trials found a reduction of approximately 1 confirmed or severe nocturnal hypoglycemic event per person per year, which is of debatable clinical significance.<sup>10</sup>

Notably, there are very limited data on the effects of Toujeo on macro- or microvascular outcomes, as well as on long-term safety outcomes.

**ARE THERE ANY OTHER SIDE EFFECTS ASSOCIATED WITH USING TOUJEO<sup>®</sup>?**

As with other insulin products, weight gain is a possibility with Toujeo [mean increase of 0.49 kg; 95 % CI: 0.14 to 0.83 kg].<sup>9</sup> Inadequate injection site rotation may also lead to lipodystrophy with long-term use.

Allergic reactions at the injection site (2.7 %) such as erythema, local oedema, and pruritus are usually self-limiting.<sup>9</sup> Generalised skin reactions, angioedema, bronchospasm and hypotension are rare. The incidence was similar in Toujeo-treated patients (5.3%) and insulin glargine 100units/mL-treated

patients (4.5 %).<sup>9</sup> Other adverse reactions include nasopharyngitis (7.1 % -12.8 %) and upper respiratory tract infection (5.7 % - 9.5 %).<sup>9</sup> There is no clinical data on the use of Toujeo in pregnant woman.<sup>3</sup>

**WHAT ARE THE SAFETY CONCERNS WITH THE USE OF TOUJEO<sup>®</sup>?**

Dosing errors related to concentrated insulin are potentially devastating as they may result in severe hypoglycaemia. The main concern with concentrated insulin products is the risk of a mix-up between different insulin dosage versions, for example Lantus (U-100) and Toujeo (U-300).

A prescribing error may occur if the prescriber selects the wrong concentration from the computer screen when the different concentrations appear one line apart from the other. Selection error may be minimized by arranging according to the brand name first, followed by the concentration and generic name. A supply chain error may happen if the two insulin products are placed next to each other in the fridge. Administration

errors are also possible- one such error occurred when a U-100 syringe was used to withdraw concentrated U-500 regular insulin, resulting in an unintentional 5-fold overdose.<sup>11,12</sup>

Patients on very high doses of concentrated insulin should also be closely monitored for ‘insulin stacking’, which occurs when repeated insulin administration at close intervals and reduced clearance leads to accumulation of insulin. Insulin stacking can lead to a prolonged duration of action and severe refractory hypoglycaemia.<sup>13</sup>

**WHO MAY BENEFIT FROM TOUJEO<sup>®</sup>?**

Patients on high doses of insulin glargine U-100 who experience significant pain upon injection are most likely to benefit from Toujeo due to its smaller injection volume.

The more gradual onset, longer duration of action, and steadier serum insulin levels of Toujeo could potentially result in reduced hypoglycemic occurrences, compared to insulin glargine U-100. A few retrospective observational studies have shown

**The more gradual onset, longer duration of action, and steadier serum insulin levels of Toujeo could potentially result in reduced hypoglycemic occurrences, compared to insulin glargine U-100.**

a significantly lower risk of hypoglycaemia with Toujeo in elderly patients aged above 65 years.<sup>14,15</sup> However, there is insufficient clinical trial evidence to conclude that there is a clinically significant benefit in older patients.

**HOW DO I DOSE TOUJEO<sup>®</sup>?**

Closer monitoring of plasma glucose levels is recommended during the switch (table 4), as well as in the initial weeks thereafter, as improved metabolic

control and the resulting increase in insulin sensitivity may necessitate dose adjustments. Dose adjustment may also be required if the patient’s weight or lifestyle changes, or if other circumstances arise that increase susceptibility to hypo- or hyperglycaemia (e.g. intercurrent illness, infections, or deterioration in liver or kidney function). Prolonged hypoglycaemia may be anticipated in the setting of renal or hepatic impairment; more frequent monitoring is hence recommended in these patient populations.

If the patient used to be on...	And is now switching to...	How do I dose the new insulin?
Non-insulin treatment (i.e. insulin-naïve)	Newly starting on Toujeo	<ul style="list-style-type: none"> <li>• Type 1 DM: Toujeo should be started once daily in combination with prandial insulin; requires individual dose adjustments.</li> <li>• Type 2 DM: The recommended starting dose is 0.2 units/kg, followed by individual dose adjustments.</li> </ul>
Insulin glargine 100 units/mL <sup>§</sup>	Toujeo <sup>§</sup>	<p>The switch can be made on a unit-to-unit basis.</p> <p>Eventually, a higher dose of Toujeo (about 10 % - 18 %) may be needed to achieve target plasma glucose levels.</p>
Toujeo <sup>§</sup>	Insulin glargine 100 units/mL <sup>§</sup>	The original Toujeo dose should be reduced by about 20 % to reduce the risk of hypoglycaemia.
Other basal insulins <sup>Δ</sup>	Toujeo	<ul style="list-style-type: none"> <li>• Switching from once-daily basal insulin to once-daily Toujeo: The switch can be made unit-to-unit based on the previous basal insulin dose.</li> <li>• Switching from twice-daily basal insulin to once-daily Toujeo: The recommended starting Toujeo dose is 80 % of the total daily dose of the previous basal insulin.</li> </ul>
Toujeo	Other basal insulins	Refer to the prescribing information of the new insulin product to which the patient is switching.

Table 4. Recommended dosing practices for Type 2 DM patients being newly started on Toujeo<sup>®</sup> or being switched to other basal insulin products.<sup>3</sup>

<sup>§</sup> Insulin glargine U-100 and Toujeo are not bioequivalent; therefore, they are not directly interchangeable.

<sup>Δ</sup> When switching from an intermediate- or long-acting insulin product to Toujeo, basal insulin dose as well as concomitant anti-hyperglycaemic treatment may need to be adjusted e.g. dose and/or timing of prandial insulin product and non-insulin anti-hyperglycaemic drugs.

**WHAT DO I NEED TO TELL MY PATIENTS IF I WANT TO START THEM ON TOUJEO®?**

Patient education is of paramount importance to minimize medication errors and to reduce the risk of hypoglycaemia due to the use of concentrated insulin. Important points to convey to patients are as follows:

- Check the insulin label carefully before each use. The label should state whether it is Toujeo or Lantus instead of simply ‘insulin glargine’, since both products contain glargine as the active ingredient but at different concentrations.
- Toujeo should be administered at the same time each day, or within 3 hours before or after the usual time of administration.<sup>3</sup>
- The Toujeo U-300 pre-filled pen should only be used with a 4-6 mm insulin pen needle. Never ever use a U-100 insulin syringe or millilitre syringe to withdraw insulin from the pen device.

- A new pen needle should be used for every injection.
- Toujeo should not be mixed with any other insulin or solution.
- Injection site should be rotated at each injection to prevent hardening of the skin and subcutaneous tissue.
- Be aware of the symptoms of both hypoglycaemia and hyperglycaemia, as well as how to manage them.
- Self-monitoring of blood glucose levels at home is recommended to check the effects of insulin treatment, as well as to detect asymptomatic hypoglycaemia or hyperglycaemia.
- Seek medical attention if any of the following side effects become severe or persist:<sup>3</sup>
  - o Hypoglycaemia with fast heartbeat, sweating, extreme drowsiness or confusion
  - o Pain, redness, itching or swelling at the injection site
  - o Shortness of breath, rash over the whole body, or swelling of face, tongue or throat

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# RADIOLOGY QUIZ

EVERY ISSUE, WE PRESENT RADIOLOGY AND ECG QUIZZES OF INTERESTING CASES SEEN IN TTSH. PUT YOUR KNOWLEDGE TO THE TEST WITH THIS ISSUE'S SCENARIOS.

A 56-year-old Malay female who is premorbidly ADL-independent and community ambulant presented at Tan Tock Seng Hospital's Emergency Department (ED) with progressively worsening back pain since the last 1 month. She reported that the pain had increased since the last 1 week, with radiation to the left lower limb.

There was a history of fall 1 week ago at home, but she did not sustain any back injury. She subsequently developed difficulty in walking, requiring a walking stick, and had bilateral feet numbness for 4 days.

She also reported having night sweats and chills for 3 to 4 days prior to presentation at ED. The patient had a past medical history of pulmonary tuberculosis,

diagnosed in 2018, for which she underwent a 6-month treatment regimen.

On examination, the patient had left paravertebral region tenderness on palpation. No overlying swelling or erythema was detected. The left sciatic stretch test was positive.

The power was 3+/5 at the L2 and L3 myotomes bilaterally, noted to be limited by pain, and 4/5 at the L4 to S1 levels bilaterally. No gross sensorimotor deficit was evident. Reflexes were normal (2+) bilaterally, although diminished at the ankles. Plantar reflexes were downgoing on both sides.

Digital rectal examination revealed normal tone and perianal sensation. She did not report any bladder or bowel incontinence.

**INVESTIGATIONS**

- WCC 6.0, Hb 10.9
- Na 140, K 2.9, Cr 57, Urea 3.9
- CRP 94.6, ESR 82
- Mg 0.6 Phos 1.0 corrected Ca 2.37 Alb 36
- ECG: sinus tachycardia
- Blood C/S - No bacterial growth

Mild left apical and right mid zone scarring were seen in the chest radiograph (figure 1). No focal consolidation or pleural effusion was detected.

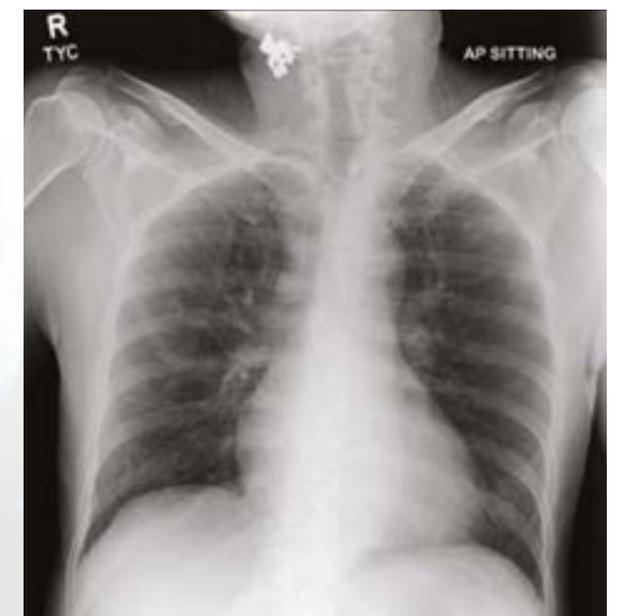


Figure 1. Chest radiograph.



Figure 2. Lumbar spine radiographs.

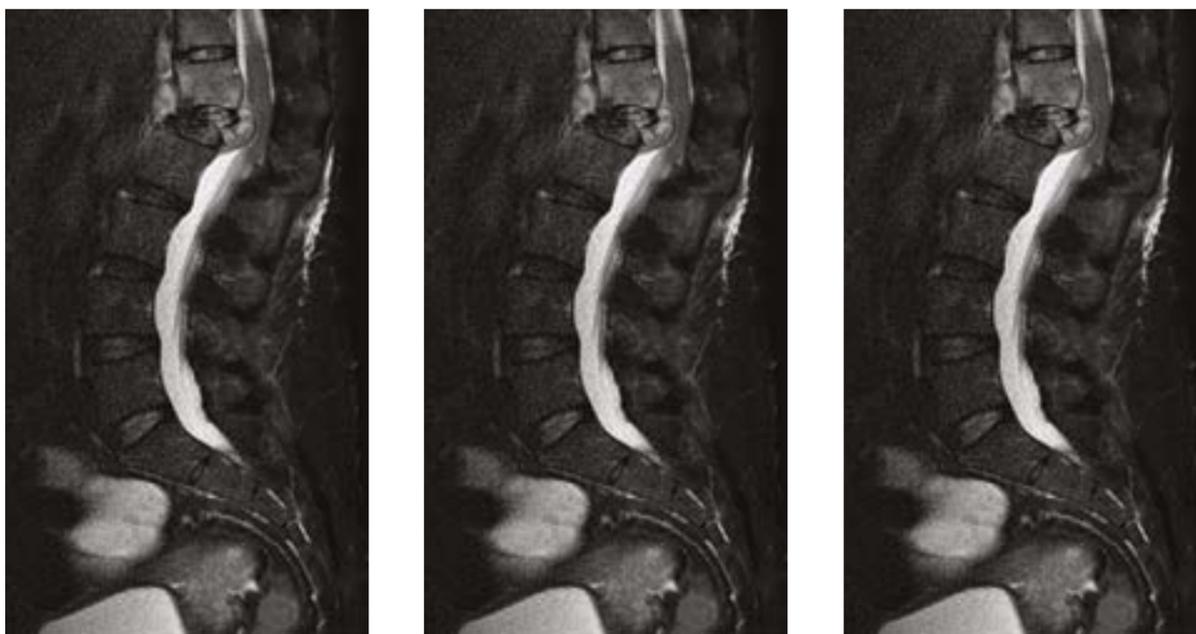


Figure 3a. Contrast-enhanced MRI of the lumbar spine: Sagittal inversion recovery (IR)-weighted MRI.

Figure 3b. Contrast-enhanced MRI of the lumbar spine: Sagittal post-contrast T1-weighted fat-suppressed MRI.

Figure 3c. Contrast-enhanced MRI of the lumbar spine: Sagittal T2-weighted MRI.

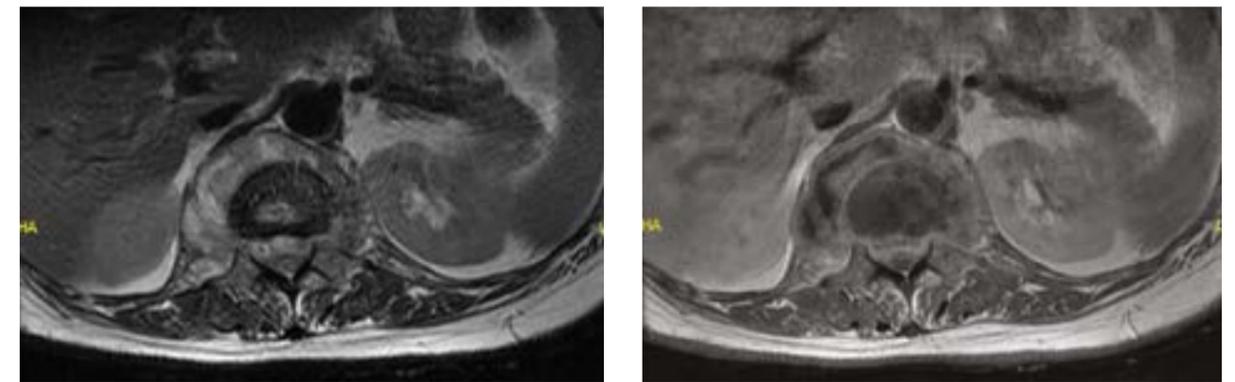


Figure 3d. Contrast-enhanced MRI of the lumbar spine: Axial T1-weighted MRI at T12 level.

Figure 3e. Contrast-enhanced MRI of the lumbar spine: Axial post-contrast T1-weighted MRI at T12 level.

### QUESTIONS

- 1) What are the findings on this patient's lumbar spine radiograph?
- 2) What additional information do the MRIs provide?
- 3) What are the differential diagnoses for this patient's condition?

### ANSWERS

- 1) There is complete collapse (vertebra plana) and destruction of the L1 vertebral body with gibbus deformity and a right-sided paravertebral soft tissue collection. Associated narrowing of the T12/L1 intervertebral disc space and bony retropulsion into the spinal canal is also seen.
- 2) Apart from the complete destruction of the L1 vertebral body, the MRIs demonstrate marrow oedema in the T12 vertebral body. There is also involvement of the T12/L1 and L1/L2 intervertebral discs as shown by the increased T2 signal intensity.

Moreover, there is paravertebral soft tissue collection at the T12/L1 level bulging into the spinal canal and causing spinal canal stenosis and compression of the distal cord. The collection was noted to also involve the right psoas muscle (not shown).

A rim-enhancing lesion is seen in the T12 vertebral body inferior half as well. Similar lesions were noted in the T3, T9 and T10 vertebrae with involvement of the posterior elements of the T9 vertebra (not shown).

- 3) *Infectious spondylitis* will be the top differential for this case, in particular tuberculous spondylitis. Brucellar spondylitis is also a consideration. However, this involves the lower lumbar spine with bone destruction limited to the endplates. Disc collapse and granulation tissue or soft tissue oedema are also characteristic findings.

*Pyogenic spondylitis* is another differential that should be considered. However, the clinical course tends to be more acute, with high grade fever, severe back pain and swelling being important clinical distinct features.

Moreover, given the multifocal involvement and posterior element involvement in T9, *metastases of undiagnosed* or occult malignancy is also an important differential that needs to be excluded.

Following aspiration of the right paravertebral collection, the diagnosis of *Tuberculous spondylitis* was confirmed with the presence of acid-fast bacilli (AFB) on AFB smear, and the detection of *Mycobacterium tuberculosis* (MTb) complex on MTb Rifampicin polymerase-chain reaction (PCR) analysis.

The patient was commenced on anti-tuberculous therapy (rifampicin, isoniazid, pyridoxine and ethambutol). She subsequently underwent L1 laminectomy and spinal instrumented fusion from T9 to L4, with good post-operative recovery.

## DISCUSSION

Tuberculous (TB) spondylitis, also known as Pott's disease, is usually secondary to an extraspinal source of infection. It is one of the more common infections of the spine in regions where TB is prevalent, such as in developing countries. It constitutes about 1-2% of total tuberculosis cases worldwide.

Patients usually present with back pain, lower limb weakness or paraplegia, and kyphotic deformity. Constitutional symptoms such as fever and weight loss are also common, but not as pronounced as with bacterial/pyogenic discitis or osteomyelitis.

The manifestation is usually a combination of osteomyelitis and arthritis involving more than 1 vertebra. The lower thoracic and upper lumbar levels of the spine are most commonly affected.

The anterior aspect of the vertebral body adjacent to the subchondral endplate is usually affected with spread underneath the longitudinal ligaments to adjacent intervertebral discs. This is typically described as 'sub-ligamentous' spread.

Progressive bone destruction leads to slow vertebral collapse and kyphosis. Associated development of abscesses, granulation tissue, or direct dural invasion may cause spinal canal narrowing, as was the case with our patient, leading to spinal cord compression and neurologic deficits.

If the infection extends to the adjacent ligaments and soft tissues, large paraspinal abscesses can occur without severe pain or frank pus, hence the term 'cold abscess'. Unlike pyogenic infections, the discs can be preserved with more common involvement of the thoracic spine.

Associated features may include vertebra plana and ivory vertebrae. As with other extrapulmonary TB, the chest radiograph may be unrevealing, with the source being a primary lung lesion that is clinically silent.

Cross-sectional imaging in the form of CT and MRI is required to better assess the extent of involvement, and to particularly detect the presence of an epidural component and cord compression. MRI is the modality of choice for this, with CT with contrast being a distant second.

Features include irregularity of both the endplate and anterior aspect of the vertebral bodies, with bone marrow oedema and enhancement seen on MRI:

- T1: hypointense marrow in adjacent vertebrae
- T2: hyperintense marrow, disc, soft tissue infection
- T1 C+ (Gd): marrow, subligamentous, discal, dural enhancement

The paraspinal collections are typically well circumscribed, with fluid centers and well-defined enhancing margins.

Treatment is mainly with anti-tuberculous therapy as guided by microbiology culture and sensitivity results. Surgical intervention for decompression of the spinal canal is also performed.

## LEARNING POINTS

- TB spondylitis is a common cause of vertebral body infection, especially in areas where TB is prevalent.
- It is characterised by an insidious involvement of the vertebrae, particularly in the thoracic or upper lumbar spine, with relatively preserved intervertebral disc spaces and subligamentous spread.
- Plain radiograph and MRI imaging are the modalities of choice in assessing the extent of the disease.

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## ECG QUIZ

A middle-aged gentleman was seen at the polyclinic for cough, fever and wheezing. He was a chronic smoker but did not have any significant past medical history. He recovered from his symptoms initially but presented to the polyclinic again 2 weeks later for exertional breathlessness. A chest X-ray (CXR) was taken (figure 1). He was referred to the cardiology outpatient clinic.



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

Two weeks later, he presented to the Emergency Department (ED) for worsening breathlessness and orthopnoea. On examination, he was comfortable and not in respiratory distress. His temperature and blood pressure were within normal limits. The jugular venous pressure appeared elevated. A resting 12-lead electrocardiogram (ECG) was performed (figure 2).



Figure 2. Resting 12-lead electrocardiogram performed on arrival at the hospital.

## QUESTION

Based on the available information, what is the most likely cause for his breathlessness?

## ANSWER

Large pericardial effusion with possible pericardial tamponade.

### DISCUSSION

The ECG shows a sinus rhythm of 89 beats per minute. The obvious abnormalities include globally small QRS complexes as well as electrical alternans (best seen in the long Lead II). These findings, together with the CXR (figure 1) showing a grossly enlarged heart silhouette, are consistent with a large pericardial effusion.

An urgent transthoracic echocardiogram performed in the ED showed a large pericardial effusion with features consistent with tamponade physiology. Pericardiocentesis was performed immediately with relief of the symptoms. A cardiac MRI scan subsequently showed features suggestive of myopericarditis. The patient also underwent extensive evaluation including microbiological investigations and body CT. No evidence of active infection (including mycobacteria), autoimmune disease or malignancy were found. In view of the preceding viral respiratory symptoms and cardiac MRI findings, viral pericarditis was felt to be the most likely cause for the pericardial effusion. A repeat echocardiogram performed in the outpatient setting a month later did not show any reaccumulation of the pericardial fluid.

The normal pericardial sac contains a small amount (10–50 ml) of fluid. Pericardial effusion occurs when an abnormally large amount of fluid accumulates in

the pericardial sac, most commonly due to infective (especially viral and mycobacteria), neoplastic or autoimmune causes. No cause (i.e. idiopathic) is found in up to 50% of cases. The rate of pericardial fluid accumulation, rather than the absolute volume of fluid, is the main determinant for clinical presentation and symptoms. This could possibly explain why our patient was minimally symptomatic and not tachycardic (figure 2), despite having a large pericardial effusion.

Apart from tachycardia, other key ECG features of pericardial tamponade include low QRS voltages and electrical alternans. These signs represent the damping effect of pericardial fluid and ‘swinging heart’ within the pericardial sac. Echocardiography is essential to demonstrate the physiological impact of the pericardial fluid (such as cardiac chamber collapse and variation of cardiac inflow with respiration). Ultrasound-guided pericardiocentesis often leads to immediate relief of symptoms and haemodynamic stabilisation.

In summary, this patient presented with a subacute onset of dyspnoea, together with an enlarged heart silhouette on the CXR. Recognition of the ECG features of tamponade, such as electrical alternans and small QRS complexes in this case, prompted urgent echocardiography which allowed prompt diagnosis and treatment to be instituted.



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### ERRATUM

In the ECG Quiz published in the April – June 2019 issue of Medical Digest, the correct answer to the question ‘Based on the ECG alone, what is the most likely cause for his sudden loss of consciousness?’ should be ‘Bradyarrhythmia (2:1 AV block) secondary to an inferior ST elevation myocardial infarction (STEMI)’, instead of ‘Bradyarrhythmia (Complete heart block) secondary to an inferior ST elevation myocardial infarction (STEMI)’. We apologise for the error.