TAN TOCK SENG HOSPITAL

MEDICAL DIGEST

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

FROM THE EDITOR

In my years of service, I have seen many doctors in leadership positions; some are good, many are bad. In this open letter to all medical leaders, I want to make a plea to all medical leaders to better tthemselves, so that life becomes better for everyone.

Dear Medical Leader

1) You are leading a group of colleagues. You will probably not be the best clinician or even the smartest person in your team (because that person would have dodged the leadership position!). Therefore treat everyone with respect and don't even think of pulling a fast one.
2) You must make sure you end up on the right side of history. In a position of power, it is easy to cajole people to do things to benefit only a small group of people. When you need to choose between the right way and the iffy way, always choose the right way. When you need to choose to be perfectly honest or to hedge the issue, well, you know my recommendation. History will judge you. Long before that, your subordinates would have judged you.
3) Your reward is the success of your unit. Because of your good work, it is right and natural that your subordinate may become better known for a specific skill than you. Do not begrudge your subordinates' success.
4) You do not have to love your subordinates. You don't even have to support them. But do not obstruct them without their knowledge. You can stunt the growth of your discipline or alter someone's career for the worse with a few lousy decisions. Be objective and work for the future, even the distant future.
5) You cannot tread water. Even if you have inherited the perfect unit, the world will move and the world will move and will render your team irrelevant. You must do your homework. You must set the pace and the tone. Leading doesn't stop when you end your day at work; you must keep thinking how you can make your team better. You must lead with your very fibre. If you do anything less, you're letting your team down.
6) You must take responsibility for any bad that comes out of your unit. You may argue, how am I to know what my employee is doing in a project that I have never heard of? Well, as a leader, you should jolly well set up a system to know everything well in advance.
7) You must be courageous and stick to your convictions. In times of stress or uncertainty, your staff will look to you. For heaven's sake, do not shirk responsibility or *tai-chi* blame. Rise to the occasion and chart the course. Of course, you risk your reputation and your bonus.
8) The financial bottom line is important, but it is not the only thing, and is often not the top one either. You need to work with those people known as administrators for the sake of your unit. Administrators are intelligent people (no kidding) who are actually on our side, if we learn to speak their language and see their concerns.
9) You must know when to say that you are wrong, when to listen to advice, and when to change course. Making small mistakes along the way to a clear destination is no big deal. Just make sure the destination is right.

There you have it! Now, that one guy who reports to me will use this against me.

Dr Leong Khai Pang
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Medical Digest

MEDICAL DIGEST

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TTSH RESEARCH NEWS

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

RESEARCH EXCERPT 1

Medical and psychosocial factors associated with antibiotic prescribing in primary care: survey questionnaire and factor analysis

Lee TH, Wong JG, Lye DC, Chen MI, Loh VW, Leo YS, Lee LK, Chow AL. Br J Gen Pract. 2017; 67(656):e168-e177.

A survey questionnaire was developed and sent to general practitioners (GPs) in private practice and polyclinics between 2012 and 2015. It elucidates the knowledge, attitudes and practices with regard to antibiotic use in acute upper respiratory infection (AURI) in the primary care setting.

Among 427 responses, 351 (82.2%) were from GPs working in private practice. We found that 58.4% of GPs in the private versus 72.4% of those in the public sector recognised that >80% of AURIs are caused by viruses (p=0.02). The majority of GPs (353/427; 82.7%) felt that antibiotics are overprescribed in primary care. Significant factors associated with low antibiotic prescribing were good medical knowledge and clinical competency (adjusted odds ratio [aOR] 3.2, 95% confidence interval [CI] 2.4 to 4.3), good clinical practice (aOR 2.7, 95% CI 2.0 to 3.6), availability of diagnostic tests (aOR 1.4, 95% CI 1.1 to 1.8), and desire to improve clinical practice (aOR 1.5, 95% CI 1.2 to 1.9). The conservative practice of giving antibiotics 'to be on the safe side' is significantly less likely to be associated with low antibiotic prescribing (aOR 0.7, 95% CI 0.5 to 0.9).

IMPORTANCE IN CLINICAL PRACTICE

It is known that antibiotics are overprescribed in primary care and bacterial drug resistance is one of the most pressing issues today. So far there have been no studies in Singapore examining the factors affecting antibiotic prescribing for AURIs among primary care physicians. This study found that good medical knowledge and clinical practice, together with availability of diagnostic tools and GPs' desire to improve clinical practice, are important factors in reducing antibiotic prescribing. These findings will help guide future studies and interventions on antimicrobial stewardship in the primary care setting.

This summary was prepared by Dr Lee Tau Hong, a consultant in the Department of Infectious Diseases, Tan Tock Seng Hospital.

RESEARCH EXCERPT 2

Assessing changes in knowledge, attitude and practices on dengue diagnosis and management among primary care physicians after the largest dengue epidemic in Singapore

Pang J, Hildon ZJ, Thein TL, Jin J, Leo YS. BMC Infect Dis 2017;17(1):428.

This is a comparative cross-sectional study which evaluates the changes in knowledge, attitude and practices on dengue diagnosis and management among primary care physicians before and after the largest dengue outbreak in Singapore in 2013. Survey data were collected in 2011 and 2014 by postal mail. The questionnaire was designed to collect four types of information: (1) practitioner demographics (gender, age, type of practice and qualification); (2) dengue management – including related knowledge, dengue diagnostic practices and clinical care; (3) attitudes toward dengue point-of-care test kits; and (4) responses to the dengue epidemic. We found that primary care physicians have good knowledge on dengue management before and after the largest dengue outbreak in 2013. However, the usage of dengue diagnosis tests for confirmation such as dengue serology, dengue NS1 assay and dengue PCR was significantly lower in 2011 (30%) than 2014 (56%). Since the introduction of dengue duo point-of-care kit, we found that about 40% of primary care physicians used the kit in 2014, and it was significantly associated with the change in behaviour of using dengue diagnostic tests to confirm dengue. We also observed that there was a significant reduction in referral of dengue patients to hospital. This trend is likely due to the high level of knowledge and confidence in dengue management reflected by the significant increase in the use of dengue diagnostic tests in the primary healthcare setting.

This summary was prepared by Assistant Professor Pang Junxiong Vincent, director at the Centre for Infectious Disease Epidemiology & Research, Saw Swee Hock School of Public Health. Prof Pang was formerly a senior research fellow at the Institute of Infectious Diseases and Epidemiology, Communicable Disease Centre, Tan Tock Seng Hospital.

IMPORTANCE IN CLINICAL PRACTICE

Early dengue diagnosis is key to prevent severe disease progression. Hence, the knowledge, attitudes and practices of dengue management, including diagnosis, among primary care physicians are critical in reducing dengue transmission and burden. This study is important because it assesses the adequacy and gaps in best practices for dengue clinical management among doctors in the primary healthcare setting. We found an increasing level of acceptance and usage of the dengue point-of-care test kits among primary care doctors to facilitate early diagnosis of dengue. This will not only provide them more confidence in the clinical management of patients, but also a reduction in referral to hospitals. Furthermore, the likelihood of picking up a new dengue hotspot in the community will be increased.

RESEARCH EXCERPT 3

Dietary and fluid restriction perceptions of patients undergoing haemodialysis: an exploratory study

Hong LI, Wang W, Chan EY, Mohamed F, Chen HC. J Clinical Nurse 2017, 26(21-22): 3664-76.

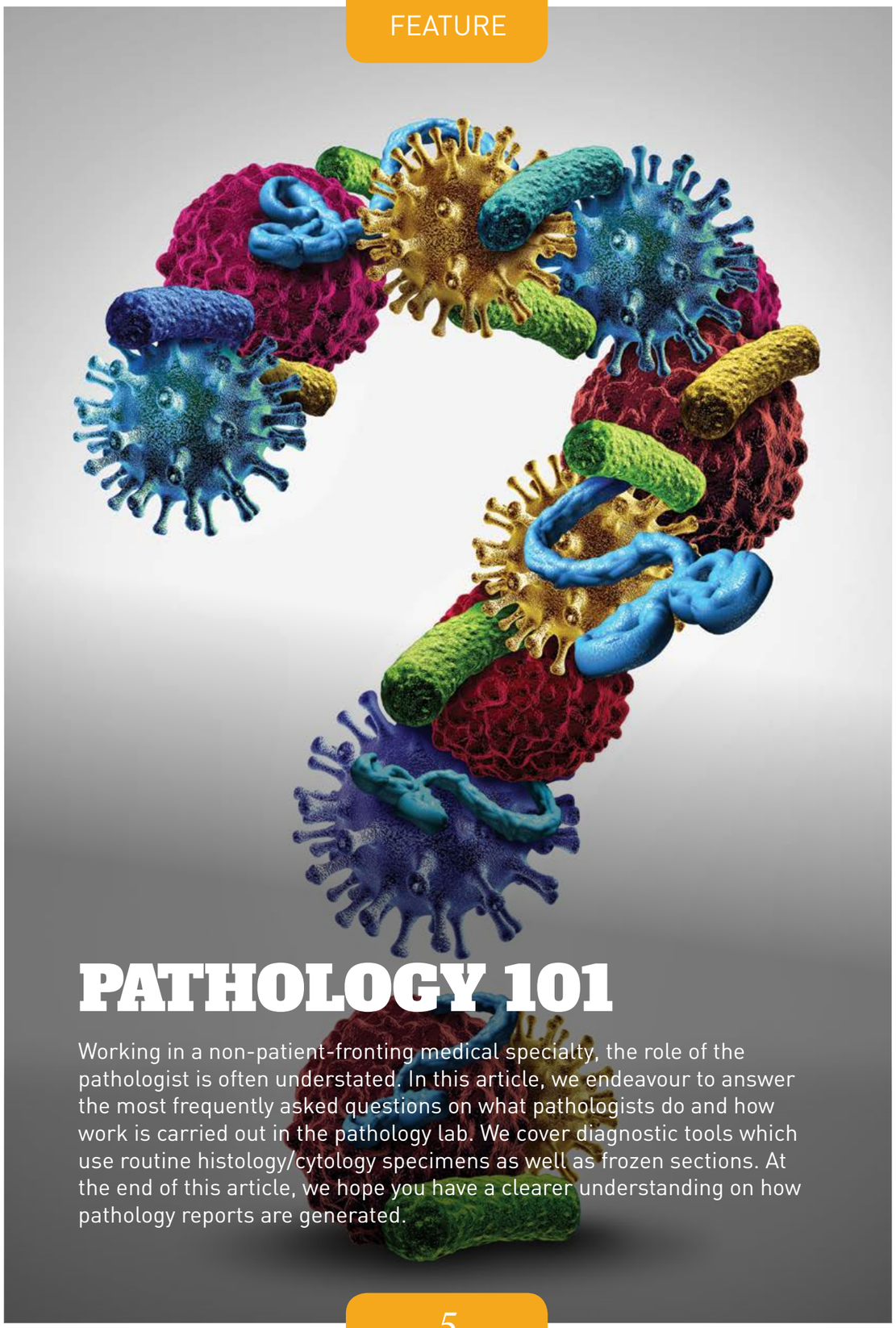
A hermeneutics phenomenological research perspective with an exploratory qualitative approach was used to explore the perspectives of haemodialysis patients on their recommended dietary and fluid restriction in Singapore. Fourteen participants of both genders and various ethnic groups were recruited via purposive sampling. Four themes, namely, pessimism, existential struggles, perceived quality of support, and immensity of self-discipline emerged from the data set. The first theme, pessimism, is reflective of an enduring dissenting attitude towards the restrictions. The second theme, existential struggle, highlights the underlying struggles and temptations experienced by renal patients on a daily basis. The third theme, perceived quality of support, demonstrates the significance of support, both social and healthcare-associated. The last theme, immensity of self-discipline, explains the techniques used by renal patients in managing their imposed restrictions.

IMPORTANCE IN CLINICAL PRACTICE

End-stage renal disease is becoming a common problem because of an ageing population and high prevalence of hypertension and diabetes mellitus. The dietary and fluid restriction with haemodialysis therapy remains a major problem worldwide that inadvertently lowers the patient's quality of life. This study highlights the hidden suffering and anguish experienced by renal patients due to the imposed restrictions. Renal patients are generally nonchalant or submissive towards their dietary and fluid restrictions. We believe that this information will streamline existing nursing care, institutional policies and dietary education to sustain consistent dietary and fluid adherence behaviours. The garnering of family support should also be encouraged to ensure a positive adherent patient behaviour over time.

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

This summary was prepared by Staff Nurse Isabella Hong in Ward 9A, Tan Tock Seng Hospital, and Senior Lecturer Chen Hui-Chen from Alice Lee Centre for Nursing Studies, National University of Singapore.



PATHOLOGY 101

Working in a non-patient-fronting medical specialty, the role of the pathologist is often understated. In this article, we endeavour to answer the most frequently asked questions on what pathologists do and how work is carried out in the pathology lab. We cover diagnostic tools which use routine histology/cytology specimens as well as frozen sections. At the end of this article, we hope you have a clearer understanding on how pathology reports are generated.

Histology/cytology

1. What do you do with the specimens once they leave the operating theatre (OT), endoscopy suite or clinic?

Once the pathology lab receives the specimen, the staff registers it by assigning a requisition number and creating a unique case number in the electronic reporting system.

After the administrative processing is complete, the specimen is kept in a fixative solution, if not already done so in the OT/endoscopy suite/clinic. In our department, the preferred fixative solution is 10% neutral buffered formalin. Depending on the nature of the specimen, fixation time ranges from several hours to a day. For example, a radical prostatectomy specimen will typically require at least 12 hours of formalin fixation while small pieces of tissue from biopsies will require a shorter time.

Tissue containing calcium, such as bones or calcified tumours, must undergo calcium removal in an additional process called decalcification. If not done, such tissues cannot be optimally embedded andthinly cut for microscopy slide preparation. This decalcification process can only be performed after the tissue is adequately fixed and may take several days depending on the size of the specimen.

After the specimen is fixed, depending on its nature and complexity, a pathologist or a medical technologist will assess it macroscopically for the presence and the extent of any lesions or tumours. Following the established protocols recommended by the College of American Pathologists (CAP), in the process called trimming (or grossing), the pathologist will cut the specimen into 2–4 mm-thick sections that will be placed into special cassettes. This is a critical process as any tumour, lesion, anatomical structure and surgical resection margin must be correctly identified. The pathologist may engage the help of the surgeon to assist with the specimen orientation, margin identification or to provide other relevant information.

The next steps is performed by trained medical technologists. In a multistep automated process, water from the obtained sections is removed by alcohol-containing solutions in the process of dehydration. After this, any excess alcohol will be removed in the process of clearing and subsequently, paraffin blocks will be made by infusing the tissue with paraffin wax. The paraffin holds the tissue into blocks to allow thinner sections to be made.

Before the pathologist receives the glass slides, the final steps of microtomy and staining are carried out.

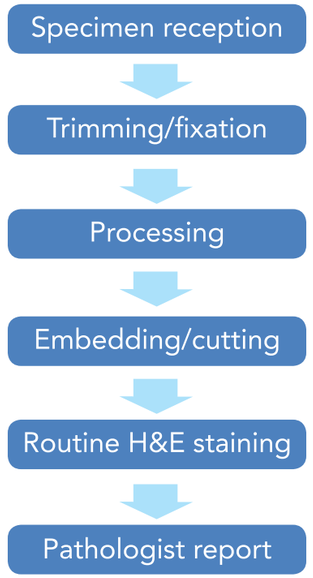


Figure 1. Summary of the work process for routine specimens.

Microtomy involves cutting the obtained tissue blocks into sections 3–4 microns thick, mounting these on glass slides and staining with haematoxylin and eosin (H&E staining). These slides are viewed by an assigned pathologist who generates the final pathology report in the electronic medical records system. The specimen processing is summarised in figure 1.

2. How long do I have to wait for the report?

The entire process delineated above takes at least two working days for non-complex and biopsy specimens. However, a delay in reporting may sometimes happen. The reasons include specimens that need to undergo further fixation or decalcification, or those that require deeper sections or additional studies such as special and immunohistochemical stains (see question 3). In some cases, a preliminary report may be generated by the pathologist, to be followed by an addendum after all the remaining results are obtained. For urgent requests, the pathologist tries to issue a report or notify the clinician verbally within 24 hours.

3. What information does the pathologist need for specimen submission? Why do you need so much information?

Think of a pathology request as a blue letter referral (especially for small samples and biopsies). A good clinical history together with specific questions that you would like answered from the biopsy would be extremely helpful (not a 'copy and paste' of the nutritional information or the patient's diet).

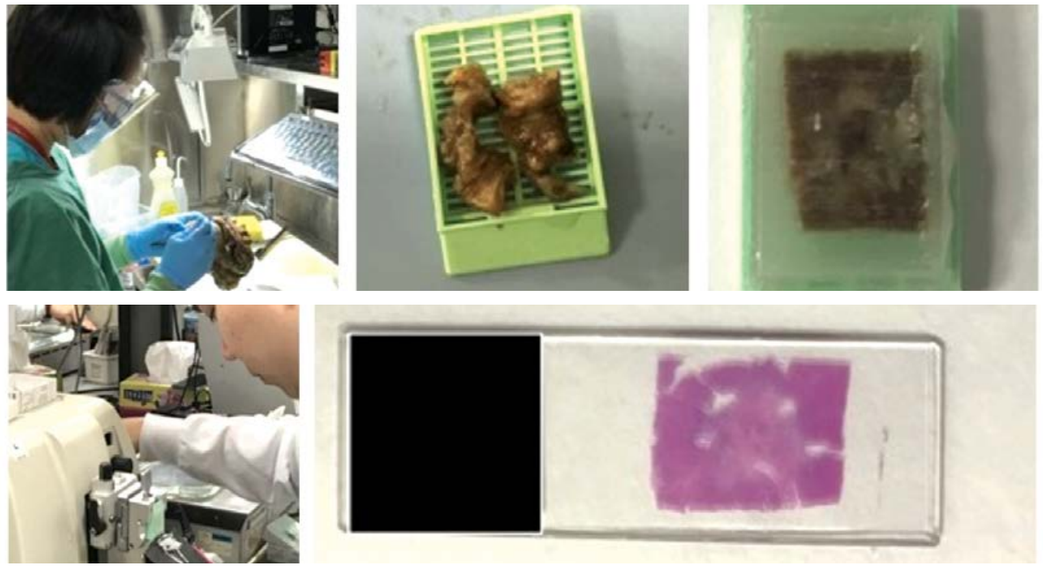


Figure 2. Images depicting each step of specimen processing. Top row, left to right: examining and trimming the specimen; cassette with the specimen section; paraffin block after tissue processing. Bottom row, left to right: microtomy; microscopy slide.

If you are sending a large resection specimen and there is an area of concern such as small structures adherent to the specimen, marking out the areas with a suture and indicating on the form what these areas are and why you are concerned is helpful. It may be useful to orientate large specimens or important margins with the use of sutures. Structures on the specimens are difficult to identify especially if they have been burnt or are very tiny. Specimens also look very different in-situ and after being fixed in formalin.

If the pathologist has queries about the specimen, he or she may call the referring clinician for clarification, so punting the call off to a junior team member who may not have sufficient understanding of the surgery or the patient is not a good idea. Do not worry you will get too many calls because pathologists are not the most social people and do not have much free time (contrary to popular myths).

4. Why can't the pathologist come up with a definitive answer?

As the human body has a limited repertoire when responding to insults, and a biopsy only represents a snapshot of the whole dynamics of the patient's condition, the histology patterns can often appear very similar. This is more pertinent to biopsies originating from the internal medicine disciplines (such as liver, renal, or dermatology specimens) where clinical correlation is essential to establish a diagnosis.

If the result is not definitive, it is important to go back to the patient history to correlate with the clinical, laboratory and imaging findings. Reaching a definitive diagnosis based on small amounts of tissue may not always be possible (or advisable) and sometimes a repeat biopsy may be necessary.

5. What does it mean if additional tests are being performed?

Additional tests may be done due to several reasons, ranging from the pathologist needing to re-gross or sample more tissue from large complex specimens, to cut additional sections from the tissue block to study deeper levels, to having special stains, immunohistochemical stains or molecular tests performed on the specimen.

For junior clinicians calling to trace results on behalf of the team, please have the patient's identifiers and pertinent clinical information ready (especially the reason why the biopsy was carried out) so that the additional data may be exchanged in one sitting.

6. What are special stains or immunohistochemical stains?

Special stains are histochemical stains such as Gomori Methenamine-Silver (GMS) or Ziehl-Neelson (ZN) stains for infectious organisms (figure 3) and reticulin for collagen fibres.

Immunohistochemical stains on the other hand are colloquially called the "brown" stains because of the colour they impart on the slides. These stains require more specialised tools and techniques to perform

which translates into a longer processing time compared to regular H&E staining or the other special stains. They basically work on the principle of antigen-antibody binding. Some examples are CK7, CK20, TTF-1 (figure 4), and ER/PR/HER-2.

7. What is the difference between histology and cytology?

Histology is the examination of the solid tissue which allows us to examine both the architecture and morphology of the cells. Cytology, as the term suggests, is the examination of liquid specimens where we study mainly the cell morphology and to a lesser extent the architecture.

8. Which is superior – histology or cytology?

Both have their benefits and limitations.

The main benefit of histology is the ability to examine the architecture of the disease process better and the availability of spare tissue that can be used to perform additional tests such as staining.

Cytology specimens are simple to collect (e.g. urine and sputum) but may have limited utility. For example, we cannot determine invasion of a capsule based on a cytology specimen. In some instances like effusions, we can turn a cytology specimen into a type of histology specimen by performing a cell-block, which then allows us to perform staining on them. However, this is limited by the quantum of material available as well as the disease process in question.

9. Can we submit cytology specimens the same way as histology?

No. The preparation methods are very different. For cytology specimens, specimen bottles should be sent to us or the central lab as soon as possible, within 2 hours of collection. If delay is anticipated, the sample must be refrigerated at 4 °C. If a fixative is needed, it can be obtained from the lab. An example is Shandon™ Cytospin™ Collection Fluid, a methanol-based fixative which allows us to prepare alcohol- or air-dried slides and cell blocks if necessary. Note that this fixative is different from the one used in histology (refer to question 1).

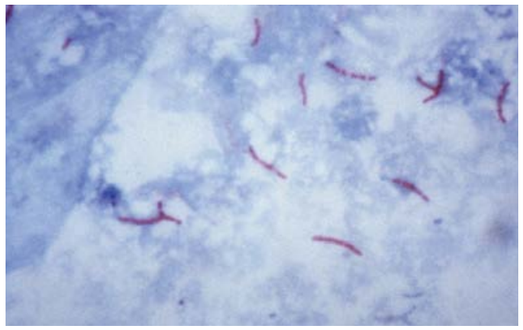


Figure 3. Ziehl-Neelsen stain for acid fast bacteria e.g. tuberculosis.

10. How much tissue is needed for cytology?

Again, the more the merrier (at least 50 ml), especially if we need to perform a cell-block, that is, converting the cytology specimen into a semi-histology like specimen which would allow us to run additional tests. Exceptions to large volume collection do apply, such as for cerebrospinal fluid.

For large amounts of accumulated fluids, such as fluid from drainage containers, collect 50 ml of the sediment from the bottom of the container. Cells tend to settle to the bottom hence the sediment provides a good yield of cells for us to examine.

We provide on-site assessment of specimen adequacy for fine needle aspirations and on-site help with preparation of slides (performed by our cytotechnicians) but a request or booking needs to be made beforehand. This on-site technical assessment is only available at Clinics 1B (ENT), Diagnostic Radiology (Ultrasound Suite) and Endoscopy as these locations have the appropriate safety equipment, in particular biosafety cabinets and fume hoods, which are required to perform the assessment.

Frozen section

1.Why was the frozen section (FS) method introduced?

The earliest description of the FS technique, also known as cryosection, for diagnosis dates back to 1892. Dr Wilson, one of the earliest pathologists employed under the Mayo brothers in the centre that now carries their names, refined and developed the technique for intraoperative diagnosis. He froze the tissue outside his window (-29 °C) in winter and used methylene blue dye to stain the tissues. The FS procedure allows rapid microscopic analysis of a specimen, which is useful for margin control during surgery.

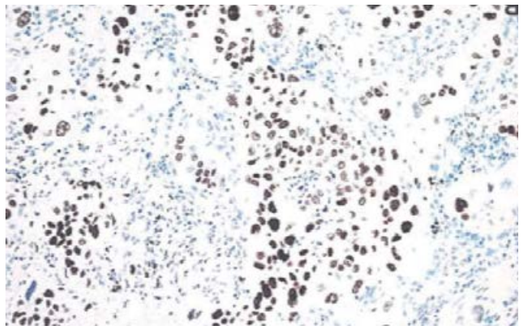


Figure 4. TTF-1 stain in a lung adenocarcinoma.

Figure 5. The Cryostat Microtome, where the specimen is frozen and shaved.

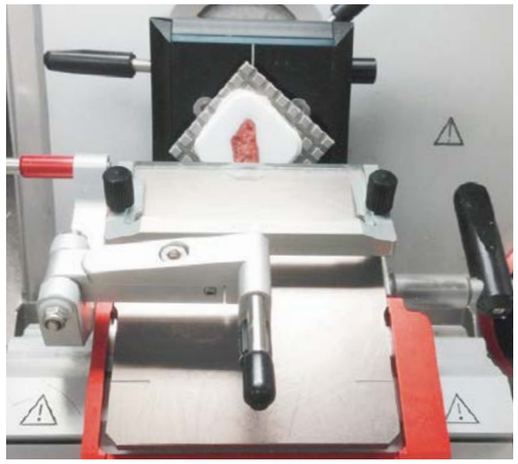


Figure 6. Using the microtome to shave the specimen.

2. What are the more common indications for FS that we see in our lab?

Frequently, we see sentinel lymph node biopsies from patients undergoing mastectomies for breast cancer. This will determine if an axillary lymph node clearance needs to be performed at the same time as the mastectomy. Other frequent FS requests are those that require histological diagnosis to guide the surgical procedure, for example intraoperative brain tumour biopsies, and the sampling of margins for skin and ENT cancers to ensure adequate resection.

3. Who is involved during the FS procedure?

A minimum of two members of the pathology department are needed for the running of the FS lab – a laboratory technician to receive and process the specimen in question, and a pathologist to take appropriate sections of the specimen and report the findings.

4. What materials are needed for submitting a specimen for FS?

Every submission requires the specimen to be placed in a container or specimen bag affixed with the relevant patient identifiers, along with a histopathological request form with the patient's details, relevant medical history and indications for FS.

5. What happens after a specimen is received in the FS room?

The laboratory technician will receive the specimen and issue a receipt before informing the pathologist on FS duty of its arrival. The process is similar to that of routine specimens except it is very much truncated. The pathologist takes a section of the specimen and hands it over to the laboratory technician who will then freeze the tissue in a cryostat machine (figure 5). This forms a block which will be sliced, mounted and stained on a glass slide. Most commonly, the H&E stain is used as the stain of choice. Cytology smears can be quickly performed during this period if required.

6. What does it mean when the technician says that the FS specimen is still being processed?

The multi-stage processes involved following the receipt of the specimen is labour-intensive and time-consuming. The cases that require only a single block or chuck would take up to 20 minutes from receipt to the issuing of the diagnosis. If two specimens or bottles are submitted consecutively, this will take another 20 minutes as there are no shortcuts to the time taken to process a second specimen.

7. What happens to the specimen after it has been reported in FS?

The frozen specimen will be thawed and placed in a formalin solution overnight to achieve fixation. The subsequent paraffin block is shaved (figure 6) and prepared as a slide (figure 7) for the next reporting pathologist to confirm the frozen findings, which will take place a few days later. For larger specimens, the remnant of the specimen will be processed the same way as routine specimens.

8. What does it mean when the diagnosis is "deferred" and when does this occur?

This means that we are unable to give a definitive diagnosis on the FS. This usually occurs when we are limited by the tissue sample provided, for instance, too little tissue, too many artefacts or if it mainly bony tissue. The diagnosis is also deferred if additional work-up is required. For example, differentiating between a thyroid follicular adenoma versus a follicular carcinoma requires thorough sampling while diagnosing

a poorly differentiated tumour requires special or immunohistochemical stains (figure 8).

9. What advice do you have for surgeons to facilitate the FS reporting process?

Think of it like a blue letter as mentioned previously (which it technically is) but with a very specific question in mind (unfortunately due to the time and technical constraints during FS we cannot answer all 20 questions).

Based on the question you have, please provide all the relevant information, especially the intraoperative findings. Ample good-quality samples always make it easier: more is better (if feasible), tone down on the cautery, do not crush the tissue, and please do not send surgical staples.

Please let us know if the patient has an infectious disease as we need to decontaminate our cryostats after that case. This means that logistically we would have to plan the rest of the frozen sections carefully as we will be short of one cryostat machine!

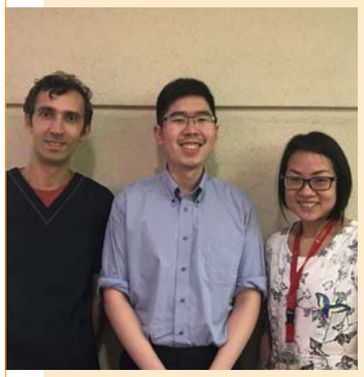
We want to give you the answer as soon as possible but if you are sending multiple specimens or a sample with many pieces, please note that it will take more time. On busy days, we receive specimens from different operating theatres, hence your request could be put in a queue. Repeated telephone calls to the FS room only delays the process as the pathologist or the technician will have to stop their work to respond.

10. Where can I find more information on the pathology lab?

Contact us for the Pathology service guide at 6357 8976 or the direct line of the pathologist reporting your case.

Figure 7. Mounting the specimen onto the slide.

Figure 8. Linear stainer machine for H&E staining.



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SARCOPENIA IN THE ELDERLY: WHAT IS ITS IMPACT AND WHY IS IT IMPORTANT TO KNOW?

Falls, delirium, urinary incontinence and functional decline – these are the common geriatric syndromes that we encounter. In the last two decades, there has been emerging literature on two linked conditions – frailty and sarcopenia – which have been touted to be 'new' geriatric syndromes. In this article, we look at sarcopenia, its significance and how clinicians can manage it.

What is sarcopenia?

In 1989, Irwin Rosenberg surmised "there is probably no decline in structure and function more dramatic than the decline in lean body mass or muscle mass over the decades of life" and coined the term 'sarcopenia' to describe this state. 'Sarcopenia' comes from two Greek words, sarx meaning 'flesh' and penia meaning 'loss'. The term 'loss of flesh' very descriptively and accurately summarises the essence of sarcopenia.

Sarcopenia refers to age-related loss of muscle mass, muscle strength and physical performance. Like other geriatric syndromes, sarcopenia is related to ageing and its prevalence increases as one gets older. There was initial debate about whether this age-related muscle loss is a physiological process that occurs naturally with ageing and whether it is amenable to any type of intervention. The current consensus is that sarcopenia is a clinical entity that can be diagnosed and can be prevented or intervened. To understand sarcopenia, we also need to differentiate between the three linked, yet different, factors that contribute to sarcopenia – muscle mass, muscle strength and physical performance.

Muscle mass refers to skeletal muscle mass. Skeletal muscle is under voluntary control and is important for movement and maintaining posture. Studies have found that absolute skeletal muscle mass decreases after the fifth decade of life, especially in the lower body. This decrease in skeletal muscle is significant – approximately 1.9 kg per decade in men and 1.1 kg per decade in women, which translates to about 8% per decade. After the age of 70, this loss accelerates to 15% per decade. *Muscle strength*, similar to skeletal muscle mass, peaks in the 20s and 30s and plateaus until the fourth decade where it then starts to decline at a rate of 8 to 10% per decade. There may be little significance looking purely at muscle mass or muscle strength if their impact on one's function is not examined. Therefore, *physical performance* measures are also examined in sarcopenia. These measures look at physical tasks such as gait speed and balance skills. We will further expound on how to measure these factors later on in the article when we explore the different diagnostic tools.

Why is sarcopenia important?

Sarcopenia is important for a few reasons. First, it has been found to be a common condition in the elderly, both internationally and locally. Second, like other geriatric syndromes, it is associated with multiple adverse outcomes. Therefore, if appropriate interventions are put in place to prevent or treat sarcopenia, a large part of our elderly population can benefit and morbidity can potentially be reduced significantly.

The prevalence of sarcopenia varies depending on the diagnostic tool used, the setting and the population. International statistics reveal prevalence rates ranging from 1 to 29% in community-dwelling older adults, 14 to 33% in long-term care populations and 10% in acute hospital care populations. It is estimated that a 10.5% reduction of the prevalence of sarcopenia could lead to a reduction of healthcare costs by 1.1 billion US dollars per year in the United States.

A local study determined that the prevalence of sarcopenia in community-dwelling older adults to be 24.8% in women and 25.4% in men. This is a surprising statistic, given that these are the elderly living in the community, who are usually deemed to be more physically well and active compared to those in long-term care settings. Another local study that looked at elderly attending medical outpatient specialist clinics found that 44.3% of them were sarcopenic. Not insignificantly, 27.0% were found to be frail.

Sarcopenia has been found to be associated with multiple adverse outcomes such as falls, fractures, disability, poor quality of life, and higher healthcare expenditure, amongst others. While causality cannot be assumed, there are compelling biological explanations linking sarcopenia to some of these adverse outcomes. One example is the link between sarcopenia and falls: patients with sarcopenia have decreased muscle strength, which can cause falls, leading to fractures and disability.

What causes sarcopenia?

The pathophysiology of sarcopenia is not completely understood at the current moment. However, it is recognised that sarcopenia is multi-factorial in origin, contributed by genetic, physiological and environmental factors.

Skeletal muscle is divided into type I and type II fibres. Type I fibres are known as the slow twitch fibres. They have a greater density of mitochondria, capillaries and myoglobin content. Type II fibres are known as fast twitch fibres. They have a higher glycolytic potential, lower oxidative capacity and faster response compared to the type I fibres. With age, there is muscle atrophy. Sarcopenia is characterised by the predominant atrophy of type II fibres, contributing to loss of muscle strength and power. While the exact molecular and cellular mechanisms underlying this are still unclear, some mechanisms have been postulated.

Age-associated hormonal declines likely contribute to muscle wasting by disturbing the balance between the anabolic and catabolic states for optimal muscle protein metabolism. Testosterone level in men is significantly associated with muscle mass and muscle function.

Testosterone concentration declines at a rate of 1% a year after the age of 30. Growth hormone promotes fusion of muscle precursor cells into myotubes and insulin-like growth factor 1 (IGF-1) regulates bone and muscle growth. Growth hormone and IGF-1 levels decrease with age and contribute to muscle wasting. Other hormones involved in muscle metabolism associated with sarcopenia include corticosteroids and insulin.

Ageing is also associated with a significant rise in serum levels of inflammatory markers. This state of chronic low-grade inflammatory state has been termed 'inflammaging' based on the related concept of immunosenescence. There is increased circulating levels of tumour necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6) and C-reactive protein (CRP) seen in the elderly. These cytokines cause muscle catabolism and anabolic resistance, thus contributing to muscle atrophy and sarcopenia.

There is a strong link between heritability and muscle mass and muscle strength. Studies have reported the role of heritability ranging from 30 to 85% for muscle strength and 45 to 90% for muscle mass. These genes are involved in synaptic function and neural maintenance, structure and function of skeletal muscle fibres, and muscle metabolism.

Exogenous factors also play a part in sarcopenia. Malnutrition is a very common problem in the elderly. Due to various physiological and pathological reasons, the older adult tends to eat less food and less nutritiously. This reduction of food intake with age, also known as anorexia of ageing, leads to poorer muscle health. Protein intake also needs to be adequate to maintain nitrogen balance, with the recommendation being at least 1.2 g/kg of body weight.

Last but not least, reduced physical activity in the older adult also contributes to muscle atrophy. Both acute and prolonged resistance exercise stimulates the proliferation of satellite cells in healthy subjects. Satellite cells then differentiate and form new myofibres. In healthy older adults, 10 days of bed rest has been shown to result in a substantial loss of lower extremity strength, power and aerobic capacity. Elderly are more prone to periods of immobility due to acute illnesses on top of their existing co-morbidities, which make their likelihood of developing muscle deconditioning from inactivity even higher. Even two to three weeks of reduced number of steps taken in walking may cause reductions in muscle strength and quality, therefore any reduction in physical activity in the elderly can be detrimental for muscle health.

How is sarcopenia diagnosed?

There are several consensus definitions put up by various workgroups around the world, but none has been unanimously agreed on to be used as the gold standard reference. Despite the differences, a majority of them utilise similar principles in their definitions (table 1).

First, there needs to be a measure of muscle mass. Computed tomography (CT) and magnetic resonance imaging (MRI) scans are considered the gold standard for muscle mass assessment. They provide anatomical details and can be used to assess skeletal muscle volume. They allow calculation of segmental and total muscle mass and assessment of fat infiltration in the muscle, which is important in the evaluation of sarcopenic obesity. However, they are costly and difficult to access, thus making them challenging for use in the clinical setting. Alternatives include using dual-energy X-ray absorptiometry (DEXA) and bioelectrical impedance analysis (BIA), both of which have been shown to be well correlated to the gold standard measurements. DEXA uses the relative attenuation of two different energy X-rays to derive a three-component model of body composition, comprising fat, bone mineral and lean tissue. Though less costly than CT and MRI, DEXA is still relatively expensive and requires specialised and trained personnel. BIA involves measuring the impedance of a small AC electric current as it passes through the body. It estimates the total muscle mass, which is the largest water-rich tissue in the body. BIA has many advantages over the other techniques of measuring muscle mass. It is portable, easy to perform at the bedside, much less costly, and does not require skilled staff. However, BIA is less reliable as it is sensitive to the hydration status and to recent activity. It should be considered more of a

	ASMI, kg/m^2		GS, kg		WS, m/s	
	Men	Women	Men	Women	Men	Women
AWGS	<7.0	<5.4	<26	<18	<0.8	
EWGSOP	<6.52	<5.44	≤28	≤18	<0.8	
IWGS	<7.23	<5.67	-	-	<1	

ASMI, Appendicular Skeletal Mass Index; AWGS, Asian Working Group on Sarcopenia; EWGSOP, European Working Group on Sarcopenia in Older People; GS, grip strength; IWGS, International Working Group on Sarcopenia; WS, walking speed.

Table 1. Comparison of the different definitions of sarcopenia.

Component	Question	Scoring
Strength	How much difficulty do you have in lifting and carrying 10 pounds?	None = 0 Some = 1 A lot or unable = 2
Assistance in walking	How much difficulty do you have walking across a room?	None = 0 Some = 1 A lot, use aids, or unable = 2
Rise from a chair	How much difficulty do you have transferring from a chair or bed?	None = 0 Some = 1 A lot or unable without help = 2
Climb stairs	How much difficulty do you have climbing a flight of 10 stairs?	None = 0 Some = 1 A lot or unable = 2
Falls	How many times have you fallen in the past year?	None = 0 1–3 falls = 1 4 or more falls = 2

Table 2. SARC-F screening test for sarcopenia. Reproduced with permission from Malmstrom TK, Morley JE. SARC-F: a simple questionnaire to rapidly diagnose sarcopenia. J Am Med Dir Assoc 2013;14:531.

surrogate measure of muscle mass, rather than a direct measure. Anthropometric measures such as mid-arm muscle circumference and calf circumference have also been used as a measure of muscle mass in some studies. Although they are simple to perform, they lack precision and are prone to over-estimation.

Most of the consensus definitions also require a measure of muscle strength and/or physical performance in addition to muscle mass. Hand grip strength, measured by a hand dynamometer, is the most commonly employed method to evaluate muscle strength. It is the recognised gold standard for measuring muscle strength. However, dynamometers are expensive and are not commonly found in healthcare setting. An alternative is to measure 1 repetition maximum strength (1-RM) such as knee flexion or extension using generic resistance type exercise equipment. This has been shown to correlate well with the gold standard dynamometry. However, the disadvantage is that the absolute value of 1-RM strength is not comparable between different sets of equipment.

Finally, physical performance measures are also included in some of the consensus definitions of sarcopenia. The most commonly used measure of physical performance is gait speed or walking speed over a short distance, usually 3 to 6 metres. The other tests include the 1) Short Physical Performance Battery (SPPB) which includes gait speed, time to rise from a chair five times and static balance tests; 2) Time Up and Go (TUG) test that measures the time to rise from chair, walk 3 meters and back; and 3) 6-minute walk test that measures the distance covered over 6 minutes. Timed usual gait has been shown to be highly predictive for the onset of disability and mortality.

Three of the more commonly used consensus definitions are presented in table 1. Which consensus definition should clinicians use? The first and most widely used definition is the European Working Group on Sarcopenia in Older People (EWGSOP) operational definition that came out in 2010. The following year, the International Working Group on Sarcopenia (IWGS) published a consensus similar to that of the EWGSOP. The challenge is applying these definitions in our Asian population where the cut-off values for the measurements of muscle mass, muscle strength and physical performance may differ compared to those in the Caucasians due to inherent differences in body size, body composition and lifestyles. To address this issue, sarcopenia experts from Asia established the Asian Working Group for Sarcopenia (AWGS), which published guidelines for diagnosing sarcopenia in 2014, using cut-off values based on relevant studies done in Asia.

In the clinical setting, such diagnostic methods are difficult to incorporate due to time and resource limitations. The five-item questionnaire SARC-F is a brief screening test that was developed based on cardinal features or consequences of sarcopenia. It has been shown to have good internal consistency and validity in predicting mortality and health outcomes. This tool could be used for screening in the community or in primary care, and individuals selected by these tools could be assessed in detail later (table 2).

How can we manage sarcopenia?

The two main strategies in the management of sarcopenia are maintaining adequate nutrition and physical activity.

Nutrition should be optimised by ensuring adequate amounts of macronutrients and micronutrients. Calories should be 24 to 36 kcal/kg per day and protein intake should be at minimum 1.0 g/kg body weight, up to 1.5 g spread over three meals. We should also ensure that vitamin D levels are replete. Practically, as clinicians, we should look out for older adults who are at risk of malnutrition and evaluate for any potentially reversible cause such as depression, constipation or poorly fitting dentures. We should also consider referring these at-risk patients to the dietician for dietary advice and nutritional supplementation.

While there are studies showing the efficacy of nutritional supplementation alone in the management of sarcopenia, the strongest evidence is in the combination of adequate nutrition and physical activity. Protein supplementation in combination with resistance training is conducive to improving muscle mass, muscle strength and physical performance, with the beneficial effects persisting for years. At present, the dose and type of exercise required for management of sarcopenia is unclear but most evidence point towards resistance exercise as the cornerstone for increasing muscle strength and physical performance.

Many of our elderly are physically inactive for various reasons. Even if they are active, only a very small minority of them engage in resistance exercises regularly. One of the considerations is to ensure that our elderly patients exercise in a safe environment with minimal risk of injury. As clinicians, we should encourage our elderly patients to keep an active lifestyle. To achieve an adequate dose of exercise and incorporate resistance exercise safely into the exercise regime, regular sessions at day-rehabilitation centres can be a very good option. In these centres, older adults can engage in individualised and graduated training programmes, under the supervision of therapists.

Thus far, no pharmacological treatment has been shown to be effective in the treatment of sarcopenia. Studies looking at ghrelin, espindolol and oestrogen based hormone replacement therapy have not revealed positive results. Testosterone has been proven to significantly increase lean body mass and fat-free mass but is of very little clinical use because of side effects, especially prostate cancer. Selective androgen receptor modulators are currently being studied as they are purported to have similar benefits to muscle cells but have fewer side effects. The evidence so far has been mixed but recent clinical trials have not detected any overall effect in reducing sarcopenia.

Conclusion

In summary, sarcopenia, together with frailty, are emerging as the next geriatric giants. Sarcopenia is prevalent and has been associated with multiple adverse outcomes. While there may not be one unifying consensus definition for sarcopenia at present, all of them similarly look at measures of muscle mass, muscle strength and physical performance. Currently, combining nutritional supplementation and exercise is the key to managing sarcopenia.

While there are studies showing the efficacy of nutritional supplementation alone in the management of sarcopenia, the strongest evidence is in the combination of adequate nutrition and physical activity.

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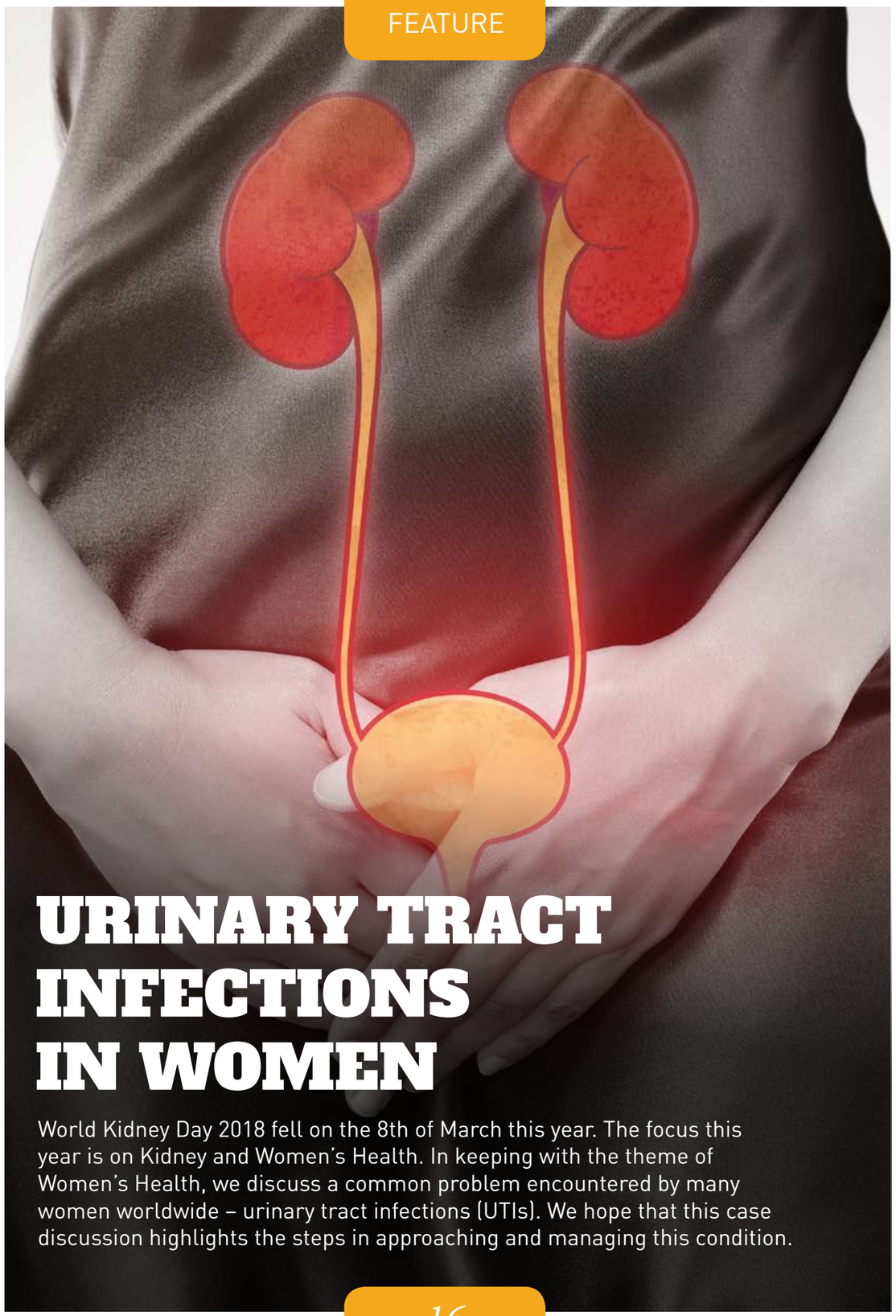

URINARY TRACT INFECTIONS IN WOMEN

World Kidney Day 2018 fell on the 8th of March this year. The focus this year is on Kidney and Women's Health. In keeping with the theme of Women's Health, we discuss a common problem encountered by many women worldwide – urinary tract infections (UTIs). We hope that this case discussion highlights the steps in approaching and managing this condition.

Case Scenario

Lilian is a 25-year-old Chinese lady who presented to her general practitioner with an increased frequency of micturition, dysuria and urgency for the past 2 days. She has no past medical or surgical history. She is recently married, and this is the first time she is experiencing such symptoms. She is diagnosed with cystitis and given a course of antibiotics.

What constitutes a UTI and why does it occur?

UTI is a collective term that describes any infection involving any part of the urinary tract, namely the kidneys, ureters, bladder, and urethra. The urinary tract can be broadly divided into the upper (kidneys and ureters) and lower tract (bladder and urethra). Cystitis (bladder infection) represents the majority of these infections.

There are four main routes of pathogen entry into the urinary tract, namely ascending infection, blood borne spread, lymphatic spread, and direct extension from other organs. The ascending route is the most common route in women. Typically, there may be contamination of the periurethral area with a uropathogen from the gut. There is subsequently colonisation of the urethra and migration of such organisms to the bladder. Colonisation and invasion of the bladder mucosa may occur, mediated by pili and adhesins. Further bacterial multiplication and damage by bacterial toxins and proteases occur, resulting in cystitis. Should there be further ascension to the kidneys and colonisation, pyelonephritis may develop.

Women are more likely to develop UTIs than men, with one study quoting a risk of up to 30 times in adult women. It is estimated that 20% of women aged 20–65 will experience at least one attack per year, and that approximately 50% of women will experience a UTI at least once in their life.[1] Several factors contribute to this phenomenon. Firstly, the urethra is shorter in women than in men, allowing bacteria to have a shorter distance to travel to the bladder. The urethra is also located closer to the rectum in women. Sexual intercourse may result in the introduction of bacteria from the genital region. The use of antibacterial vaginal douches, spermicides and oral antibiotics may also cause a change of vaginal bacteria. Lastly, menopause can cause a change in vaginal bacteria that may increase the risk of bacterial infection.

How does the patient present?

The presentation of a UTI depends mainly on whether it is an upper or lower tract infection. Our patient had an uncomplicated cystitis, which may manifest with dysuria, urinary frequency, urinary urgency, and suprapubic pain. Patients may also present with gross haematuria. In the elderly the diagnosis of cystitis can be more challenging, as symptoms of chronic dysuria or urinary incontinence may be present, which may not necessarily indicate a UTI.

It is important to consider other diagnoses should the clinical picture not be in keeping with a UTI. Symptoms of dysuria, frequency, urgency, suprapubic pain, and haematuria may be present in other conditions, for examples, vaginitis, urethritis or pelvic inflammatory disease. The presence of vaginal discharge or odour, pruritus or dyspareunia should prompt a consideration of vaginitis. The presence of dysuria and pyuria in the absence of bacteriuria may indicate the presence of urethritis. Lastly, the findings of mucopurulent endocervical discharge or cervical motion tenderness may indicate the presence of pelvic inflammatory disease.An uncomplicated cystitis typically does not present with fever. Should a patient present with fever, flank pain, costovertebral tenderness or other symptoms of a systemic illness, a diagnosis of pyelonephritis should be made. Patients may also present with nausea and vomiting. Symptoms of cystitis may or may not be present.

What is a complicated UTI?

Complicated UTIs occur when there are concomitant conditions that increase the rate of treatment failures, impair the host defence, or compromise the urinary tract. These can be broadly divided into structural, metabolic, hormonal or functional abnormalities. Structural causes could be calculi, renal cysts, or catheters. An example of a metabolic/hormonal cause is pregnancy. Functional causes include urinary obstruction and a neurogenic bladder. The management of a complicated UTI consists of appropriate antibiotics and urological intervention to remove or correct the predisposing cause where possible.

What organisms typically cause a UTI?

UTIs can be caused by both Gram-positive and Gram-negative organisms, and less commonly by fungi. The majority of infections are caused by Gram-negative organisms. The leading cause

in both uncomplicated and complicated UTIs is uropathogenic *Escherichia coli* (UPEC). For uncomplicated UTIs, *Klebsiella pneumoniae*, *Staphylococcus paprophyticus* and enterococcus species are other causative organisms. For complicated UTIs, enterococcus species, *Klebsiella pneumoniae* and *Candida* species are the other causative organisms.[2] These organisms typically possess virulence factors that enable them to cause a UTI. For example, UPEC have pili that allow them to adhere to the bladder epithelium. They are able to produce toxins and proteases that release nutrients from the host cells. The bacterium also adopts a filamentous morphology, rendering it more resistant to neutrophil killing than in its bacillary form. Knowledge of the typical causative organisms and their resistance pattern is important to guide empirical therapy of UTIs.

How should I confirm my diagnosis?

A properly collected urine specimen is essential in the evaluation of a UTI. A clean catch specimen aims to prevent bacteria from the skin of the genitalia from contaminating the specimen. Ideally, patients should be advised to spread the labia with one hand and cleanse from front to back with soaped swabs with the other hand, then pass a small amount of urine into the toilet, and finally urinate into the specimen cup. The patient's hands should be washed with soap before and after collection, and care should be taken to avoid touching the inside of the cup or the lid.

The diagnosis of uncomplicated cystitis can be made with an accurate history in a patient with no risk factors for a complicated UTI, and a routine urine culture is not necessary. A urine dipstick is convenient and cost effective as a diagnostic tool, making it an alternative to urinalysis and urine microscopy. It should be used to confirm the presence of urine leucocytes and nitrites. A positive urine leucocyte esterase test correlates well with pyuria, however it may be falsely negative with antibiotic therapy, glycosuria, proteinuria or with a low bacterial count. A positive urine nitrite test is a surrogate marker of bacteriuria. Nitrates in the urine are converted to nitrites in the presence of Gram-negative bacteria like *E. coli*. A negative test however does not exclude an infection, as there may be Gram-positive organisms causing the infection or the presence of dilute urine giving a false negative test. The test has a positive predictive value of 95% and a negative predictive value of 25–70%.

Urine microscopy can also be performed. Typically, pyuria is present in patients with a UTI. The presence of white cell casts may indicate kidney inflammation and pyelonephritis. The absence of pyuria in the presence of bacteriuria may indicate bacterial colonisation rather than true infection. Significant pyuria is defined as the presence of ≥10 white blood cells per cubic mm in a urine sample or a urine dipstick that is positive of leucocyte esterase.

A urine culture is indicated in patients with suspected acute pyelonephritis, patients whose symptoms do not resolve with appropriate treatment or recur within 2–4 weeks of completion of appropriate treatment, patients who present with atypical symptoms, and patients with risk factors for development of a complicated UTI. The presence of $>10^5$ CFU/ml in a clean catch specimen in the appropriate setting is suggestive of a UTI. The presence of $>10^3$ CFU/ml may still indicate a UTI in a patient, where the specimen is obtained during a cystoscopy or other invasive procedures.

My patient has bacteriuria without any symptoms suggestive of a UTI; what should I do?

Asymptomatic bacteriuria is defined by the 2005 Infectious Diseases Society of America (IDSA) guidelines[3] as the presence of two consecutive clean-catch voided specimens with isolation of the same organism in counts of $\geq 10^5$ CFU/ml. There is an absence of clinical signs or symptoms suggestive of a UTI. The frequency of asymptomatic bacteriuria increases with age.

Screening and treatment of asymptomatic bacteriuria is generally unnecessary except in special populations. The IDSA guidelines recommend that pregnant women should be screened for bacteriuria by urine culture at least once in early pregnancy, and should be treated if positive (Level A-1 evidence). The rationale is that bacteriuria in pregnancy increases the risk of pyelonephritis and has been associated with adverse outcomes, including preterm labour and low birth weight infants. Anti-microbial treatment has been associated with improved pregnancy outcomes, as well as reduced risk of development of pyelonephritis. In women undergoing genitourinary surgery where mucosal bleeding is anticipated, asymptomatic bacteriuria should also be treated. An example of such procedure is cystoscopy with or without manipulation or upper tract instrumentation.

My patient has sterile pyuria; what should I do?

Sterile pyuria is defined by the presence of >10 white cells per cubic mm in the urine in the absence of any bacteria, as determined by culture in the laboratory. Sterile pyuria is highly prevalent and has been stated to be as high as 13.9% in women and 2.6% in men in one study.[4] The most common cause of sterile pyuria is infection, including sexually transmitted infections, fungal infections and genitourinary tuberculosis. Inflammatory causes may also lead to sterile pyuria, such as interstitial nephritis due to chronic analgesic use. The combination of interstitial cystitis and painful bladder syndrome in women may need to be considered when sterile pyuria is found. Less commonly, renal stones, polycystic kidney disease and intrinsic renal disease may cause this presentation.

When should I refer the patient for further evaluation?

Most female patients with uncomplicated UTIs may be managed at the primary care level. Patients suffering from UTIs with the following features should be considered for referral for specialist opinion:

- Severe symptoms
- Failed medical therapy (documented)
- Evidence of retention (acute or chronic)
- Abnormalities documented on ultrasound or cytology, such as calculi or bladder tumours
- Recurrent UTIs (≥three in 12 months) with the following characteristics:
  - Presence of risk factors for complicated UTI
  - A surgically correctable cause is suspected
  - A diagnosis of recurrent UTI is uncertain for recurrent lower urinary tract symptoms
  - A complicated UTI is suspected, as such patients may benefit from a urological review and follow up.

How should I manage and treat a female patient with a UTI?

The management of a UTI can be broadly divided into non-pharmacological and pharmacological means. Non-pharmacological management of UTIs include maintaining a high fluid intake, ingestion of cranberry juice and eating yoghurt that contains lactobacillus cultures. However, the evidence for these interventions is still inconclusive.

Antibiotic use for the treatment of UTIs needs to be carefully considered. The use of appropriate antibiotics leads to significantly higher relief of symptoms and bacteriologic cure rates. It also allows for better prevention of reinfection in women with uncomplicated cystitis. However, the inappropriate use of antibiotics predisposes to antibiotic resistance.

The 2010 IDSA guidelines[5] on the treatment of acute uncomplicated cystitis and pyelonephritis in women made several recommendations for the use of antibiotics for the above mentioned conditions. For the treatment of acute uncomplicated cystitis, trimethoprim-sulfamethoxazole, nitrofurantoin, fosfomycin, and pivmecillinam were recommended (Level A-1 evidence). The considerations in the use of these antibiotics took into account the level of resistance as well as the propensity for collateral damage. Collateral damage was defined as the ecological adverse effects of antimicrobials. Trimethoprim-sulfamethoxazole (160/800 or one double strength tablet) was recommended to be dosed twice daily for 3 days, if local resistance rates for uropathogens causing acute uncomplicated cystitis did not exceed 20% or if the infecting strain was known to be susceptible. Nitrofurantoin monohydrate/macrocrystals (100 mg twice daily for 5 days) was deemed to be an appropriate choice due to low resistance rates and low collateral damage, and was comparable in terms of efficacy to 3 days of trimethoprim-sulfamethoxazole. Fosfomycin tromethanol (3 g in a single dose) was also deemed to be an appropriate choice. Pivmecillinam (400 mg twice a day for 3–7 days) was deemed to be an acceptable therapy when it was available, but it is less efficacious compared to other therapies. The fluoroquinolones are effective in three-day regimens, however, due to its high propensity for collateral damage, it was recommended to reserve this class of antibiotics for important uses other than acute cystitis. B-lactam agents in three- to seven-day regimens were assessed to be appropriate choices for therapy when other agents could not be used (Level B-1 evidence), noting that this class of drugs generally had a lower efficacy and more adverse effects than other classes.

The Singapore Ministry of Health Clinical Practice Guidelines (2006) on the use of antibiotics in adults recommended a three-day course of trimethoprim-sulfamethoxazole for the treatment of uncomplicated cystitis in women (Grade A, Level 1b). Alternatives are nitrofurantoin, B-lactam-lactamase-inhibitor combination, fluoroquinolones, trimethoprim, and first or second generation cephalosporins.

These Guidelines have been withdrawn (MOH Guidelines are considered withdrawn 5 years after publication), and have not been updated.

The management of acute pyelonephritis may differ from an acute cystitis. Acute pyelonephritis may potentially be managed on an outpatient basis, with admission being advocated for patients who may be severely ill, pregnant or elderly, or who may have co-morbidities whereby the infection may affect their overall care. In contrast to an acute uncomplicated cystitis, a urine culture and susceptibility test should always be performed. The choice of initial antibiotics should be made on the basis of the suspected infecting pathogen, as well as local antibiotic resistance data. The 2010 IDSA guidelines recommends oral ciprofloxacin 500 mg twice daily, for a total duration of 7 days (with or without an initial intravenous dose) as an appropriate treatment for women not requiring hospitalisation and where the resistance of community acquired uropathogens does not exceed 10% (Level A-I evidence).[5] If the prevalence of resistance is thought to be >10%, an initial one-time intravenous dose of a long acting parenteral anti-microbial e.g. 1 g of ceftriaxone or a consolidated 24-hour dose of an aminoglycoside is recommended. Should once daily dosing of a fluroquinolone be considered, a dose of 1000 mg of extended release ciprofloxacin for 7 days or levofloxacin 750 mg for 5 days may be alternatives. Oral trimethoprim-sulfamethoxazole (160/800 mg) at one double-strength tablet twice daily for 14 days is also an appropriate therapy if the uropathogen is known to be susceptible. If trimethoprim-sulfamethoxazole is used when the uropathogen susceptibility is not known, an initial dose of a long-acting parenteral anti-microbial is recommended. It is important to note that oral B-lactam agents are less effective compared to other anti-microbials for the treatment of pyelonephritis. Nitrofurantoin and fosfomycin should not be used for the management of pyelonephritis as low levels are found in tissue although high concentrations can be obtained in the urine. Should the patient require hospitalisation, the initial anti-microbial regimen should be intravenous, with the choice of drug dependent on local resistance data, then tailored to susceptibility results as they become available.

What is the resistance pattern locally?

Bahadin et al.[6] reviewed the aetiology of community acquired UTIs and susceptibility patterns of uropathogens isolated in a single centre (SingHealth Bedok Polyclinic). The commonest organism isolated across all age groups and gender was *E. coli* (74.5%) and *Klebsiella* spp. (8.7%). Other organisms were *Proteus mirabilis* (2.7%), *Staphylococcus saprophyticus* (2.7%) and *Citrobacter koseri* (2.7%). In this study, amoxycillin-clavulanate had the greatest sensitivity amongst the enterobacteriaceae family (90.4%), followed by nitrofurantoin (84.2%), ciprofloxacin (76.9%), cephalothin (66.7%), co-trimoxazole (64.2%), and ampicillin (42.4%). The authors proposed that amoxicillin-clavulanate should be the drug of choice for empirical treatment. As this study has not been reproduced in other centres locally, it would not be possible to make a recommendation based on this single study. However, it highlights the importance of understanding the local resistance pattern in determining the choice of antimicrobial therapy in the management of UTIs.

Her symptoms resolve, but she presents twice within the next 6 months with recurrent urinary symptoms. How should she be managed?

This patient has had a recurrent UTI, which is a common presentation to urologists and general practitioners. It is recurrent when it follows the complete clinical resolution of a previous UTI and typically occurs due to bacterial reinfection. They are common among young, healthy women even though these women generally have anatomically and physiologically normal urinary tracts. However, the presence of risk factors for complicated UTI should prompt consideration of a complicated UTI aetiology. A threshold of three or more symptomatic UTIs in 12 months is used to define a recurrent UTI, or two or more symptomatic UTIs within 6 months.

Recurrent UTIs can be diagnosed clinically without performing a urine culture, although urine cultures are essential in management. For women with recurrent UTIs, imaging of the upper urinary tract and cystoscopy are not routinely recommended for evaluation given its low pre-test probability. However, they should be performed without delay in patients with atypical symptoms, such as obstructive symptoms or persistent microscopic haematuria after resolution of infection.

What are the risk factors for developing recurrent UTIs?

Risk factors for developing recurrent UTIs differ according to age groups. Table 1 lists the risk factors described by the European Association of Urology based on several studies.[7-9]

What is the role of antibiotic prophylaxis in preventing a recurrent UTI?

Post-coital antibiotic prophylaxis is an effective way to prevent UTIs in women when sexual activity usually precedes UTI. Patients should be advised to take a course of antibiotics within 2 hours of intercourse. A study by Melekos et al.[10] showed that long-term post-intercourse prophylaxis with ciprofloxacin proved to be equally effective as daily prophylaxis and the major advantage was use of only a third of the amount of drug compared with daily prophylaxis. However, sexually active woman suffering from recurrent UTIs and who are using spermicides should be encouraged to consider an alternative form of contraception.

Self-start antibiotic therapy is an option for women in the management of recurrent UTIs. For women to be able to benefit from this, they should be able to recognise UTIs symptomatically and start treatment. Patients should be given a prescription for a three-day treatment dose of antibiotics. As the concordance between the urine culture and self-diagnosis is high in an appropriately selected population, it is not necessary to culture the urine after UTI self-diagnosis. However, patients are advised to contact a healthcare provider if symptoms do not resolve after the course of antibiotics.

Continuous low dose antibiotics is another treatment option. The patient should be informed that antibiotics prophylaxis is usually not a life-long treatment, and there is potential for side effects including vulvovaginal infection with *Clostridium difficile* and an increased likelihood of infection with resistant organisms. Antibiotics are prescribed in this manner to allow a period of bladder healing, which makes recurrence of UTI much less likely. There is no evidence of any additional benefit beyond 6–12 months' treatment. A summary of the possible antibiotic regimens for the three treatment options is shown in table 2.

Young and premenopausal women	Postmenopausal and elderly women
Sexual intercourse	History of UTI before menopause
Use of spermicide	Urinary incontinence
A new sexual partner	Atrophic vaginitis due to oestrogen deficiency
History of UTI	Cystocele
	Increased post void urine volume
	Urine catheterisation and functional status deterioration in institutionalised women

Table 1. Risk factors for developing recurrent UTIs.

The role of non-pharmacological treatment to prevent recurrent UTIs

Cranberry products

Cranberry juice has been used to prevent UTIs because it contains a substance that prevents bacteria from sticking on the walls of the bladder. A recent Cochrane review[11] of 24 studies found no substantial reduction of risk of repeated UTI with cranberry treatment in women compared with placebo or no treatment. Many people in the studies stopped drinking the juice suggesting it may not be an acceptable intervention in the long term. Optimal doses and formulations have not been established.

Probiotics

No significant benefit was demonstrated for probiotics compared with placebo or no treatment, but a benefit cannot be ruled out as the data come from small studies with poor methodological reporting.

Methenamine

A Cochrane review by Lee et al.[12] found that methenamine may be effective for preventing UTI in patients without renal tract abnormalities, particularly when used for short-term prophylaxis. It does not appear to work in patients with neuropathic bladder or renal tract abnormalities.

Immunoactive prophylaxis

Bacterial extracts have been administered with the goal of increasing the immune defence of organs with a mucosal lining. That the use of oral immunostimulation with *E. coli* fractions (Uro-Vaxom®) was more effective than placebo in female patients with recurrent uncomplicated UTI was

demonstrated in several initial small double-blind, placebo controlled studies. A meta-analysis conducted by Naber et al.[13] to assess the safety and efficacy of bacterial lysates in the management of recurrent UTIs reported that the oral vaccine was effective under conditions of daily practice, while the vaginal vaccine appeared effective but needed further studies.

Conclusion

UTIs in women are commonly encountered both at the primary and tertiary levels of medical care. The proper management of such infections is essential in ensuring that patients receive prompt and appropriate treatment, as well as preventing the development of anti-microbial resistance.

Continuous prophylaxis	
Trimethoprim-sulfamethoxazole	40/200 mg daily
Trimethoprim-sulfamethoxazole	40/200 mg 3x/week
Trimethoprim-sulfamethoxazole	100 mg daily
Nitrofurantoin monohydrate/macrocrystals	50–100 mg daily
Cephalexin	125–250 mg daily
Norfloxacin	200 mg daily
Ciprofloxacin	125 mg daily
Post-coital prophylaxis (single dose)	
Trimethoprim-sulfamethoxazole	40/200 mg
Trimethoprim-sulfamethoxazole	80/400 mg
Nitrofurantoin macrocrystals	50–100 mg
Cephalexin	125–250 mg
Ciprofloxacin	125 mg
Ofloxacin	100 mg
Norfloxacin	200 mg
Acute self-treatment	
Trimethoprim-sulfamethoxazole	160–800 mg twice daily x 3 days
Ciprofloxacin	250 mg twice daily x 3 days
Norfloxacin	200 mg twice daily x 3 days

Table 2. Antimicrobial prophylaxis regimens for women with recurrent urinary tract infections.

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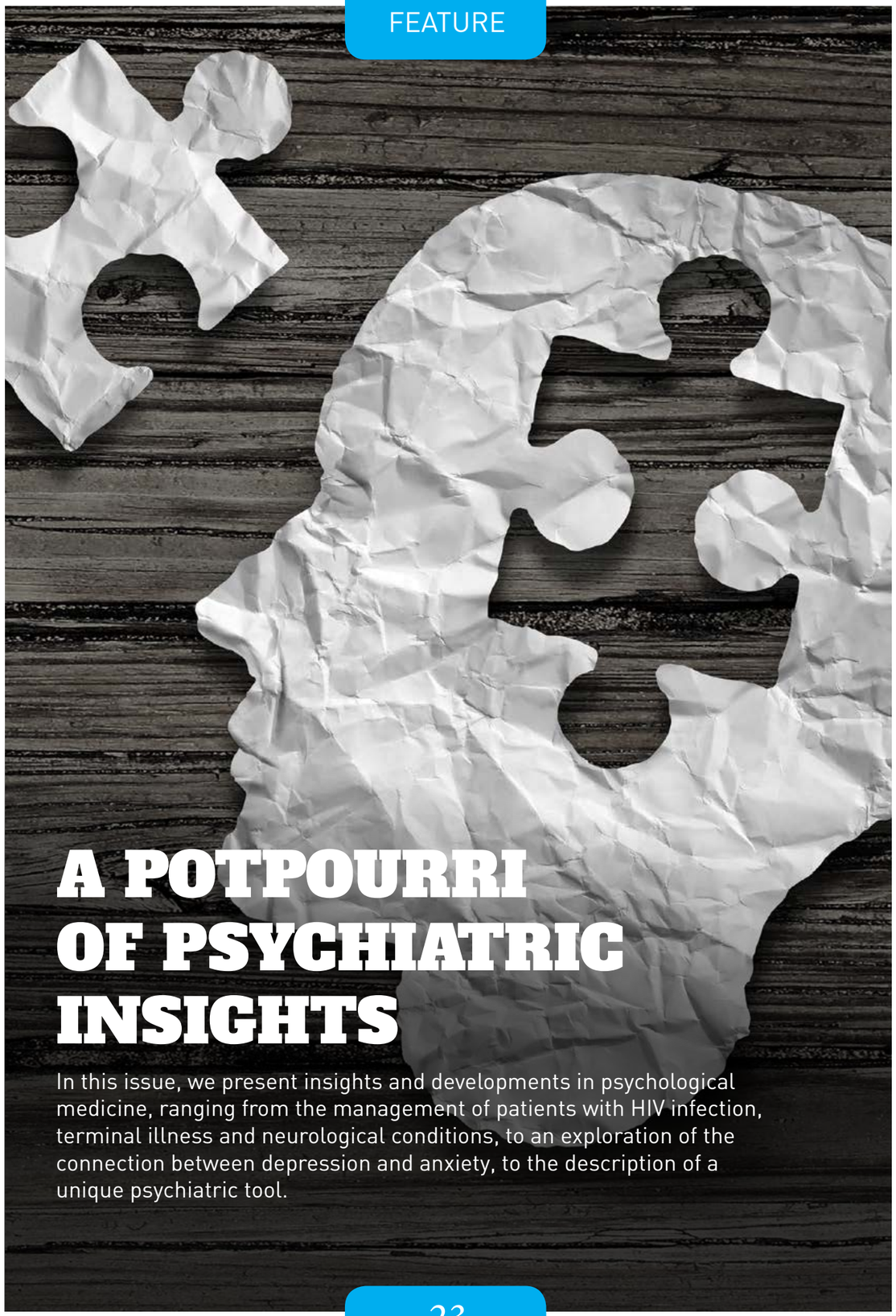

A POTPOURRI OF PSYCHIATRIC INSIGHTS

In this issue, we present insights and developments in psychological medicine, ranging from the management of patients with HIV infection, terminal illness and neurological conditions, to an exploration of the connection between depression and anxiety, to the description of a unique psychiatric tool.

"COPY & PASTE"

Most of us clinicians, over time and practice, develop our own unique clinical approaches to manage our patients. More often than not, we do a good job and receive affirmation when our patients return to us for more therapy and new patients come through our doors.

Since we are always looking for new tools to add to our collection and yet are reluctant to part with our safe and comfortable old ways, what if I were to tell you that there is a new, yet easy to master with success, technique that could allow you to keep your own clinical styles? Better still, this technique employs a conversational approach, making change work often at the deep unconscious level.

Usually it is in the unconscious mind that the problem lies even though the patient may be consciously aware of the problem. Thus the saying goes "A conscious solution to a problem at the unconscious mind is doomed to fail." With conversation we can communicate with both the conscious and the unconscious at the same time, surpassing conventional clinical hypnosis when we attempt to communicate with the unconscious after we put the conscious mind into a restful state.

This technique consists of basically four simple steps:

1. Associate into the presenting problem state
2. Dissociate from the problem state
3. Associate into the 'resource' state
4. Associate – collapsing the resource state into the problem state.

At the end of the entire process we have formed a new memory of the experience for the patient.

Let's start by addressing basically about the whole approach, the core of which centres on memory. All memory of experiences is false, not accurate recollections. In other words, memory is unreliable and can be changed all the time. Every new bit of information, whether true or false, can alter and distort memory. It is a fluid process. Memory remains malleable.

There are some neuroscience theories to explain the rationale of this technique/approach. Neural networks firing at the same time become sensitive to each other. Hebb's Law states that "neurons that fire together, wire together". Shifting the attention will shake up the neural network, interrupt patterns and help rewire the brain for change. This means that we can re-imprint memory for positive change. We have that opportunity within a short period to build new neural connections for a new memory experience.

So how does all this translate in clinical practice? We go through the four steps.

1. **Association**
   In this stage, the patient is presenting his problem e.g. chest pain, giddiness, loss of appetite, etc. As he relates it, he is in the state of re-experiencing all the emotional, cognitive and behavioural physiology of his problem.

   All these are evident through the voice, posture, gestures, breathing, pallor, and tone/speed of voice, etc. Let him talk about these in the present tense. Take notice of the areas of concern, worry and apprehension as he describes his problem.

2. **Dissociation**
   Next we get patient to break his state, which simply means dissociating or moving away from the problem state. You can do it with humour by cracking a joke, or, if you are a strait-laced person, simply asking him questions that need thinking. You can make a voice shift or physically move the patient. You can ask questions outside the presenting problem to have a better idea of the patient and his resources.

3. **Associate into the 'resource' state**
   This refers to a positive state, allowing the patient to have better control through good choices and actions. Here we get the patient to talk about the positive things in his life.

4. **Associate the resource state with the problem state which is simply collapsing the resource state into the problem state.**
   This is done by firing the problem state with the resource state at exactly the same time. In this way we light up two neural networks simultaneously to create a new pathway, a new understanding, a better resolution. It is important that the resource state that we fire is more powerful than the problem state. The patient will notice how different it is, if we ask how things have changed for him. Essentially we are copying the resources to paste to the problem state in a conversational way.

Allow me to briefly illustrate this approach with a short summary of two recent clinical cases.

Case A

A 47-year-old Indian female complained of feeling very depressed and having suicidal ideations. Examination revealed a very distraught lady about to give up on life. She was crying, saying that her life has been totally unlucky, that she was jinxed. She had been on treatment earlier for biological depression.

Following a routine health screening, she was found to have a huge aortic aneurysm that needed immediate surgical intervention. To her it meant certainty of death. This was her problem state. She became immediately immersed in that state. This means she is associated in the problem state.

The next step was to get her dissociated from the problem state. It is necessary for me, the therapist, to speak in the past tense so that I can observe the areas of her concern as reflected cognitively, physiological and behaviourally. I went on to ask her for details of her investigations, her background that she brought with her, to have a better understanding of her. In this process of her narrating the past events, she became dissociated from the problem state.

Next I went on to explore the resources she had. Among other things, I noted she was a staunch Christian and that could be a good resource. I then proceeded, at the end of our session, to copy all of her resources and paste them onto her problem state. I did this by telling her that she did the right thing by doing the health screening and going through all the investigations. As a result she got to her hidden problem early before any disaster happened. It was God that brought her to the discovery in the absence of symptoms. Or as she put it, it was good luck, not bad luck. The fact that she had found a capable surgeon meant that she can look forward to be in a better state of health and be symptom-free. In short, she had many years to live healthily; it is the beginning not the end of a wonderful life ahead. These resources were reiterated over many times to her until I could see a change in her demeanour.

She confidently went on to have an uneventful operation. Months later, without any hesitation, she went on to have an operation on her hip.

The positivity of having God look after her and directing everything (divine guidance rather than bad luck), a capable surgeon in charge of the treatment, a timing where she will be in the best state of health and symptom-free – all wired into her depressive aneurysm problem state to result in a changed outlook.

Case B

A 53-year-old Chinese male was referred for an assessment of postoperative confusional state following brain surgery for meningioma. As he related to me all that had happened [associating into the problem state] he was clearly very depressed and anxious. His mood was labile. Like the previous patient, he thought it was all over for him, that it was downhill all the way for him from now on. He was upset that he was getting so forgetful, throwing away useful household items, feeling very impatient and just getting angry with everyone for no good reason. This behaviour was not like his previous self and he was aware of this change.

I then got him to describe in the past tense all that had happened that led to this referral to me, to have

him dissociated from the problem state. Apparently he presented with forgetfulness and headaches. So he obtained a referral from the polyclinic to see the neurologist. He then underwent all the investigations including an MRI scan of the brain. After being advised, he went ahead with the surgery. In the postoperative period he became confused and more forgetful, necessitating a referral to me. Other significant findings are that he had looked after his mother with dementia before she passed on, and his father who suffered from a stroke before succumbing more than a year later. He has two teenage children.

Having some idea as to where his resource state was I proceeded to collapse that into his problem state. I told him that he had done everything right. To have been able solve his problem by seeing a neurologist, getting the surgery and getting rid of the meningioma was simply amazing. That no one could have been more resourceful and positive. No time was lost in dealing with the problem which is now totally gone. I told him that his confused state and memory difficulty were only a temporary decompensation from which he will recover. He could see that he was getting better. I emphasised that his fear of suffering the same fate as his deceased parents was unfounded. That he would live many more wonderful years seeing his children grow up. I could see the relief on his face and his improved outlook.

At the next follow-up appointment he was happily discussing how well he felt. It only left me to discharge him from further review. The "copy and paste" approach did the trick.

Conclusion

This "copy and paste" technique can be used clinically in the simplest to the most complex problem states. Its applicability spans many varied situations, in clinical presentations, speeches, negotiations, sales promotion, or even in everyday casual conversation. Yes, even in talking to oneself when confronted with negative life issues.

It is possible that oftentimes the patients seem to have no resources to offer. This is when we innovate to create resources for them. At times it means demonstrating to them a major shift in thinking to a wider, more positive view. This needs to go on until it becomes impossible for him to hold on to the disabling old memory of the problem. This reframing corrects a self-defeating frame of mind. It may necessitate throwing many different reframes at him [known as the scatter approach] to get the necessary therapeutic change.

This "copy and paste" approach is really a "fun" technique once you get familiar with it. It is powerful at initiating transformation and new learning in a subtle way. It allows the patient to move beyond his limitations and what seems like insurmountable emotional issues. The patient may not even know what you had done but at the end of the session, a good feeling prevails for them. This technique satisfies the three factors of reaching the unconscious mind – "it is easy, it is fun, it is effective".

Certainly it is no rocket science, but an approach that many of you may have used unconsciously and routinely. However, when delivered in an intentional, purposeful and calculated manner this technique will without doubt land accurately on the problem with a deadly hit. Simply put, it works effectively.

Just in case you are still pondering on its intricacies, fret not, this is merely a "copy and paste" technique that I borrowed from good old Microsoft! Do have fun with it in your next case.

"Oftentimes you do not need to look beyond the familiar and the simple things around you for effective solutions to problems."

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HIV PSYCHIATRY

The treatment of HIV has come a long way in the past 20 years. It has fundamentally shifted the way we perceive the illness – viewed no longer as a 'death sentence', but more as a chronic illness. However, it is important not to focus just on the improved prognosis and quality of life. We must also remember the more practical and human aspects of a chronic illness, with all its attendant challenges. These include the costs and inconvenience of lifelong medications and doctor visits, necessary lifestyle changes, the need for social support and acceptance, and its effects on a person's psychological well-being.

In Singapore, the number of newly-diagnosed HIV patients has remained stable (at around 450 per year) over the past 10 years. It is estimated that there are approximately 6000 patients living with HIV in Singapore today. A significant majority of these patients (about 70 percent) seek treatment at the Communicable Disease Centre (CDC) at Tan Tock Seng Hospital. It was in this way that the Department of Psychological Medicine first got involved in helping to manage the sometimes unique psychiatric needs of this patient population.

Our department started weekly HIV Psychiatry clinics in 2006, in response to a clear demand for psychiatric care. The clinic was sited at CDC to provide holistic care under one roof – with easy access to Infectious Diseases physicians and allied health workers, especially the medical social workers (MSWs). This setup allowed us to work closely with our colleagues from the Department of Infectious Diseases, and improved each other's awareness of our respective specialties. It has also provided many opportunities to educate, learn and support one another as we walk with our patients on their journey with HIV.

The spectrum of symptoms and disorders seen in the HIV Psychiatry clinic is wide-ranging. Most commonly, we manage the symptoms of psychological distress – such as anxiety and depression, in patients who have been newly diagnosed with HIV. Since 2010, we have been conducting routine screening for symptoms of anxiety and depression in all newly-diagnosed HIV patients presenting to CDC. Our data suggest that 30 percent of all newly-diagnosed patients had significant symptoms of anxiety and/or depression. This routine screening of all patients has allowed us to help many patients whose distress may have gone unrecognised.

As a psychiatric service in a specialised setting, we also take over the management of patients who require long-term psychiatric follow-up from other institutions. These include, but are not limited to, patients with schizophrenia, bipolar disorder, recurrent major depression, or chronic anxiety disorders who also have HIV illness. The benefits of this approach include greater awareness of possible drug interactions and facilitating easier discussion and communication between the treating doctors. A significant proportion of patients with newly-diagnosed HIV also have problematic substance abuse issues, especially methamphetamines. Unfortunately the resources to manage this are unavailable in our setting at this time, and such

patients are referred to the National Addictions Management Service (NAMS) at the Institute of Mental Health (IMH).

Psychiatrists are commonly consulted in cases of delirium (which may arise due to a multitude of reasons in an immunocompromised patient), where behaviour may be challenging and interfering with treatment. We also encounter patients who may present with symptoms that mimic psychiatric symptoms such as hallucinations, delusions, disorganised speech and behaviour, or apathy. A healthy suspicion for organic causes must be entertained in this population, as there are many opportunistic intracranial infections which can produce such symptoms. Examples include *Toxoplasma* encephalitis, *Cryptococcus* meningitis, central nervous system lymphoma, and mycobacterial infections such as *Tuberculosis* meningitis or abscesses. Additionally, highly active antiretroviral therapy (HAART), although generally safe and effective, can sometimes also cause neuropsychiatric side effects. These include minor problems such as sleep disturbances and vivid dreams, to more serious side effects such as mood disturbances and confusional states. These must also be considered in the list of differential diagnoses.

Cognitive impairment is a possible sequelae of long-standing HIV illness, and its presence and severity is associated with poor illness control and high viral loads. With improvements in treatment over the past two decades, a severe dementia-like illness has become increasingly rare. Clinical attention has shifted to subtler forms of cognitive impairment that nevertheless have the potential to impair the individual's socio-occupational functioning. These patients with HIV-associated neurocognitive disorder (HAND) often require neuropsychiatric assessments to specify the deficits and our department has been doing important research in this area.

The practice of psychiatry in the HIV population can be challenging and requires specific knowledge of the illness and how it interacts with the patient, both from a medical as well as a psychosocial perspective. It also provides a good opportunity to learn from our colleagues, and to guide and support them – key goals in the practice of Consultation-Liaison Psychiatry.

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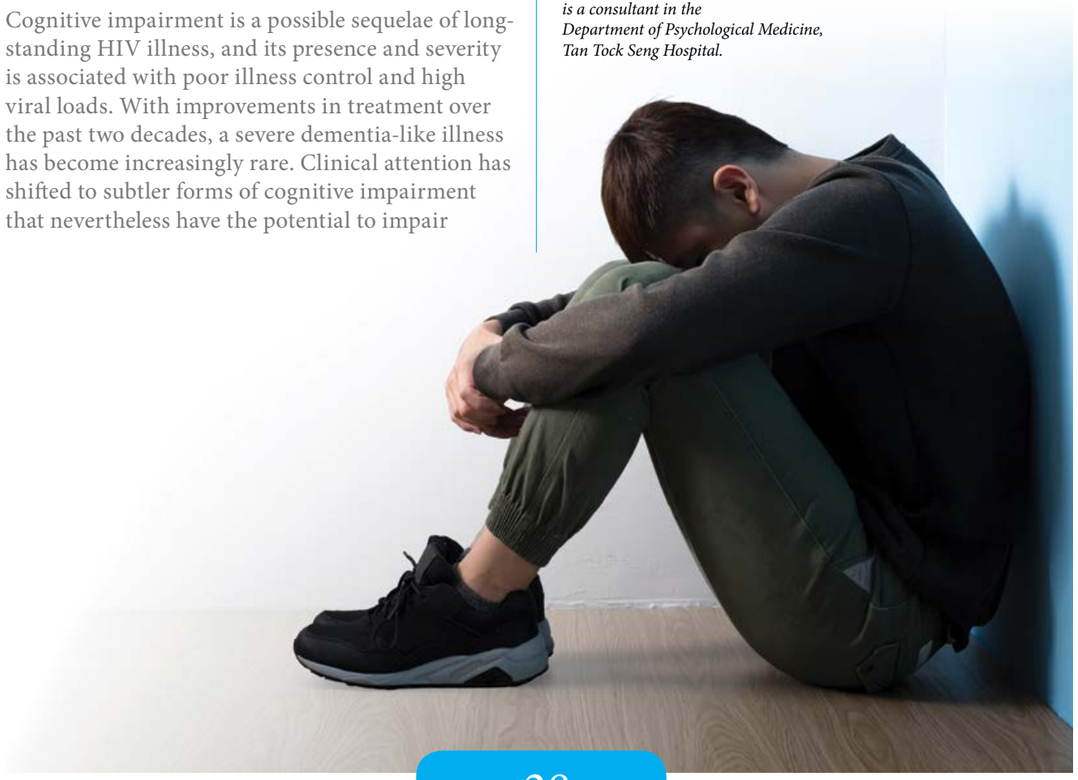

MASTER AND SERVANT, ANXIETY AND DEPRESSION 101

In the course of my work I have encountered several patients who have been referred for physical symptoms of anxiety.

I remember a young man I encountered more than a decade ago – he had been referred as he had presented repeatedly to his local general practitioner and had sought treatment at the Emergency Department for various physical symptoms over the duration of half a year. His main symptoms were body pains and abdominal discomfort, and he also reported a few episodes of what he believed to be a heart attack – cold sweat, gripping chest pain, and feeling faint and almost passing out. Many investigations had been ordered over the months, but despite all findings being normal, he continued to experience these physical symptoms which prevented him from his work as a legal assistant.

Eventually a cardiologist he had seen prompted a psychiatric referral, and he came to my clinic with little hope that a psychiatrist could treat his body.

He presented as a very well-groomed young man who was anxious from the start. He spoke rapidly, trying to accurately report as many of his physical symptoms as possible, for fear of missing something out. As he spoke about each symptom (recorded meticulously in a small diary he carried at all times with him), he focused on his body more and more, until he had to stop as he was on the verge of another 'heart attack'. At that point, it became clear that what he was experiencing was a panic attack – his mind was racing, he had started to breathe more rapidly with shallow breaths, and was gripping the chair tightly for fear of passing out. Unsurprisingly, his chest pains were felt strongly, and his hand and feet were starting to spasm from hyperventilation.

It was fortunate that at that point he responded well to a simple exercise in regaining control of his breathing, and steadying himself once again. As we spoke about his recent triggers, a conscious effort was made to slow down the conversation, and to reduce the expressed anxiety. Eventually, as his thoughts slowed down enough, he started to tear, and surprised himself at how he felt that he needed to cry at that moment. He spoke about losing his father when young, and approximately half a year ago, his mother sustained a cardio-embolic stroke which had led to her admission to a nursing home. He had begun to perform poorly at work and found himself unable to cope with work as his thoughts

were frequently with his ill mother. When he visited his mother at the nursing home, he found himself worrying about his work. What started off as innocent worry unfortunately spread to various other aspects of his life, and soon he was aware of always being anxious and not being able to sit still. It was at this time that he started to have his 'heart attacks' and various physical symptoms he could not explain. He left that session with me feeling lighter, and a little more in control of his life once again.

Depression and anxiety (obsessive-compulsive disorder) are the most common mental illness in Singapore, according to our last mental health study. But anxiety is a common comorbidity of depression and vice versa. The most recent iteration of the Diagnostic and Statistical Manual of Mental Disorders, DSM-V, now includes a specifier for "anxious distress" in the context of a major depressive disorder, including feelings of being tense, restless and having difficulty concentrating due to worry, with a fear that something awful may happen, or that the person may lose control of themselves. One may note that it is not too different from what the period before a panic attack feels like.

Thus in this group of patients, one of the presenting symptoms of the depression may actually be anxiety, and a careful history taking and mental state may unmask the underlying low mood. Anxious thoughts are also at times a reaction to the state of depression – a defence of sorts. A patient experiencing the intensity of emotions associated with depression tries his or her best to avoid those feelings, and this is perfectly understandable from an evolutionary perspective. In fact, small doses of anxious worry help to 'guard' against perceived losses in future, loss being the archetype of depression. The adaptive functioning of anxiety soon becomes maladaptive however, and layer upon layer of anxiety forms, in increasingly desperate attempts to bury the depression. It is said that depression is a 'past-oriented' state, whereas anxiety is a 'future-oriented' state, thus taking the patient from an unhappy past into a worrisome future. The unfortunate sequelae of both states is that the present is missed. In my practice, therefore, when an anxious patient sits in front of me, one of the manoeuvres that have proven useful is to slow the patient down, and to be prepared for the tears and depression that emerge in the calm state. Once done, the patient is able to get behind the wheel again and regain control of their negative automatic thoughts.

Beyond psychological processes, we also know that anxiety and depression share many biological contexts. The same medication we use to treat depression is effective for anxiety, and vice versa. I am often asked why we would prescribe antidepressants for anxiety, and the simple answer is that the same neurochemicals (there are remarkably few that we can target reliably with the medications we currently prescribe) are responsible for the emotions we feel. Increasingly there is evidence that what we thought of as separate monoamines (serotonin, noradrenaline, dopamine) all contribute in degree to the experience of depression and anxiety, and form a complex network in our brains of pathways that complement in some areas, and compete in other areas. What we also know is that hormonal changes are common between depression and anxiety, mainly involving the hypothalamic-pituitary-adrenal axis. Once triggered, a cascade of autonomic functions takes over, and therefore prevention strategies are the best way to manage these changes.

Ultimately it is difficult to answer which is the master and which is the servant – anxiety or depression, or, the disorder or the patient. For healthcare givers, trying to walk in the patient's shoes as they regain their lives would be the best approach, being mindful that while anxiety is an initial friend, it often lets the patient down again. Without uncovering the anxiety, it will be hard to treat the depression, without treating the depression, it will be hard to cure the anxiety. And the mode of management will need to address biological, psychological and social function.

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PALLIATIVE PSYCHIATRY PARABLES

The following cases illustrate the highly personalised experience of grief, loss and despondence, and how the treatment of depression in life-limiting situations needs understanding of the patient's hopes, beliefs and values.

1. "Where have you hidden my husband?"

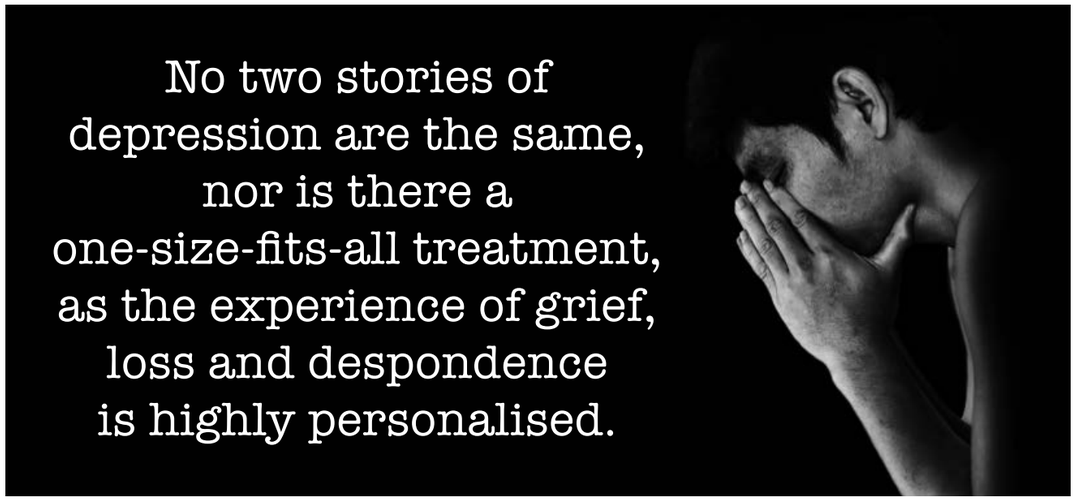
Mr N was a patient with stage IV colon cancer; at the time of his passing, he left behind his teenage son and his widow Mrs N.

In the year after Mr N's death, Mrs N began to turn up in various clinics that he once frequented, asking staff if they knew of his whereabouts. On some occasions, she would bring along his identification card, already rendered void by a punched hole. Puzzled healthcare staff alerted the social workers, who conducted home visits and offered supportive counselling. Bizarrely, Mrs N was able to acknowledge that she received his death certificate, witnessed last offices, and attended his wake, yet stopped short of accepting the fact that he was indeed, dead. Corroborative history proved difficult, as her son coped with Mr N's passing by disengaging from the family. Furthermore, she was a foreigner with no family or friends.

Her social workers were caught in a bind as she continued to hop from clinic to clinic, demanding that healthcare staff return her husband. The situation came to a head when she presented to the social worker's office one day, alluding to an untoward event that was to happen should she fail to find her husband. Concerned over her welfare, social workers arranged for her to be admitted to psychiatry.

With a longitudinal assessment of her mental state, extensive sleuthing and corroborative history, Mrs N was discovered to have exhibited signs of mental illness even before her husband passed away. With his passing, the cumulative effects of grief, social isolation and mental illness rendered her incapable of coping with a future without her husband. Fortunately, she received the appropriate treatment, and was referred to community mental health services.

With the passing of a loved one, surviving family members not only lose a parent, a spouse or a companion. Sometimes, the departed person may have acted as a caregiver for a loved one with mental illness. With good care and support, symptoms may not become noticeable until the passing of the caregiver. Post bereavement care is imperative, and should include an evaluation of mental health symptoms, with early access to mental healthcare if required.



2. The angry Teochew gentleman

"I am so angry with my life."

Mr C stopped in his tracks, contrite that he began the consultation with such jarring words. He shifted in his chair uneasily as he tried to gather his thoughts. His elbow nudged the blood pressure monitor. As he settled into his seat, the consultation room again fell silent.

"You see," he explained, "It took them three X-rays before they found the tumour in my lung. Had they found it at the first one, it would have been treatable. I would still be driving my taxi now. Day shift. I always drive the day shift." He glanced up to look at me. "Night time is always for family."

Two weeks later, he was admitted to the ward. He developed adverse effects to chemotherapy. His skin blistered and his fingernails peeled off. His pillow case was stained by blood from the broken blisters. As he saw me enter the ward cubicle, he nodded to acknowledge my presence, then let out a long sigh. "I'm so angry *lah*. Seek treatment also can get side effects. Damned if you do, damned if you don't!" To manage the persistent irritability and insomnia he was experiencing, yet his vulnerability to side effects, we spent weeks adjusting his antidepressants.

In the days to come, he continued to develop adverse effects from both the illness and its treatment. Numbness in his hands rendered him unable to drive his taxi, which represented both his livelihood and freedom. Brain metastases left him weak and unable to control his movements, an undignified effect that led to his avoidance of social interactions. With chemotherapy-induced nausea, he could not eat *chwee kueh*, his daily breakfast staple that he loved so much. During our consultations, he would tear, whine and grumble, though being the polite Teochew gentleman he was, he never once raised his voice or lost his temper in spite of his anger.

The last time I saw him marked the first time I saw his family: his wife, his young daughter and grandchild. As I entered his room, he managed a wry smile and beckoned me to come closer. "I feel so happy today, doctor. My daughter told me she is very proud of Papa. She said Papa must fight, cannot lose to the cancer."

"I asked the oncologist if there are other chemotherapies I can try, since the current one is giving me so many side effects. I want to try. My mood and sleep is okay now, if you are busy you don't have to come and see me so often. I will be okay."

He passed away in his sleep two nights later.

No two stories of depression are the same, nor is there a one-size-fits-all treatment, as the experience of grief, loss and despondence is highly personalised. Similarly, depression in patients with life-limiting illnesses cannot be addressed simply by prescribing a stock prescription of antidepressants. Pharmacotherapy must be accompanied by a clinician's exploration and understanding of the patient's hopes, beliefs and values.

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WHAT NEUROPSYCHIATRY IS ALL ABOUT

Neurological disorder	Common neuropsychiatric sequelae	
Stroke	• Depression • Apathy	• Emotional incontinence • Cognitive impairment
Traumatic brain injury	• Agitation/aggression • Personality change • Cognitive impairment	• Sleep disturbances • Mood dysregulation
Parkinson's disease	• Depression • Anxiety/panic disorder • Apathy	• Non-motor fluctuations • Psychosis
Central nervous system infections	• Cognitive impairment • Circadian rhythm disturbances • Cognitive impairment • Functional decline	• Apathy • Depression • Sleep disturbances

Table 1. Common neuropsychiatric sequalae associated with neurological disorders.

Neuropsychiatry is not an accredited subspecialty and yet, some psychiatrists will profess to have a special interest in it. So what exactly is neuropsychiatry? Some will say it is the organic/biological basis of psychiatric disorders, whereas others will say it is to do with patients who do not have a clear neurological or psychiatric diagnosis and whose symptoms lie somewhere in between.

Our experience in TTSH has tempered our definition of neuropsychiatry into something quite different. As we work closely with our colleagues from neurology, neurosurgery and neurorehabilitation, we have developed substantial clinical experience with the psychiatric aspects of disorders such as stroke, traumatic brain injury, movement disorders, central nervous system infections, etc. These psychiatric aspects encompass mood, behaviour, cognition, and sleep. These aspects have hitherto not been regarded as "hard" neurological signs.

The practice of neuropsychiatry is challenging and intriguing. First of all, the neuropsychiatrist has to differentiate between the patient's psychological reaction to functional losses and the psychopathology that is caused by the neurological disorder. This requires expertise to interpret investigations like neuroimaging and correlate the findings to psychopathology. Next, the neuropsychiatrist has to be familiar with the different spectrums of neuropsychiatric sequelae of the individual disorders and manage them accordingly (table 1).

The practice of neuropsychiatry necessitates interprofessional and multidisciplinary involvement with other specialists and allied health colleagues such as the psychologist, medical social worker and occupational therapist. There is also a need to engage and involve caregivers from an early stage, as patients often lose insight into their own illness. It is crucial for caregivers to be psychoeducated about the neuropsychiatric aspects of the disorder and to understand their critical role in the care of their loved ones. Patients themselves also need to be empowered to cope with their functional limitations.

Clearly, the neuropsychiatrist needs to have an adequate understanding of management of the underlying neurological disorder, psychosocial strategies, psychopharmacology and available community resources, in order to manage the patient holistically.

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MANAGING DRUG INTERACTIONS IN TRANSPLANT RECIPIENTS

Immunosuppressants are often prescribed in combination to prevent transplant allograft rejection or to treat auto-immune diseases. There are four main classes of maintenance immunosuppressive agents for transplant recipients: the glucocorticoids, calcineurin inhibitors (CNIs), mammalian target of rapamycin inhibitors (mTORis), and antimetabolites.

The co-administration of prophylactic anti-infectives, stress ulcer prophylaxis and other medications for underlying chronic diseases in these patients lead to polypharmacy, increasing the potential for serious drug interactions and adverse drug events.[1] Polypharmacy may affect the drug levels of immunosuppressants (table 1) via pharmacokinetic or pharmacodynamic interactions.

In pharmacokinetic drug interactions, the administration of one drug may alter the absorption, distribution, metabolism, and elimination of another drug. For instance, being CYP450 3A4 substrates, drug levels of CNIs may be affected by the inhibition and induction of CYP450 3A4-mediated metabolism.[1] Furthermore, co-administration with drugs that affect P-glycoprotein, a well-studied drug efflux transporter, may significantly alter the pharmacokinetic profiles of immunosuppressants.[1] In pharmacodynamic drug interactions, the use of one drug may affect the efficacy or increase the toxicity profile of another agent.

Given their narrow therapeutic indices, immunosuppressants are prone to problems due to drug interactions as low drug levels predispose to increased rates of graft rejection while high drug levels are associated with side effects such as susceptibility to infections and malignancies.

Common drug-drug interactions

HMG-CoA reductase inhibitors (statins)

Lipid abnormalities are prevalent in post-transplant patients and pose significant risk to the development of cardiovascular events. Statins are often the first line medications used in the treatment of dyslipidaemias. However, both CNIs and statins are potent CYP3A4 substrates which may compete with each other for metabolism. In addition, CNIs are known inhibitors of CYP3A4, with recent reports suggesting that cyclosporine exhibits a stronger inhibitory effect of the enzyme in vivo compared to tacrolimus. This could explain the higher association of cyclosporine-statin-related toxicities in clinical studies.

Simvastatin, atorvastatin and lovastatin are primarily CYP3A4 substrates and are susceptible to drug-drug interactions with known inhibitors of these enzymes, carrying a potential risk of elevated serum statin levels with myopathy, rhabdomyolysis, and liver toxicity. On the other hand, pravastatin, pitavastatin, fluvastatin, and rosuvastatin have alternative metabolic pathways and a lower risk of drug-drug interactions.[2] Studies have shown the effect of cyclosporine increasing the area under the curve of statins by two- to 25-fold, with more significant increases reported for simvastatin, lovastatin and atorvastatin, and the least with fluvastatin.[3] Furthermore, cyclosporine has a dominant inhibitory effect on a liver-specific transporter of statin (OATP1B1), blocking its entry into hepatocytes and thus resulting in higher systemic exposure of statins. The increase in statin drug levels for non-CYP3A4-dependent statins like pravastatin and fluvastatin may be explained by the inhibitory effect of cyclosporine on transport proteins such as OATP1B1.[3]

Being substrates of CYP3A4, everolimus and sirolimus have also been postulated to cause undesirable interactions with statins. However, in a small crossover study of kidney transplant patients on everolimus, the use of atorvastatin 20 mg daily was not associated with any drug-induced rhabdomyolysis.[4] On the other hand, data on sirolimus is limited.

In general, the preferred low-intensity statin of choice include pravastatin and fluvastatin due to the absence of CYP3A4 metabolism.[5] In product label inserts, the use of cyclosporine with simvastatin, lovastatin and atorvastatin are contraindicated. If a high-intensity statin is required with cyclosporine, a maximum daily dose of rosuvastatin 5 mg daily may be considered. As the interactions with tacrolimus are less clinically significant, statins such as atorvastatin may be

Class	Examples
Calcineurin inhibitors	Tacrolimus, cyclosporine
Antimetabolites	Azathioprine, mycophenolate mofetil, mycophenolate sodium
Mammalian target of rapamycin inhibitors	Sirolimus, everolimus
Glucocorticoids	Prednisolone, methylprednisolone

Table 1. Classification of oral immunosuppressants.

initiated at the lowest dose of 10 mg daily with gradual dose titration and close monitoring for symptoms of toxicity.[2]

Ezetimibe is the second-line anti-lipidemic agent that is considered safe in transplant patients.[6] In patients receiving tacrolimus, ezetimibe may be used safely. However, for those on cyclosporine, case reports have demonstrated supra-therapeutic levels of ezetimibe with concurrent use; hence, ezetimibe has to be started at low doses and up-titrated to a maximum of 10 mg daily.[7] On the other hand, the use of fibrates with cyclosporine is generally not recommended due to decreased cyclosporine concentrations and potential for renal dysfunction with concurrent use. Gemfibrozil should be avoided in patients with creatinine clearance below 30 ml/min.[2,6] Bile acid sequestrants should be avoided in patients taking mycophenolate preparations where the absorption of the latter will be impaired due to this drug-drug interaction.

Anti-hypertensives

Hypertension is a common condition prevalent in transplant patients on immunosuppressants Causes of hypertension in this population include drug-related causes (e.g. usage of CNIs or glucocorticoids), or factors related to the presence of the native organs or other comorbid conditions. Amongst the various anti-hypertensives used in transplant patients, non-dihydropyridine calcium channel blockers (CCBs) (e.g. verapamil and diltiazem) are known to increase blood levels of CNIs and mTORis via inhibition of the CYP3A4 enzymes.[8] Consequently, diltiazem has been used in clinical practice as a CNI-dose sparing agent. Careful therapeutic monitoring is required as raised drug levels may increase blood pressure and worsen kidney function.[9] The abrupt removal or addition of verapamil or diltiazem to the immunosuppressive regimen can result in drastic changes in immunosuppressant levels and should be done judiciously with close monitoring of drug levels by the transplant physician.

Anti-infectives

One of the leading complications of immunosuppression is bacterial infections, with the risk of infection proportionate to the intensity of immunosuppression. Apart from the site of infection and susceptibility of the pathogens, the pharmacokinetic and pharmacodynamic effects of antimicrobials on immunosuppressants should be considered when selecting an antibiotic for treatment.

Drug interactions that involve moderate to strong inhibitors of CYP3A4 can lead to raised CNI and mTORi levels due to a decrease in their metabolism. Anti-infectives which are potent inhibitors of CYP3A4 include macrolide antibiotics such as erythromycin and clarithromycin. Azithromycin, which is also commonly used to treat respiratory infections, is a safe and recommended alternative for transplant patients because it is not extensively metabolised via CYP450 unlike the other macrolides described above. Generally, when potent CYP3A4 inhibitors are used, frequent monitoring of immunosuppressant levels is required with considerations for pre-emptive dose reductions and close consultation with the patient's transplant physician.[10]

While there are concerns about drug toxicities due to over-immunosuppression, under-immunosuppression due to drug interactions with inducers of CYP3A4 is worrisome for graft rejection. When rifamycins are initiated with CNIs or mTORis, a two-fold dose increase and frequent drug level monitoring is recommended till stable drug levels are achieved.[10]

Penicillins, cephalosporins and doxycycline are generally safe to be prescribed with immunosuppressants. Co-trimoxazole and nitrofurantoin are frequently prescribed as infection prophylaxis for *Pneumocystis* pneumonia and urinary tract infections, respectively. Table 2 provides a summary on the key interactions between common anti-infectives and immunosuppressants.[10]

Gout medication

Hyperuricemia secondary to immunosuppressant use like cyclosporine or diuretics may also be a common problem encountered by transplant patients. During the acute onset of gout, colchicine is often prescribed for rapid relief of gout pain. Colchicine is metabolised by CYP3A4 and is also a substrate for the P-glycoprotein transporter. Cyclosporine, a strong CYP3A4/P-glycoprotein inhibitor, markedly increased colchicine total exposure, half-life and peak concentration when it was co-administered with colchicine in reported drug-drug interaction studies.[11] Therefore, the combination of colchicine and cyclosporine may predispose patients to colchicine toxicity, with diarrhoea, myo-toxicity and life-threatening myelosuppression. The colchicine dosing recommendation for patients on cyclosporine is 0.5 mg for one dose, to be repeated no earlier than 3 days. At the same time, it is prudent to monitor for colchicine-associated toxicities during concomitant therapy.[11]

In cases where a chronic urate-lowering agent has to be initiated to prevent recurrent gout attacks, pertinent drug interactions with immunosuppressants have to be closely monitored. One commonly used agent is allopurinol, which reduces uric acid production via inhibition of the enzyme xanthine oxidase. There is a significant interaction when allopurinol is used concurrently with azathioprine as its active metabolite, mercaptopurine, is partly inactivated by xanthine oxidase. With the inhibition of xanthine oxidase by allopurinol, levels of mercaptopurine increase substantially, predisposing patients to a higher risk of myelosuppression. Therefore, this combination should be avoided. In circumstances when concurrent use is required, it is recommended to reduce the dose of azathioprine by 50–75% before adding allopurinol, starting with the lowest dose of allopurinol and constantly monitoring for adverse effects via blood tests.[11] This same mechanism of interaction is observed between febuxostat and azathioprine, therefore this combination should be avoided as well. Conversely, allopurinol or febuxostat may be used in combination with mycophenolate preparations which do not interact with both agents.

Uricosuric agents such as probenecid and benzbromarone lower plasma uric acid by increasing renal excretion of uric acid. Although both agents may be used in patients on immunosuppressants, caution needs to be exercised when using probenecid in renally impaired patients due to the risk of urate nephropathy. When using benzbromarone, it is recommended to monitor for potential hepatotoxicity.[11]

Gastric medication

Proton-pump inhibitors (PPIs) are often administered in transplant patients for the treatment or prophylaxis of gastric ulcers. Majority of the available PPIs, except rabeprazole, are metabolised by CYP2C19 and CYP3A4. Rabeprazoles metabolism only moderately involves the CYP450 pathway and 80% is involved in a thioether non-enzymatic reduction mechanism. The degree of interaction between PPIs and CNIs is more significant when higher PPI doses (e.g. omeprazole >40 mg/day) are used. It also varies with the extent of inhibition of CYP isoenzymes by the different PPIs, of which the most significant is omeprazole, followed by esomeprazole and lansoprazole.[12] No significant effect on immunosuppressant drug levels was observed when rabeprazole was used with tacrolimus.[13] Therefore, rabeprazole has a low potential for pharmacological interaction with immunosuppressive drugs and may be administered safely in standard doses with immunosuppressive drugs.

Another noteworthy drug interaction with PPIs is mycophenolate. The higher gastric pH with PPI treatment and subsequent hydrolysis of mycophenolate is the postulated mechanism for this interaction. Consequently, the enteric coated formulation (mycophenolate sodium) is less susceptible to this interaction compared to mycophenolate mofetil.[14] When antacids and mycophenolate preparations are used concurrently, it is recommended to separate the administration of these drugs by at least 2 hours as mycophenolate preparations may bind to magnesium or aluminium ions and form less soluble complexes.

Another alternative class of agents prescribed for the treatment of gastric disturbances are the H2-receptor antagonists. Drugs in this class include cimetidine, ranitidine and famotidine. Cimetidine has been shown to inhibit multiple CYP enzymes including CYP1A2, CP2C, 2D6, and 3A4.[15] Ranitidine has lower affinity for the CYP enzymes and famotidine does not have effect on the isoenzymes. Therefore, should H2-receptor antagonists be considered, famotidine should be the drug of choice over ranitidine or cimetidine.

Pain medication

Pharmacodynamic interaction between immunosuppressants like cyclosporine and nonsteroidal anti-inflammatory agents (NSAIDs) is another important drug interaction to look

out for. Concomitant usage of NSAIDs, in particular non-selective agents like naproxen and diclofenac, may enhance the nephrotoxic effect of cyclosporine, thereby predisposing patients to acute kidney injury and potentiating cyclosporine-induced nephrotoxicity.[16] Due to the concerns of nephrotoxicity with NSAIDs, analgesics such as paracetamol and tramadol are preferred.

Conclusion

Drug-drug interactions in patients receiving immunosuppressants continue to be a clinical challenge, and the list of drug-drug interactions with immunosuppressants provided here is non-exhaustive. The prevention, detection and management of pharmacokinetic and pharmacodynamic drug-drug interactions are important aspects of care for these patients. Careful consideration and close monitoring are warranted when addition, deletion or dose changes are made to the patients' overall drug regimen. When possible, physicians should consider an alternative agent or dose adjustments to avoid the occurrence of an adverse drug event.

Antimicrobials	Immunosuppressants	Interaction	Recommended actions
Fluoroquinolones			
- Ciprofloxacin	CSA, TAC	May increase IS levels	Nil adjustment / consider monitoring IS levels
- Levofloxacin	CSA	May increase IS levels	
- Moxifloxacin	CSA, TAC, SRL, EVR	None	
Macrolides			
- Erythromycin	CSA, TAC, SRL*, EVR	Increase in IS levels	Avoid concurrent use. Substitute with a non-interacting antibiotic
- Clarithromycin	CSA, TAC, SRL*, EVR*	Increase in IS levels	Avoid concurrent use. Substitute with a non-interacting antibiotic
- Azithromycin	CSA, TAC, SRL, EVR	Increase in IS levels, but less significant compared to erythromycin or clarithromycin	Nil adjustment / consider monitoring IS levels
Rifampicin	CSA, TAC, SRL*, EVR, MMF	Decrease in IS levels	Avoid concurrent use / monitor IS levels
Acyclovir	MMF	Increase in ACV, Decrease in MPA	None

Indicates agents that are contra-indicated.
ACV, per oral acyclovir; AZA, azathioprine; CSA, cyclosporine; EVR, everolimus; IS, immunosuppresant; MMF, mycophenolate mofetil; MPA, mycophenolic acid; SRL, sirolimus; TAC, tacrolimus.
Adapted with permission from Am J Transplant 2013; 13:318-26.[10]

Table 2. Pharmacokinetics interactions of antimicrobials and immunosuppressants.

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RADIOLOGY QUIZ

A 48-year-old Indian gentleman who emigrated to Singapore 10 years ago has been suffering from a long-term condition affecting his left leg since his teenage years. Radiographs of his legs were ordered (figure 1a and 1b). The right ankle radiographs are shown for comparison.

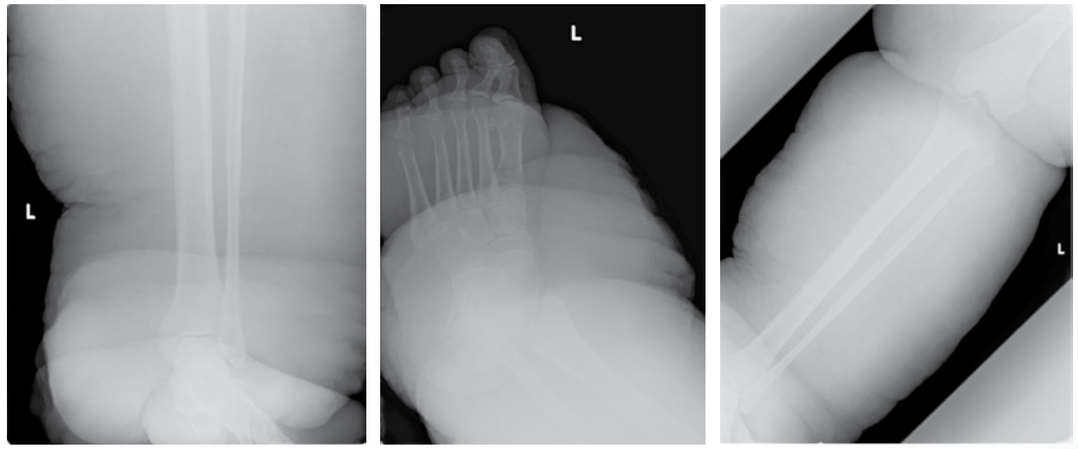

Figure 1a. Radiographic images of patient's lower limbs.

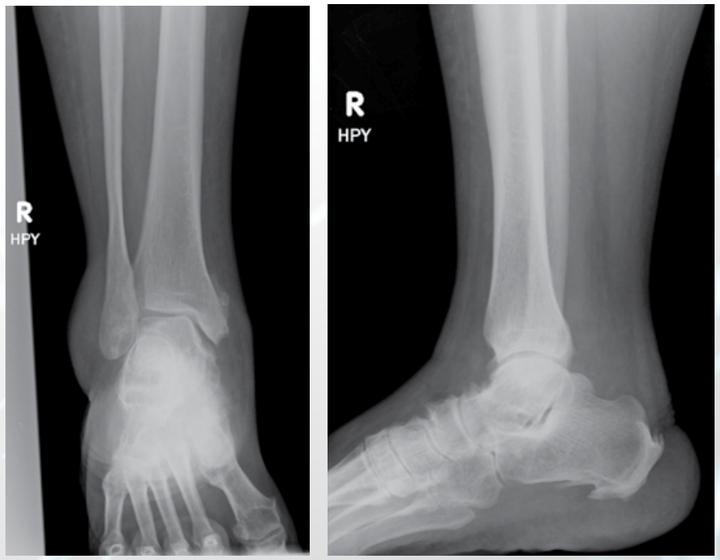

Figure 1b. Radiographic images of patient's lower limbs (right).

QUESTION 1

What do the radiographs show and what does this patient suffer from?

QUESTION 2

What are the differential diagnoses?

ANSWER 1

There is marked, diffuse soft tissue swelling of the left leg compared to the right. There is no evidence of underlying bony erosion, soft tissue gas or calcification. Given the chronicity of the problem, the diagnosis is elephantiasis of the left leg, most likely secondary to previous filarial parasitic infection.

ANSWER 2

The radiographic appearances can also be due to congestive cardiac failure (although the appearances would be bilateral), chronic venous stasis or deep vein thrombosis.

Discussion

Lymphoedema is an abnormal collection of protein-laden fluid in the soft tissues from lymphatic obstruction. This leads to extravascular water accumulation and soft tissue swelling. It affects primarily the lower extremities (80%). The primary form involves a congenital defect in the lymphatic system and may be associated with Turner, Klinefelter and Trisomy 21, 13 or 18 syndromes. The secondary form may be due to neoplasm, filariasis, obesity, trauma, surgery or radiation therapy.

Lymphatic filariasis, transmitted by mosquitoes, is the commonest cause of lymphoedema in endemic countries. Among 120 million infected people in 83 countries, up to 16 million have lymphoedema.[1] Microfilariae ingested by mosquitoes grow into infective larvae. These larvae are transmitted to humans by bites of an infected mosquito. The larvae grow in the hosts' lymphatics into adult worms that cause damage to the lymph vessels resulting in dilatation.

This earliest pathology is demonstrated in adults as well as in children by ultrasonography, lymphoscintigraphy and histopathology studies. Once established, this damage is thought to be irreversible.

The lymphatic damage predisposes individuals to bacterial infection that causes recurrent acute attacks of dermato-lymphangio-adenitis in the affected limbs. Bacteria, mainly streptococci, enter the lymphatics through lesions like interdigital fungal infections, injuries, eczema or similar causes that disrupt integrity of the skin.

Elephantiasis is a late manifestation of lymphatic filariasis, which, apart from limbs may involve genitalia or breasts.

Lymphoedema management includes the use of antifilarial drugs in early stages, treatment and prevention of acute attacks through 'limb-hygiene', antibiotics and antifungals where indicated, and physical measures to reduce the swelling such as compression bandaging and elevation of the affected limb.

Imaging is usually not useful in making the diagnosis but radiographs may be useful at assessing underlying bony erosion when osteomyelitis is considered and MRIs may be helpful for evaluating any underlying veno-occlusive disease.

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ECG QUIZ

A 20-year-old gentleman presented to his family physician complaining of right frontal headache for a few days. He also reported having occasional episodes of light headedness at rest for the past 1 year with no syncope. He is otherwise physically active and plays competitive soccer with no problems.

In view of the history of light-headedness, a resting 12-lead electrocardiogram (ECG) was ordered (figure 1).

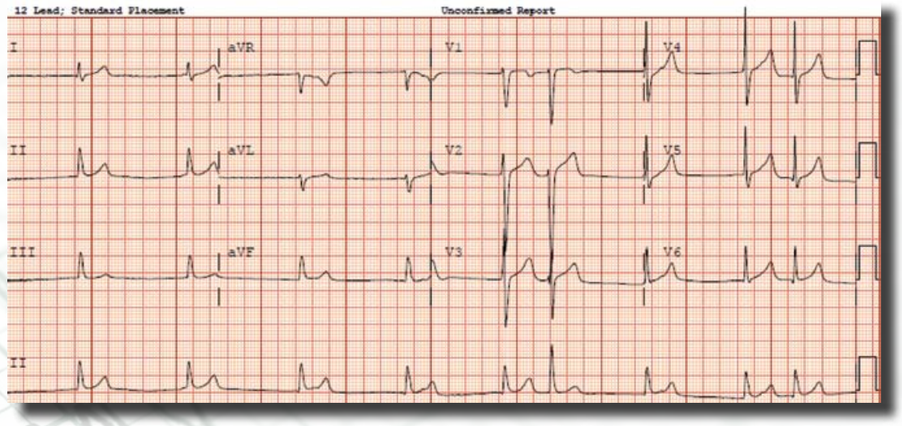

Figure 1. Resting 12-lead ECG performed in the polyclinic.

QUESTION

What is the ECG diagnosis?

ANSWER

Junctional rhythm with ectopics.

Discussion

At first glance, the ECG shows an irregular rhythm with no clear P waves and a diagnosis of atrial fibrillation was initially considered. On closer inspection, however, one can appreciate that the first five complexes are regular and occurring at a rate of approximately 50/min. A small P wave can be seen between the QRS complex and the corresponding T wave especially in the third, fourth, seventh and eighth complexes. The presence of a regular narrow complex (QRS <120 ms) rhythm at a rate of 40–50/min with associated retrogradely conducted (occurring after the QRS) P waves is consistent with a junctional rhythm. The sixth QRS complex is likely to be a ventricular ectopic given its different QRS morphology and the associated compensatory pause occurring after it.

A junctional rhythm may be normal in a young individual and is likely to be related to high vagal tone. According to international guidelines, junctional rhythm is considered a physiological adaptation to regular exercise and does not require further investigation when seen in an asymptomatic athlete.[1] Given that this patient is able to perform strenuous activity with no symptoms, reassurance and conservative management is appropriate. In sedentary individuals with no history of physical training, a formal evaluation of chronotropic competence (i.e. ability to increase heart rate when required) with holter monitoring or exercise stress testing may be required.

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