TAN TOCK SENG HOSPITAL

MEDICAL DIGEST

OCTOBER-DECEMBER 2016

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HOSPITAL

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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.

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MCI (P) 094/08/2016

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MEDICAL DIGEST

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For millennia, men have been using machines to do physical work. Humans cannot out-lift a forklift, out-run a car or out-stir a food processor, and we can live with this knowledge.

Using machines to do cognitive work is a much newer phenomenon. We still think our brains work better than electronic ones. We think we are more flexible, more capability of streaks of brilliance and less likely to miss important pieces of information.

In March this year, the Google-sponsored programme AlphaGo beat the strongest Go player in the world, Lee Sedol. This was an earth-shaking landmark in the progress of artificial intelligence. The game of Go is vastly complex and was thought to be beyond the calculating power of any computer. AlphaGo uses a Monte Carlo tree search to find moves based on what it has "learned" by playing millions of games against itself.

I am not an expert in chess or in computers, but I can describe what I feel when I play against the computer. I offer no resistance to my handphone computer at chess; this is a phone the company gives you for free when you subscribe. I am beaten in almost every game. In an interview in the Financial Times published on 5 October 2016, World Chess Champion Magnus Carlsen said, "That is detrimental to your confidence because most of the time you will lose to the computer". I know that it does not make any oversight, does not fall for tricks, or get tired. It may not be brilliant, but it makes very good decisions at every turn. Humans simply cannot perform at this level consistently.

We routinely use computers to read ECGs. Computers can already interpret X-rays. IBM Watson is already making significant headway in clinical practice, by assimilating massive amounts of medical knowledge and applying it in specific situations. If a professor of medicine is pitted against Watson in a contest to diagnose 100 difficult cases, I will place a big bet on the machine.

Can computers replace doctors? For history taking, physical examination and counselling, no (at least, not yet). For cognitive work such as making diagnosis and choosing the best treatment strategy, yes. When will it happen? It will happen when human beings place more trust in computers than themselves. We routinely use machines to buy and sell shares in the stock market, make air travel reservations, and control traffic. I think that machines will displace humans for much of the cognitive work in Medicine gradually and imperceptibly, and it will be as natural as a baby's smile.

Anyway, we hope that you will like Medical Digest with her new committee and new format. You will discover the new features and new writers. Tell me what you think.

As we look forward to the New Year, we hope that you achieve everything you wish for in your medical practice.

Dr Leong Khai Pang
EDITOR
Medical Digest

TTSH RESEARCH NEWS

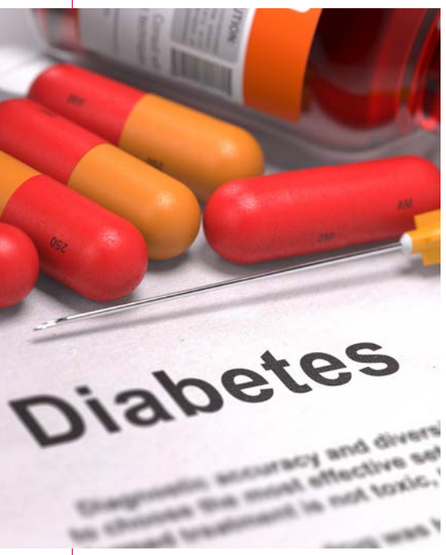
Welcome to this new feature of Medical Digest. Every year, TTSH publishes a few hundred scientific reports. We select a few, ask the authors to summarise them and discuss their clinical application, thereby saving you the trouble of reading the actual papers, unless you want to. Our theme in this issue are the surgical disciplines.

RESEARCH EXCERPT 1

Does Diabetes Mellitus Affect Presentation, Stage And Survival In Operable Pancreatic Cancer?

Chia CL, Lee AY, Shelat VG, Ahmed S, Junnarkar SP, Woon WW, Low JK. HepatoBiliary Surg Nutr 2016; 5:38-42.

Diabetes mellitus (DM) is associated with pancreatic cancer, both as a cause and effect, and is characterised by peripheral insulin resistance.[1] Approximately 80% of patients diagnosed with pancreatic cancer have concomitant diabetes. The incidence of pancreatic cancer in new-onset DM is 5–14%.[2,3] The association is particularly strong within 2 years of DM diagnosis in one large United States cohort study, accounting for 58% of identified pancreatic cancer.[4] Our study aimed to investigate differences in clinical presentation, disease stage and survival of operable pancreatic cancer patients with new-onset DM compared to long-standing DM patients and non-diabetics. We reviewed our pancreatic cancer surgery database from January 2006 to August 2012. Only patients with a histological diagnosis of pancreatic carcinoma were included in the final analysis. DM was defined as HbA1c >6.5% or any patient on anti-diabetic treatment regardless of HbA1c value. Diabetes diagnosed within 2 years preceding surgery was defined as new-onset DM. Patients were stratified into two groups: DM and non-DM. Among the DM patients, patients with new-onset DM were studied separately. We found a tendency for patients in the DM group to be older, asymptomatic and to present at an early stage (stage I and stage II). The median duration of new-onset DM prior to diagnosis of pancreatic cancer was 2 months (range, 1–23 months). However, there was no difference in survival for new-onset DM compared to long-standing DM and non-DM patients.



This summary was prepared by Dr Clement Chia, registrar, and Dr Low Jee Keem, consultant, both from Department of General Surgery, Tan Tock Seng Hospital.

IMPORTANCE IN CLINICAL PRACTICE

Pancreatic cancer is the 5th and 6th commonest causes of cancer mortality in males and females in Singapore, respectively.[5] Despite advances in technology and improvement in surgical outcomes, eventual prognosis remains poor. Operable pancreatic cancer patients with new-onset DM hold particular research interest because they gain the maximum benefit from early diagnosis and treatment. As of now, routine surveillance for pancreatic cancer in new-onset DM patients cannot be recommended based on our study due to the uncertain association between the incidence of pancreatic cancer and of new adult-onset DM in large populations. There is also a lack of data showing survival benefit with this surveillance strategy. However, we believe physicians should exercise vigilance when assessing the elderly patient with new-onset DM in the general practice clinic especially those who have no family history of DM and are asymptomatic as this may be an ominous sign of underlying pancreatic cancer. Physicians should have a high index of suspicion of underlying malignancy and have a low threshold of referring these patients for further workup in the specialist clinic, especially if the patients are cachectic.

RESEARCH EXCERPT 2

Safety And Complications Of Intravitreal Injections Performed In An Asian Population In Singapore

Xu Y, Tan CS. Int Ophthalmol. 2016 May 28.

Summary prepared by Dr Xu Yanping, an associate consultant in the Department of Ophthalmology, Ng Teng Fong General Hospital and Dr Colin S. Tan, senior consultant at the Department of Ophthalmology, Tan Tock Seng Hospital.

There has been a rapid rise in the use of intravitreal injections, such as anti-vascular endothelial growth factor (anti-VEGF) agents in the past few years for the treatment of ocular neovascular diseases. Commonly treated ocular diseases include age-related macular degeneration (AMD), diabetic retinopathy, retinal vein occlusion, neovascular glaucoma, intraocular tumours, and retinopathy of prematurity.[6-11] There are currently three commonly used anti-VEGF agents. Ranibizumab (Lucentis, Novartis, Basel, Switzerland) and Aflibercept (Eylea, Bayer, Leverkusen, Germany) are both Food and Drug Administration (FDA) approved for intraocular use, while Bevacizumab (Avastin, Genentech, California, USA) is used off-label. Bevacizumab is one of the most widely used anti-VEGFs in Singapore and around the world.[12] The invasive nature of intravitreal injections and the potentially life-threatening risks involved with anti-VEGFs have prompted the vigilant monitoring of complications arising from the intravitreal administration of these agents. Furthermore, many of these patients require repeated injections for extended periods, which increases these risks accordingly. Many of the complications arising from anti-VEGF agent use are reported from multicenter clinical trials in Caucasian populations. Real-world data from clinical practice is more limited and, in particular, there is a paucity of data on complications from these drugs described in Asian populations. Our study reported the frequency of systemic and ocular adverse events over 8 years and compared it among the various anti-VEGF agents. A total of 14001 intravitreal injections were performed on 2225 patients from January 1, 2007 to December 31, 2014, and this included 9992 Bevacizumab (71.4%), 3306 Ranibizumab (23.6%) and 703 Aflibercept (5.0%) injections. The rate of both ocular and systemic complications at our tertiary centre was low, especially with regards to infective endophthalmitis (0.04%). This rate of infection was much lower compared to that reported from large clinical studies involving intravitreal injections of these drugs.

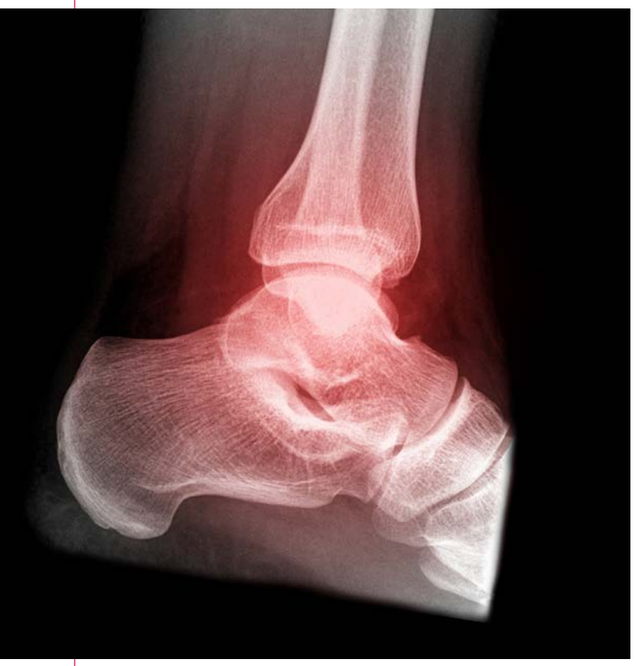
IMPORTANCE IN CLINICAL PRACTICE

Our study demonstrates the safety of intravitreal treatments at our centre, even for patients with multiple injections. Overall, there was no statistical significance between non-fatal thromboembolic events, fatal thromboembolic events, and death between all three treatment groups. We believe that the low rate of endophthalmitis reflected the high standards of sterility and administration adopted in our institute, such as safe preparation of the intravitreal injections, a well-established intravitreal injection protocol, and careful patient selection. These findings are reassuring for our patients requiring intravitreal anti-VEGF injections.

RESEARCH EXCERPT 3

Infection Rates In Singaporeans With And Without Complicated Diabetes After Ankle Fracture Surgery

Tan TL, Oh JY, Kwek EB. J Orthop Surg (Hong Kong). 2015; 23:59-61.



This is a retrospective study of 45 patients with diabetes who underwent surgical fixation for ankle fractures over a 9-year period. Twenty-seven percent (12 patients) had complicated diabetes, defined as presence of end organ damage. Statistical analysis was done to determine if age, sex, operative duration, adequacy of fixation, severity of diabetes, type of diabetic treatment and complicated diabetes had an influence on post-operative infection rates. Overall infection rate in our population was 18%, with no mortality or amputation. Subgroup analysis showed an infection rate of 6% in patients with uncomplicated diabetes and 50% in complicated diabetes. Complicated diabetes was a significant factor in post-operative infection (p=0.013) with an odds ratio of 11.85 compared with the group of patients with uncomplicated diabetes. Type of diabetic treatment and adequacy of diabetic control were not significant factors.

IMPORTANCE IN CLINICAL PRACTICE

Diabetes mellitus is a common and important metabolic disease, and often implicated as a factor for poor surgical outcome. Such patients may be at risk following ankle fixation. The aim of this study was to determine post-operative infection rates in an Asian population and if the severity of diabetes was a risk factor. Overall infection rates in our study are lower than previously thought; however, attention to patients with complicated diabetes is advised as they are an at-risk group and careful pre-operative planning is recommended.

Summary prepared by Dr Tan Tong Leng, registrar in the Department of Orthopaedic Surgery, Tan Tock Seng Hospital.

> “Overall infection rates in our study are lower than previously thought; however, attention to patients with complicated diabetes is advised as they are an at-risk group and careful pre-operative planning is recommended.”

RESEARCH EXCERPT 4

Prostate Cancer Detection: The Impact Of Obesity On Asian Men

Lee A, Chia SJ. Urol Oncol. 2015; 33:266.

We studied 458 men who had undergone transrectal ultrasound guided prostate biopsy in our institution over a period of about 28 months. We found that men who were overweight or obese [body mass index (BMI) ≥25 kg/m^2] were 2.6 times more likely to have prostate cancer found on biopsy, compared to men with normal BMI. This trend also applied for clinically significant cancers (Gleason sum ≥7). Compared to other studies on western men, the BMI threshold for Asian men to be at increased risk of prostate cancer detection appears to be lower (BMI ≥25 kg/m^2 versus BMI ≥30 kg/m^2).

IMPORTANCE IN CLINICAL PRACTICE

Prostate-specific antigen (PSA) testing is common in clinical practice, where it is offered as part of individualised screening or during the work-up of lower urinary tract symptoms. Overweight men may be exposed to a higher risk of having prostate cancer detected on biopsy as there are several obesity-related confounding factors. For instance, PSA may be subject to haemodilution in an obese man and be lower than in a man with normal BMI, despite being having same age and prostate volume. This data could help the clinician and patient make a better informed decision regarding prostate biopsy. However, there is still no strong evidence that being overweight leads to a delayed diagnosis of prostate cancer.

Summary prepared by Dr Alvin Lee, a medical officer in the National University Hospital and Dr Chia Sing Joo, senior consultant in the Department of Urology, Tan Tock Seng Hospital.

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

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HOT TOPIC

ZIKA VIRUS: AN EMERGING INFECTIOUS DISEASE

Zika outbreaks are currently happening in several parts of the world such as The Americas, Oceania and Pacific Islands, Cape Verde, Africa and Florida, United States. As of 15 September 2016, 72 countries and territories have reported evidence of Zika virus transmission since 2007. Given that Singapore is a major travel hub, it was inevitable that Zika would eventually find its way to our shores. We experienced our first imported case of Zika infection in May 2016 in a patient who had travelled to Sao Paulo, Brazil. Having been put on the alert, four thousand patients were tested before the first locally acquired case was found on 27 August.

Since then, there was national and international alarm when the numbers rapidly rose, in large part due to back-testing of previously collected specimens. On 1 September, the first pregnant patient, who lives in the Aljunied Crescent-Sims Drive area, was reported in the press. Two hundred and forty two cases were diagnosed by 4 September. From 6 September, the Ministry of Health (MOH) no longer requires suspect Zika cases to be isolated while waiting for results. On 8 September, it was announced that the viral strain in local cases was different from the South American one, but is similar to the one which has been circulating in the region since the 1960's. Therefore, there could be biological differences in the way the virus affects the host. By 15 September 2016, 355 local cases have been tested positive for Zika. In Tan Tock Seng Hospital, a total of 93 patients were admitted for suspected and confirmed Zika virus infections.

first recognised to cause human illness when viral infection was confirmed in three persons in Nigeria in 1953.[3] Prior to 2007, only sporadic human disease cases have been reported in Africa and Southeast Asia. In 2007 an outbreak with an estimated 5000 infections was reported on Yap Island, Federated States of Micronesia.[4] Figure 1 shows the areas in which Zika virus infections in humans have been noted in the past decade.

The incubation period of the Zika virus disease is not clear, but is likely to be 3 to 7 days, with a range of 2 to 12 days. The symptoms (figure 2), which are generally mild and short-lived, are similar to other arbovirus infections such as dengue and chikungunya (table 1), include fever (65% of patients) for 5 to 7 days, macular or papular rash (90%), arthritis or arthralgia (65%), non-purulent conjunctivitis (45%), myalgia (48%), headache (45%), retro-orbital pain (39%), oedema (19%) and vomiting (10%).

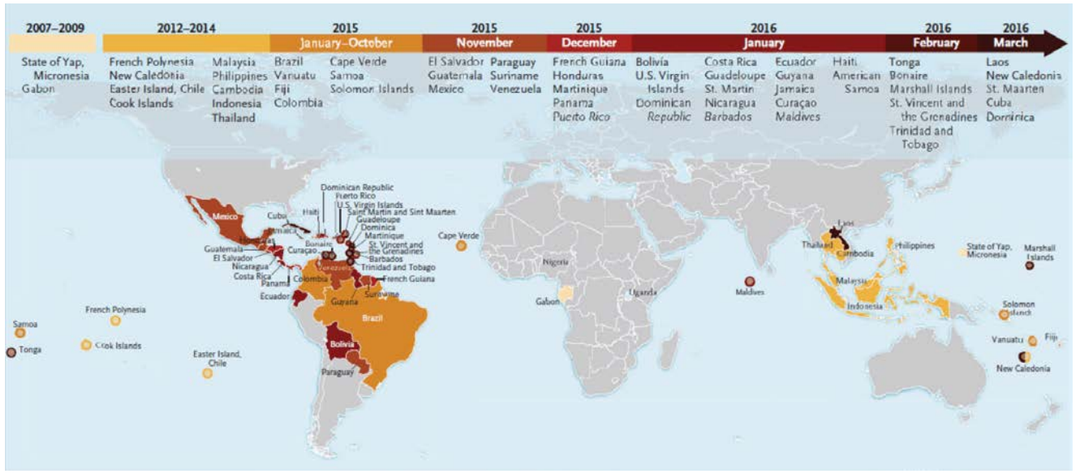


Figure 1. Parts of the world in which Zika virus infections in humans have been reported, up to March 2016. Reproduced from the New England Journal of Medicine with permission.

What is the Zika virus?

The Zika virus is a single-stranded RNA virus of the genus *Flavivirus* belonging to the family *Flaviviridae*.[1] It causes a mosquito-borne infection that is transmitted by the bite of an infected *Aedes* mosquito (*A. aegypti* and *A. albopictus*), the same vector that spreads dengue, chikungunya and yellow fever. The virus can also be transmitted through sexual intercourse and blood transfusion, and from the mother to the baby during the intrauterine or the perinatal periods.

The Zika virus was discovered in a monkey in Uganda in 1947 (Dick, cited in Peterson 2016[2]). It was

However, about 80% of Zika virus infections are asymptomatic.[1] Dr Tay Seow Yian, senior consultant at the TTSH Emergency Department mentioned that in our patient population, abdominal symptoms apparently were not prominent, in contrast to our dengue patients.

Severe disease requiring hospitalisation is uncommon and fatalities are rare. The disease affects all age groups with an infection rate of 73%. There is currently no antiviral and no vaccine. Treatment is symptomatic and usually consists of fluids and paracetamol. NSAIDs should be avoided until dengue fever is ruled out. Based on what we know about

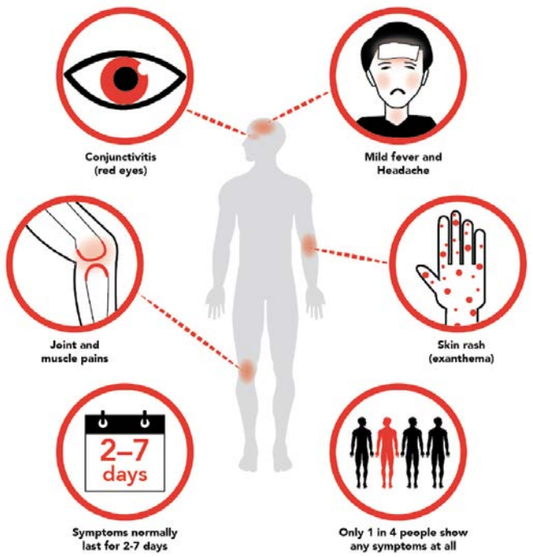


Figure 2. Symptoms of Zika virus infection

similar infections, once a person has been infected with the Zika virus, he or she is likely to be protected from future Zika infections.

The Complications Of Zika Virus Infections

Studies have shown a temporal and geographic relationship between Guillain-Barré Syndrome (GBS) and Zika virus outbreaks in the Pacific and the Americas.6 However, only a small proportion of people with recent Zika virus infection develop GBS.

Zika infection during pregnancy can cause birth defects such as microcephaly (figure 3), eye defects, hearing deficits and impaired growth. Quoting Peterson et al: "The findings of Zika virus RNA in the amniotic fluid of foetuses with microcephaly and in the brain tissue of foetuses and infants with microcephaly as well as the high rates of microcephaly among infants born to mothers with proven antecedent acute Zika virus infection, provide strong evidence linking microcephaly to maternal Zika virus infection. The timing of the Zika virus and microcephaly epidemics in Brazil and French Polynesia indicate that the greatest risk of microcephaly is in the first trimester. In case reports of microcephaly, documented maternal Zika virus infection most often occurred between 7 and 13 weeks of gestation, but in some cases it occurred as late as at 18 weeks of gestation."

Based on the available evidence, a non-pregnant woman infected with the Zika virus does not bear a risk of birth defects in future pregnancies after the virus has been cleared from her blood.

Symptom	Zika	Dengue	Chikugunya
Fever	++	+++	+++
Rash	+++	+	++
Conjunctivitis	++	-	-
Arthralgia	++	+	+++
Myalgia	+	++	+
Headache	+	++	++
Haemorrhage	-	++	-
Shock	-	+	-

Table 1. Clinical features of Zika virus infection compared with dengue and chikugunya. The table is adapted from the Centers for Disease Control and Prevention.[5]

Clinical Case Definition Of Zika Virus Infection

On 19 May 2016, the MOH Singapore issued a circular on the updated guidance on Zika virus infection. The case definition for Zika virus infection was:

a) Suspect Case

- Any individual with possible exposure to Zika
  - Recent travel history (within 2 weeks) to Zika-affected countries; OR
  - Living or working in the vicinity where a confirmed Zika case is reported, within 6 weeks of isolation of the confirmed case; OR
  - Living and working in an area where on-going Zika transmission is being reported.

AND

- Presenting with fever AND maculopapular rash

AND

- Any of the following:
  - Arthralgia
  - Myalgia
  - Headache
  - Non-purulent conjunctivitis

b) Confirmed Case

- A case with laboratory confirmation of acute Zika virus infection.

On 5 September 2016, the MOH issued another circular in response to the increasing number of sporadic cases with Zika virus infection not linked to known clusters of disease. The following changes were made: (a) doctors no longer needed to refer suspect or confirmed Zika patients to hospital for testing and isolation unless clinically indicated (b) patients can be sent home after samples are taken for Zika testing (c) the case definition for suspect Zika cases will no longer include geographical clusters as a criterion.

Revised Clinical Case Definition of a Suspect Case

- Any individual presenting with
  a. Fever AND
  b. Maculopapular rash AND
  c. Any of the following:
     i. Arthralgia
     ii. Myalgia
     iii. Headache
     iv. Non-purulent conjunctivitis

Precautionary measures

Travellers to countries where Zika transmission is active should avoid getting bitten by mosquitoes by wearing long, covered clothing, applying insect repellent and sleeping under mosquito nets or in rooms which have wire-mesh screens to keep out mosquitoes.

Pregnant women should postpone non-essential travel to countries with ongoing outbreaks to reduce the risk of brain malformation in foetuses and infants.

There have been reports of transmission via sexual contact. Male travellers returning from countries with ongoing outbreaks should adopt safer sexual practices e.g. using condoms during sex or consider abstinence for at least 8 weeks after returning. Sexual partners of pregnant women returning from areas with ongoing outbreaks should practise safer sex e.g. using condoms during sex or abstaining from sex throughout the pregnancy.

Travellers who have returned to Singapore from affected areas should monitor their health for the next 14 days and consult a doctor if they have symptoms of Zika.

The breeding of the *Aedes* mosquito must be prevented. The *Aedes* mosquito has distinctive black and white stripes on its body and breeds in clean, stagnant water. To prevent breeding, the National Environment Agency (NEA) is actively working to search and destroy potential breeding sites around Singapore.

The Health Science Authority (HSA) has a small inventory of leukodepleted red cells which have been tested as non-reactive for Zika virus. These cells are meant only for transfusion of pregnant women only in non-emergency and non-massive transfusion situations.

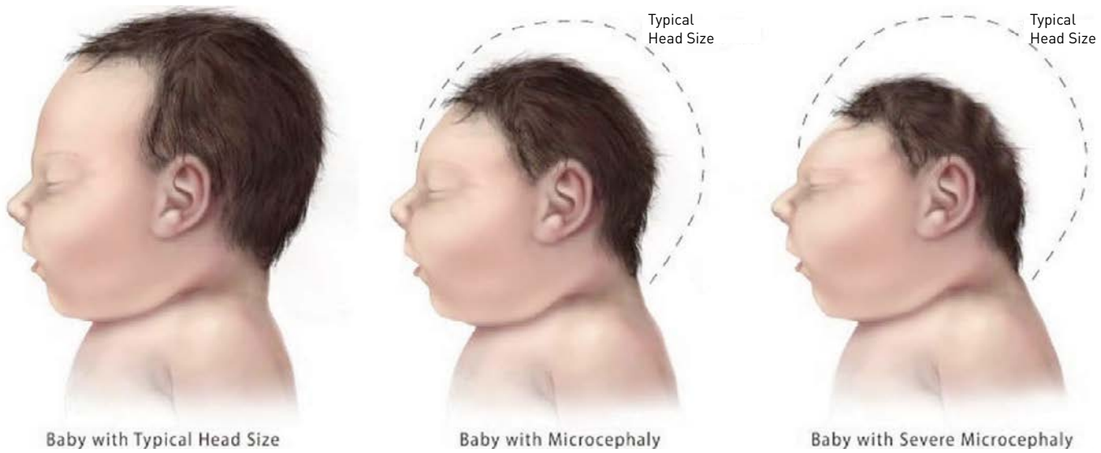


Figure 3. Infants moderate and severe microcephaly associated with Zika virus infection. The picture is obtained from the Centers for Disease Control and Prevention.

We spoke with doctors at the frontline in the national effort to contain the disease.

First in our lineup of specialists is Dr Tay from the TTSH Emergency Department (ED), which has always been in the frontlines when it comes to controlling potential outbreaks. He said that "Formulation of protocols pertaining to the management of the Zika virus, staff education and training, coordination with MOH, other departments and hospitals are some of the first things we have done to prepare for, and respond to, an outbreak. Staff vigilance is invaluable in times like this."

When should a GP or member of the public send a patient to the ED for Zika screening?
Based on the 19 May 2016 MOH guidelines, any individual who meets the clinical definition of suspect Zika should be referred for Zika screening. However, from 6 September 2016, MOH has shifted gears towards vector control instead of isolation of patients for Zika. Therefore, screening for Zika is no longer required. Doctors no longer need to refer suspect or confirmed Zika patients to hospital for testing and isolation unless clinically indicated.

How does the ED screen patients suspected with Zika virus infection?
Initially, as per the 19 May 2016 MOH guidelines, a patient who meets the criteria for suspect Zika will be seen in our isolation room. Other patients with possible exposure do not need isolation if they do not meet the case definition (figure 4).

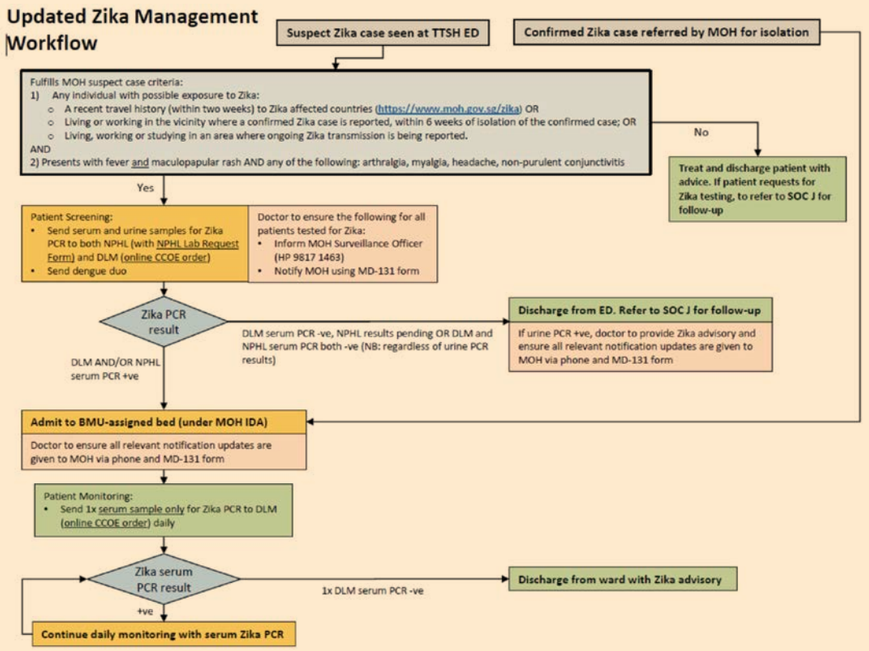


Figure 4. Zika management workflow for TTSH Emergency Department or specialised outpatient clinics (SOCs) (Prepared by TTSH Infectious Disease Outbreak Committee, 28 August 2016)

Between 27 August 2016 and 6 September 2016, patients presenting for Zika screening were seen in our Decontamination Facility. This was an air-conditioned space capable of holding about 25 patients at a time. As patients could wait for hours for PCR results, our air-conditioned EDTC non-subsidised beds were used as additional holding space.

From September 6, patients presenting for Zika have been seen in our ED's fever area but no longer require isolation.

What investigations are done? How long does it take to get the results?
Based on the 19 May 2016 MOH guidelines, for individuals who meet the clinical definition of suspect Zika virus infection, blood (about 2 ml in a yellow top tube) and urine specimens (about 5 ml in a sterile container) are obtained for PCR in addition to the usual blood tests (i.e. full blood count, renal panel, liver panel as indicated). BOTH blood and urine specimens are sent to the National Public Health Laboratory (NPHL) for testing and are not charged to the patient. The turn around time for the Zika test results is 48 hours. With the discovery of local transmission on 27 Aug 2016, our Laboratory Services has correspondingly ramped up capacity to achieve a turnaround time of between 4-8hrs. A pregnancy test is also performed for females of childbearing age. Blood and urine investigations for Zika testing are NOT required if patient does not meet clinical case definition for suspect.

From 6 September 2016, for non-pregnant patients, the need for testing will be based on clinical judgement of doctors after discussion with the patient. If testing is done, urine samples are preferred as detection of Zika virus in the urine can occur from 2 days of symptom onset and lasts for at least 14 days. The urine samples are sent to the TTSH laboratory. There is no longer a need to test both blood and urine. Among Singaporean and permanent residents, public sector labs will extend free Zika tests to eligible pregnant women.

Are all patients who are confirmed to have Zika virus infection admitted?
Not all patients confirmed to have Zika virus infection have to be admitted. Patients are admitted only if clinically indicated, except during the initial containment phase of the local outbreak, where admission for isolation was briefly practised.

How does TTSH ED manage pregnant or paediatric patients who are suspected to have Zika virus infection?
We will refer all pregnant suspected Zika patients to KK Women's and Children's Hospital (KKH) within 2 weeks if they are stable for discharge. Paediatric patients will be referred to KKH.

Can individuals who want to be screened for Zika virus infection come to the ED and request for Zika testing?
We do not encourage asymptomatic patients to be routinely tested. Zika testing in ED is available but is no longer free.

DR TAY SEOW YIAN
is a senior consultant and the Head of Department in the Emergency Department, Tan Tock Seng Hospital.

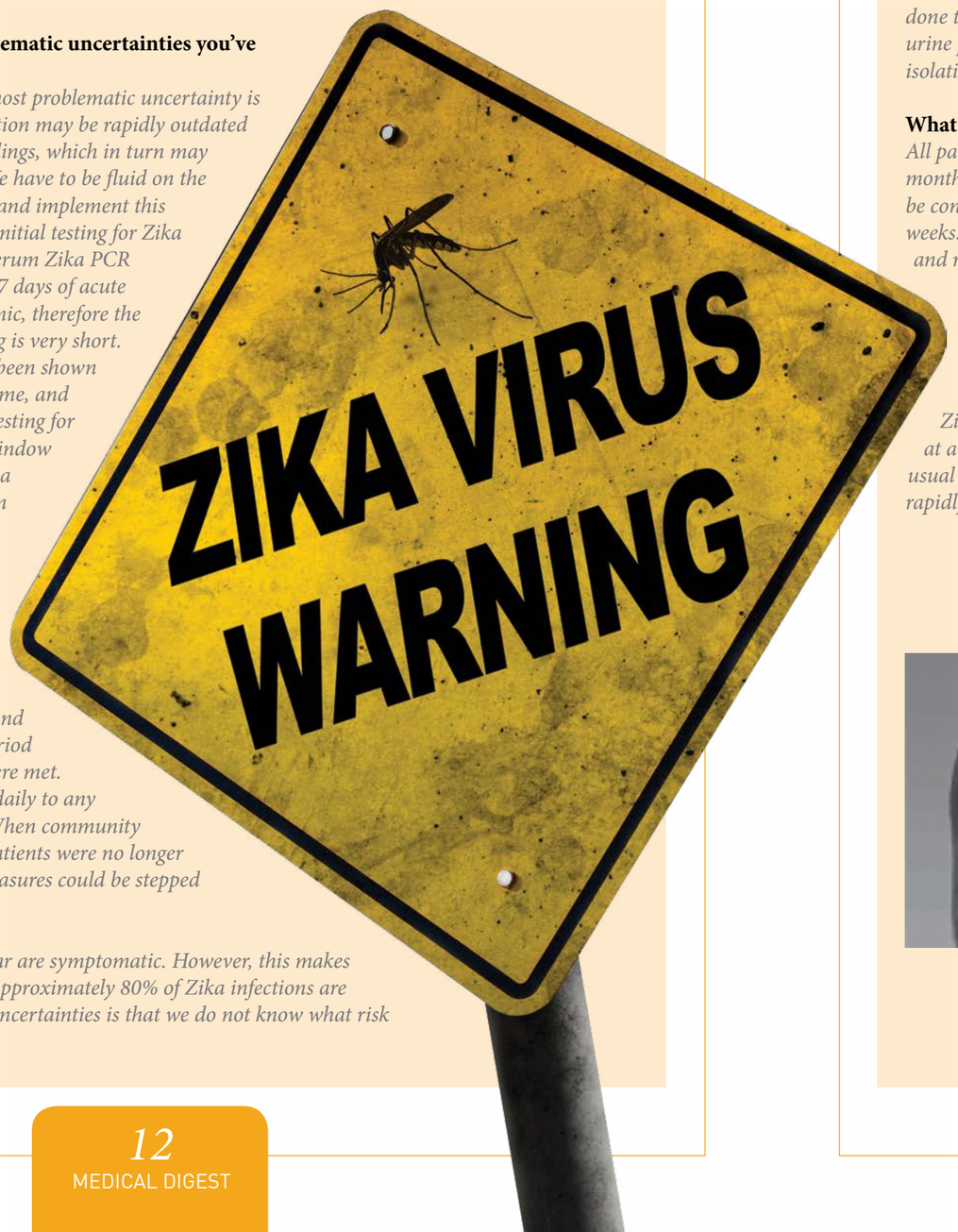
Next, we spoke to Dr Chan who has been deeply involved in Zika work now, especially since TTSH had its first case in May.

When the MOH travel alert came out, what first steps did you and your colleagues take to care for patients and keep them informed?

The first MOH circular was released on 27 January 2016. In preparation for an anticipated Zika outbreak, the TTSH Infectious Disease Outbreak Committee (IDOC) had prepared clinical pathways, workflows and information leaflets. These workflows and clinical pathways were useful to help guide the hospital doctors, nursing and healthcare workers about the screening criteria, investigations and management. By standardising the approach, management of patients could be optimised and important findings emphasised, even to healthcare workers who may not be familiar with the disease. All this material was made available on the TTSH intranet. Patient information pamphlets and advisories were also prepared to help patients understand more about the disease.

What are some of the most problematic uncertainties you've dealt with?

With any emerging infection, the most problematic uncertainty is that current knowledge of the infection may be rapidly outdated by new literature and scientific findings, which in turn may impact policy and management. We have to be fluid on the ground, review important changes and implement this where necessary. For example, the initial testing for Zika was for testing of serum by PCR. Serum Zika PCR detects Zika infection within the 5-7 days of acute infection when the patient is viraemic, therefore the window for serum Zika PCR testing is very short. Subsequently, urine Zika PCR has been shown to persist for a longer duration of time, and provides an additional method of testing for patients that may be outside this window of acute infection. Hence, urine Zika PCR is now tested and this has been incorporated into our workflows. When the MOH guidance was for containment and isolation of serum Zika positive patients, we had to respond quickly, activate the necessary manpower and support services, create additional rosters, open up additional wards and outpatient clinics within a short period of time to ensure these demands were met. We had to keep ourselves updated daily to any additional guidance from MOH. When community transmission was confirmed and patients were no longer admitted, then these additional measures could be stepped down.



The patients that we have seen so far are symptomatic. However, this makes up only 20% of all Zika cases and approximately 80% of Zika infections are asymptomatic. One of the biggest uncertainties is that we do not know what risk this large group of people present – whether they are also able to transmit the virus and to what extent. With more research on Zika, we will hopefully answer these questions more confidently.

Guidelines are available from the CDC and Singapore MOH. How helpful are they, given the unknowns?

The local Singapore MOH guidelines are very helpful. While the CDC guidelines have been providing guidance internationally, the MOH guidelines provide a framework that is more suitable to the Singapore context and can be adapted based on locally relevant information.

How does TTSH IIDE manage patients confirmed to be tested positive for Zika?

We follow the MOH guidelines. The guidelines initially mandated hospital admission and isolation in an air-conditioned room. Daily serum Zika PCRs were performed and patients discharged when the serum Zika PCR was negative. Other investigations for dengue, malaria, leptospirosis, rickettsial infections would be done to rule out other causes of infection where applicable. If the patient was a female of child-bearing age, a urine pregnancy test may be ordered. Since community transmission of Zika is now present within Singapore, isolation of the patient in hospital is no longer required and patients can be managed in the community.

What advice would you give the patient on discharge?

All patients would be advised on safe sex (i.e. condom use) practices after recovery – for men, at least 6 months and for female patients, at least 8 weeks. For male patients with pregnant partners, safe sex should be continued throughout the duration of the pregnancy. Patients should avoid blood donation for at least 8 weeks. Patient would also be advised to monitor for any symptoms suggestive of Guillain-Barré syndrome and return to hospital if this occurs.

Based on a growing body of preliminary research, there is scientific consensus that the Zika virus is associated with Guillain-Barré syndrome (GBS). How do we manage these patients? Is there a difference in the way these patients are managed?

The risk is quite low. A case-control study in French Polynesia found that the estimated incidence of Zika-virus related GBS was.[2] 4 cases per 10,000 Zika virus infections[2]. Neurological symptoms developed at a median of 6 days after the diagnosis of the viral syndrome. Patients are managed the same way as usual GBS cases. Intravenous immunoglobulin therapy or plasmapharesis can be provided for patients with rapidly progressive symptoms.

> "We have to be fluid on the ground, review important changes and implement (changes) where necessary."

DR MONICA CHAN
is a consultant at the Institute of Infectious Diseases and Epidemiology, Tan Tock Seng Hospital.

Laboratory testing is also a crucial component in the response to an outbreak. Here, we spoke to Dr Barkham to gain insights on the role of the TTSH Laboratory Medicine Department.

Are there special protocols with regard to handling of specimens to be tested for Zika?
Everything we do is special! … but as our processes are all designed with safety in mind, our protocols are routine for us, not special! A sample with Zika in it is treated like any other sample because any sample might contain unexpected pathogens, such as HIV, HBV and HCV! We are a biosafety level 2 laboratory so all our routine processes mean that our staff should be safe whatever pathogen happens to come through our doors, so long as they adhere to the protocols. Zika is not a very dangerous organism for most people and is not spread by the respiratory route, so it is far less of a hazard compared with many other pathogens we juggle with.

How does the TTSH lab test for Zika virus infection?
We use a nucleic acid test to detect the Zika virus RNA. This involves extracting the nucleic acids, then amplifying them with the polymerase chain reaction (PCR) and then detecting them with fluorescent probes. We look in both blood, urine and conjunctival swabs.

As per the MOH Circular, Zika virus RT-PCR can be performed on urine within 14 days of the onset of symptoms. Zika virus RT-PCR testing of urine should be performed in conjunction with serum testing if specimens are collected within 7 days of symptom onset. A positive result in either specimen type provides evidence of Zika virus infection, and the patient should be counselled and managed as a confirmed case of Zika infection (figure 5).

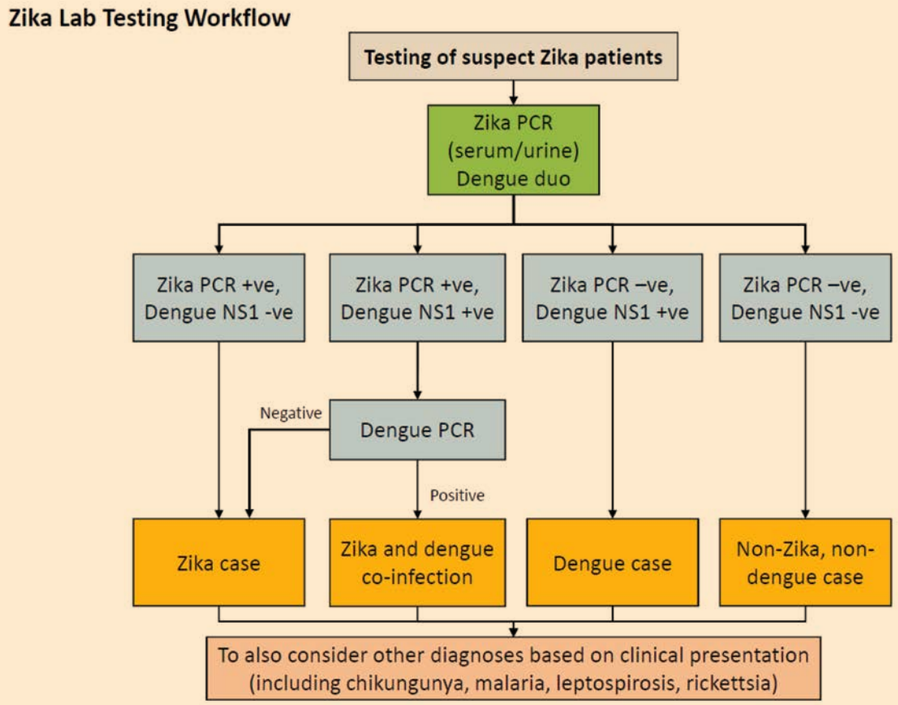


Figure 5. Zika lab testing workflow for TTSH Department of Laboratory Medicine or specialised outpatient clinics (SOCs) (Prepared by TTSH Infectious Disease Outbreak Committee, 24 June 2016)

Why did we need initially send blood and urine specimens to the NPHL?
NPHL offered the test before we did and all hospitals sent their samples to NPHL. Earlier in 2016 the number of test requests increased and NPHL asked the various hospitals to set up their own tests. When the outbreak began we initially continued to send samples to NPHL because they asked for them! With new pathogens that we (everyone in Singapore) don't have much experience with it can be helpful to test samples in parallel, so it is good to work with colleagues and help each other achieve better results. We no longer send samples to NPHL.

When the amount of Zika in a sample is very low and approaches the limit of detection of the assay, repeat testing of another sample or even the same sample can give different results in the same laboratory. If these samples are tested in different laboratories then there is, inevitably, a certain degree of variability in the results, even if they are using the same assay. This can be troublesome if patients are isolated and only allowed to be discharged when results are negative, as different laboratories might issue different results. Our initial assay, which was also used by other centres, was based on a protocol published in 2008 and has numerous mismatches with the Singapore virus. We have replaced it with an in-house assay which matches 100%, developed in a collaboration between TTSH, the Experimental Therapeutics Centre (ETC) and the Bioinformatics Institute (BII). It is over ten times more sensitive!

Does the possibility of cross-reactivity with other flaviviruses, like dengue or yellow fever, complicate the interpretation of what a positive immunoglobulin M test means?
Yes, the cross reactivity with closely related viruses means serology is non-specific, so although many people are making serology tests for Zika, both IgM and IgG, we don't currently offer serology ... This is less of a problem if the patient is from a place or country without cross-reacting viruses but in Singapore we have dengue! Zika serology can also be complicated by previous vaccination with yellow fever virus and other flavivirus vaccines. As the CDC (USA) say, 'a conservative approach to the interpretation of antibody test results is now recommended!'.

Is there a rapid test kit for the Zika virus?
Nucleic acid tests are pretty rapid! I expect faster point of care tests to become available but … they are not here yet. The race is on to develop a Zika specific antigen test.

Are there any researchers in Singapore working on developing a rapid test kit for the Zika virus?
I'm not aware of local people developing a point of care test. However, we use a PCR assay developed in a collaboration between TTSH (Dr Tim Barkham) and the Experimental Therapeutics Centre (Dr Masafumi Inoue) and the Bioinformatics Institute (Dr Sebastian Maurer-Stroh). This builds on a long term collaboration.

DR TIMOTHY BARKHAM
is a senior consultant in the Department of Laboratory Medicine, Tan Tock Seng Hospital.

We asked our colleagues in KKH to provide us their perspective on handing Zika in pregnant women and their infants who might be potentially affected. Drs Thoon and Yung told us, "The key difference in the treatment of pregnant women confirmed infected with the Zika virus would be the impact on the unborn foetus. They will undergo close monitoring with serial ultrasounds, and/or amniocentesis, and when their infants are born, they would be fully evaluated for evidence of congenital Zika virus infection (clinical examination as well as placental examination, cord, infant blood, urine, and hearing/ visual assessment). For non-pregnant women with Zika virus infection, the primary approach would be to advice against getting pregnant for 6 months as per MOH guidelines, via abstinence or use of condoms."

How does KKH manage pregnant women who are suspected or infected with the Zika virus? Do you have a protocol in place?
For symptomatic pregnant women, the same as anyone else (per MOH guidelines). Our internal protocols mirror those of MOH. For asymptomatic women, we worked within MOH to develop a slightly more refined second set of guidelines which were updated in May then June.

What is the risk of developing microcephaly in a baby whose mother is infected with the Zika virus?
True figures are unknown. It was estimated to be 1% (to 13%) in French Polynesia (but major methodological caveats apply).

How long must a patient who is confirmed infected with the Zika virus wait if they wish to postpone pregnancy because they are worried about microcephaly?
The answer depends on which side of the Atlantic you are in! Currently we adopt the WHO and hence MOH position, which is 6 months.

How far into a pregnancy can you determine whether the foetus would have microcephaly, and how do you counsel the mother if that appears to be the case?
It depends on serial ultrasound findings. These can be measured in any trimester although the first ultrasound is done at "booking" around 14 weeks, then a foetal anomaly scan at around 19-20 weeks. Usually the foetal anomaly scan measurements would inform subsequent action. However ultrasound scans done later in pregnancy can also indicate microcephaly according to existing references. However, ultrasound diagnosis of microcephaly is not always sensitive or specific, and it can occur late in pregnancy.

Counselling – if microcephalic, and in the context of suspected or confirmed Zika virus infection, we state the facts, what we know and don't know, and consider offering amniocentesis. Currently, with the exception of very severe cerebral malformations that may be visualised on ultrasound or MRI, there is no way to predict whether a foetus with microcephaly will be delivered microcephalic, or have any long term negative neurodevelopmental outcomes. The reality is that even in the countries with documented foetal infections with Zika and microcephaly, we see case reports of the worst clinical cases, but do not hear of the spectrum of disease. Several countries are collecting data and developing registries on this – but even then it is hampered by the absence of a reliable denominator, as we may not be able to know how many women actually developed asymptomatic Zika infection during pregnancy (or even symptomatic infection without routine regular PCR screening) and delivered completely normal children. The current position is "refer to Maternal Foetal Medicine Specialist" for more "personalised counselling".

Can mothers infected with the Zika virus breastfeed?
Zika virus RNA has been detected in breast milk. However, there is no evidence of disease transmission via breast milk. Such detection is not surprising as dengue, West Nile and yellow fever virus which are from the same family have also been detected in breast milk. However, despite detection, there has only been documented West Nile transmission via breast milk in a small number of cases. In addition, we also do not know what the outcome spectrum is if infants are infected via breast milk which may manifest in a mild form.

WHO continues to recommend breastfeeding in infants born to Zika infected mothers and this is the current position.

Counselling on the risk for sexual transmission is also involved. What does this entail? Are patients surprised by that?
For pregnant women, the counselling is fairly straightforward, and the advice as per MOH. Patients in general have been receiving some information through internet and are usually not excessively surprised, although they can be emotionally affected by the diagnosis, similar to receiving bad news. The information delivered by obstetricians are usually to make sure they understand exactly what has been written in the papers/internet.

Are all pregnant patients with suspected Zika virus infection admitted?
As above, any patient, pregnant or otherwise, who fulfils MOH's criteria for suspect Zika virus infection, will be screened. However, very, very few have been admitted, as most are well enough to be discharged from the Women's 24-hour Clinic or Children's Emergency.

How is an infant born to confirmed/suspected women managed? Do you have a protocol in place?
This depends on when the confirmation/suspicion was made. We do have a protocol in place for infants who are just born to mothers with confirmed infection, and even mothers with suspect infection – but it largely begins with clinical evaluation, followed by progressively more invasive tests as indicated. However, for infants who are past the first week of life and are brought with some suspicion of maternal infection or may have features that may suggest Zika infection itself, evaluation is tricky and not straightforward, since serological testing is currently not available. In this group, evaluating for other congenital intra-uterine infections are critical, as well as other cause of microcephaly or cerebral malformations e.g. genetic, traumatic, hypoxic, toxic (alcohol, smoking) etc. If no other cause is found, we may offer Zika virus testing but we know that negative results do not rule it out.

DR THOON KOH CHENG *is a senior consultant and the Head of Infectious Disease Service, and* ***DR YUNG CHEE FU*** *is a consultant at the Department of Paediatrics (Infectious Disease Service), KK Women's and Children's Hospital.*

Conclusion

Zika virus infection has reached Singapore. Thanks to our national culture of organisation and preparedness, our hospitals and laboratories are well poised to handle the threat. Time will tell if the different strain of Zika virus found in Singapore compared to that in South American translates to a lower risk of neurological complications in infants and adults.

Information in this article is accurate up to 20 September 2016.

By: ***DR MANAUIS CHARMAINE MALENAB****, associate consultant in the Department of Emergency Medicine, Tan Tock Seng Hospital, and Ms Safiyya Mohamed Ali, senior medical writer in the Clinical Research & Innovation Office, Tan Tock Seng Hospital.*

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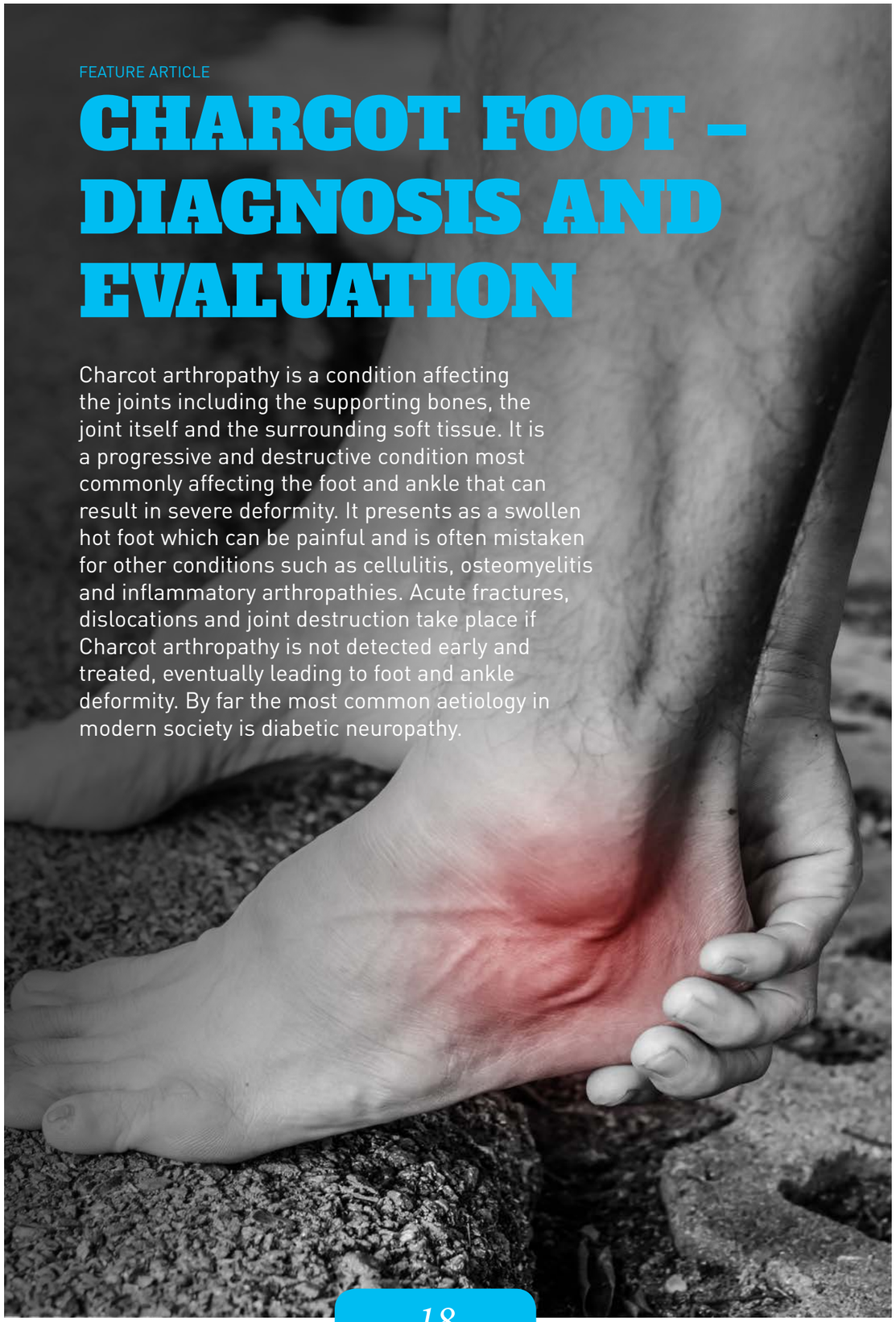
FEATURE ARTICLE

CHARCOT FOOT – DIAGNOSIS AND EVALUATION



Charcot arthropathy is a condition affecting the joints including the supporting bones, the joint itself and the surrounding soft tissue. It is a progressive and destructive condition most commonly affecting the foot and ankle that can result in severe deformity. It presents as a swollen hot foot which can be painful and is often mistaken for other conditions such as cellulitis, osteomyelitis and inflammatory arthropathies. Acute fractures, dislocations and joint destruction take place if Charcot arthropathy is not detected early and treated, eventually leading to foot and ankle deformity. By far the most common aetiology in modern society is diabetic neuropathy.

Sir William Musgrave is believed to be the first to describe the entity of "neuropathic arthritis" in 1703 as a complication of venereal disease. The medical community remained unaware of this condition until it was noticed by John Kearsley Mitchell in 1831 in patients with spinal tuberculosis who developed hot swollen asymmetrical joints; this was affirmed by Silas Weir Mitchell in wounded American Civil War soldiers with spinal injuries in 1864. In 1868, Jean-Martin Charcot recognised the importance of this destructive disease and in 1883, together with Féré, published the first observation of this process in the "short bones and small joints of the foot" (la pied tabetique). Widely acclaimed at the Seventh International Medical Congress in London, the prominent Sir James Paget, in recognising this distinct pathological entity declared that it be known as Charcot's disease. It was only in 1936 though that William Riely Jordan established the link between Charcot arthropathy and diabetes mellitus.[1]

The true prevalence of Charcot foot is unknown but a number of population-based studies report an estimate of 0.4-13% in patients with diabetes.[2] In Singapore, at the moment, this condition is often diagnosed late after complications have set in, limiting treatment options. The condition is becoming more prevalent. The 2010 National Health Survey found that diabetes mellitus affects 11.3% of our population, an increase from 8.2% in 2004. Major chronic complications from microvascular and macrovascular disease resulting in a three-fold increase in mortality and three- to seven-fold increase risk of coronary artery disease, make the treatment (both non-invasive and surgical) of Charcot foot extremely challenging.

The pathogenesis of Charcot neuroarthropathy does not consist of only one cause but the disease results from a particular trigger in a susceptible individual. The current belief is that the precipitating trigger starts uncontrolled inflammation within the foot that leads to osteolysis and subsequently progressive fractures and dislocations. If the patients does not sense the pain or tolerates it, and delays seeking treatment, he or she develops progressive deformity. The hallmark of Charcot foot is midfoot collapse resulting in a 'rocker-bottom' deformity. A neurally mediated vascular reflex leading to increased peripheral blood flow and active bone resorption has been proposed as an aetiological factor; however, this relationship has not been conclusively defined. The evidence for joint neuropathy and repeated trauma is also largely circumstantial.

Classification of a condition helps to prognosticate and influences direct treatment of that condition. In 1966, Eichenholtz published a landmark article on a classification based on radiographic appearance and physiologic course.[3] He described three stages - developmental, coalescent and reconstructive - that occur in a linear manner. In 1990, Shibata et al modified the classification by adding an earlier stage, which describes the appearance of an early inflammatory phase without radiographic evidence of destruction (table 1).[4]

Stage	Phase	Clinical description	Radiological findings
0	Inflammatory	Localised warmth, swelling and redness	Minimal to no radiographic abnormalities; MRI may show undisplaced fractures and increase marrow oedema
1	Development	Localised warmth, marked swelling and redness	Radiographic appearance of bony debris, fragmentation of subchondral bone, periarticular fracture, subluxation and/or dislocation
2	Coalescence	Continued but decreased warmth, swelling and redness	Radiographic presence of absorption of fine debris, new bone formation, coalescence of fragments, fusion of joints and sclerosis of bone ends
3	Remodelling/ Reconstructive	Marked decrease or absence of warmth, swelling and redness; physically enlarged fixed deformity	Radiographic appearance of remodelled and new bone formation, decrease sclerosis and/or possible gross residual deformity

Table 1. Classification of Charcot neuroarthropathy based on clinical course and radiological findings[4]

There are also anatomical classifications of Charcot arthropathy based on the prevalence of the most commonly affected joints e.g. Brodsky,[5] and Sanders and Frykberg.[6,7] However, it is more useful to gauge essentially whether a Charcot foot is active or inactive, which would correspond to inflammation or stability, respectively, regardless of the joints involved. Unfortunately, even in the modified Eichenholtz classification, the transition between the stages is often based on opinion and discretion rather than strict criteria. Nonetheless, the goals and methods of treatment differ between the active and inactive stages.

For assessment, diagnosis and management, we will refer to the systematic review by Milne et al in 2013[2] and the Consensus Report by the panel of international experts from the American Diabetes Association and American Podiatric Medical Association in 2011.[8] These guidelines are based mainly on case series and expert opinion, and very few good quality controlled trials; therefore some recommendations are controversial.[9]

Diagnosis is primarily clinical and requires a high level of suspicion from the treating clinician. Acute signs are localised unilateral swelling, erythema, warmth, and pain of the involved region in 50% and deformity in 50%. Late signs usually entail some form of deformity. A referral to a multidisciplinary high-risk foot service is recommended to obtain expert opinion to start appropriate management.

As many as half of the patients presenting as acute cases recall a preceding traumatic event to the foot, or a recent surgery. Due to the insensate limb, there is a recall bias and history of trauma may be unreliable. If recent surgery includes a ray amputation, this may also incite Charcot changes as the weight bearing points shift abnormally, increasing the risk of repetitive microtrauma.

The risk of Charcot and duration of diabetes is fairly well-established in both Type 1 and 2 diabetes. Diabetics of more than 10 years' duration are at risk of developing Charcot arthropathy. Peripheral neuropathy will almost always be present. There have been no reported cases in its absence. Peripheral arterial perfusion is usually good and described as "bounding". Soft tissue swelling sometimes impedes examination and a Doppler ultrasound is a good way around it.

Dermal thermometry will show a difference of more than 2 degrees between the feet. There are some

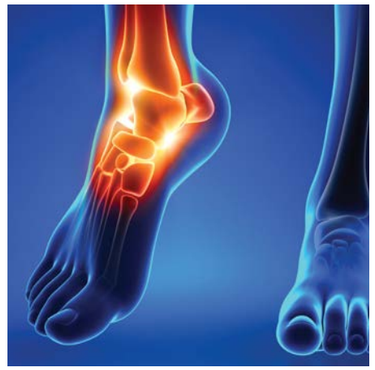
Diagnosis is primarily clinical and requires a high level of suspicion from the treating clinician. Acute signs are localised unilateral swelling, erythema, warmth, and pain of the involved region in 50% and deformity in 50%. Late signs usually entail some form of deformity.

precautions regarding its use: cast or footwear must be off for 15 minutes, sensitivity of the dermal thermometer must go down to ±0.1 degrees and different sites of the foot must be measured.

Orthogonal weight-bearing foot and ankle x-rays are important as a screening or diagnostic tool. Repeat radiographs are useful to monitor the patient through the different stages of Charcot. Magnetic resonance imaging (MRI) of the foot and ankle has become more useful now with the recognition of a Stage 0 Eichenholtz disease. It can also be useful to provide more information on the foot when there is a question of co-existent osteomyelitis with Charcot athropathy. The pattern of involvement provides one clue: Charcot arthropathy shows diffuse changes and affects joints while osteomyelitis is often focal. Labelled white blood cell scanning can be used to provide more specific distinction between infection and Charcot but it is not commonly available. All scans must be interpreted in relation to clinical findings.

Bone biopsy should only be undertaken when diagnosis remains inconclusive after all other imaging options are exhausted or if osteomyelitis is likely. The procedure itself can be the trigger for Charcot changes and so care must be taken when considering this option. The local and systemic inflammatory responses in an acute Charcot are dissociated according to recent studies.[10,11] Serum WCC,

CRP and ESR values remain within the reference range for patients with acute Charcot despite local inflammation. Therefore in patients with a hot swollen foot without a rise in inflammatory markers, acute Charcot must be strongly considered.



Glycosylated haemoglobin is a good marker for glycaemic control in a patient. Poor control increases the risk of Charcot neuroarthropathy.[12] A recent case study cites that an elevated HBa1c is associated with a 30% increase risk of developing Charcot foot.[13] Renal failure is also associated with an increased incidence of acute Charcot[14] with one study suggesting a two-fold risk.[13]

We will not delve into the management but only cover the principles here. The aim of treatment is to allow the patient to ambulate with a plantigrade foot and ankle which is stable and shoeable with minimal abnormal weight bearing pressure points. Education is paramount to maximise patient compliance and understanding as the treatment takes time, often over many months to more than a year. Prevention of deformity is key, hence early detection is important. Immobilisation and offloading is absolutely necessary. Weight bearing is controversial as more weight on the contralateral foot can initiate Charcot changes on the other side. Non-weight bearing is sometimes impossible so protected partial weight bearing is a reasonable compromise.

Orthotic and podiatric follow-up is important and instructions on use of specialised footwear must be adhered to. Generally surgery is indicated only when all conservative measures have failed. It is usually performed for reconstructive reasons in the late stage but sometimes carried out in early stages to prevent further deformity where intervention is judged to provide more benefit than risk. Wound care subsequently becomes important as the risk of infection and delayed wound healing is high.

In summary, all diabetic patients should undergo annual screening of the foot and ankle as recommended in the MOH Clinical Practice Guidelines 2014.[15] Clinical suspicion of Charcot arthropathy must be high in the chronic diabetic with more than 10 years' disease who presents with a hot swollen foot, in the context of past trauma to the involved limb, peripheral neuropathy, renal failure, and poor glycaemic control.

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Podiatric Management of Diabetic Foot Ulcers

In the management of diabetic foot ulcers (DFUs), podiatrists are involved not only in the decision making for wound dressing regimen, but also in the institution of appropriate offloading strategies. Depending on the complexity of the offloading measures, podiatrists also work closely with prosthetics and orthotics counterparts to deliver quality service to the patient.

In TTSH, the Podiatry Department attends to approximately 350 patients for wound care every month, constituting around 40% of the department's outpatient workload. Almost all of these 350 patients have DFUs, with auto-immune related wounds (e.g. vasculitis, scleroderma and others) taking up a minor proportion. Other wound types such as venous or lymphoedema related wounds are managed by the nursing wound team. As a result of the clinical experience, the Podiatry Department has established strong expertise in assessing and managing DFUs.

This article illuminates the rationale guiding the decisions of podiatrists in TTSH as they manage DFUs.

Assessment of DFUs

Diabetes patients with peripheral neuropathy tend to overload certain areas of the foot or develop shear forces in footwear due to foot deformities as they are unable to sense pain. Over time, the repeated pressure and/or shear forces cause the skin to break down resulting in a wound. Diabetes patients with peripheral vascular disease or reduced peripheral arterial supply to the feet may develop wounds which are difficult to heal due to the loss of blood perfusion to the area. Therefore, diabetics develop foot ulcers due to neuropathy, ischaemia or a combination of the two.

INCREASING SEVERITY OF SYMPTOMS

Contamination	Colonisation	Critical colonisation	Local infection	Systemic infection
Presence of non-replicating micro-organisms in wound – these are rapidly cleared by host defences	Presence of replicating micro-organisms adherent to wound bed without causing cellular damage to host	Increasing bacterial burden. These wounds fail to heal but may not manifest the classic signs of infection. The clinical signs and symptoms are delayed healing, pain or tenderness, increased serous exudate, change in colour of the wound bed, friable granulation tissue, absent or abnormal granulation tissue, and malodour.	Classic signs of infection (redness (erythema), warmth, swelling, and pain) are present with or without surrounding cellulitis. Often described as bacterial burden of $>10^5$ organisms per gram of tissue or mm^3 of pus.	Increasing bacterial burden in the wound. If untreated, this will result in systemic dissemination resulting in sepsis; progression may lead to multiorgan failure and even death.

Table 1. Assessment of wound for infection (adapted from Healy and Freedman 2006)

The majority of the wounds seen in Podiatry are neuroischaemic in nature and are typically recalcitrant and difficult to heal. Assessment tools include using the 10-g monofilament (Semmes-Weinstein 5.07)

Stage	Group			
	0	I	II	III
A (no infection or ischaemia)	Pre- or post-ulcerative lesion completely epithelialised	Superficial wound not involving tendon, capsule, or bone	Wound penetrating to tendon or capsule	Wound penetrating to bone or joint
B	Infection	Infection	Infection	Infection
C	Ischaemia	Ischaemia	Ischaemia	Ischaemia
D	Infection and ischaemia	Infection and ischaemia	Infection and ischaemia	Infection and ischaemia

Table 2. University of Texas Diabetic Wound Classification System

to test for neuropathy and a handheld Doppler machine to assess the patency of the dorsalis pedis and posterior tibial arteries. An immediate referral to the Vascular Surgeon is necessary if signs of acute ischaemia limb are present (pain, pallor, pulseless, paraesthesia, paralysis, and poikilothermia).

After establishing the aetiology, the wound should be assessed for infection. While the cardinal signs of inflammation (erythema, oedema and warmth) are easily observed, DFUs may be chronic, in a phase of colonisation or critical colonisation (table 1). It is important to differentiate the different stages of infection to effectively manage the wound. Wound swabs of an infected DFU (critical colonisation and above) can help to guide antibiotic therapy but cultures taken from colonised DFUs may yield inconclusive results due to the chronic contamination of the wound.

The base of the wound must also be assessed for tunnelling or sinuses that indicate the presence of a deep infection. If the bone can be probed, we must suspect osteomyelitis and further investigations such as imaging (x-ray and/or magnetic resonance imaging) and bone biopsy are required to confirm the diagnosis.

Wound exudate affects the way we manage the wound. Optimal wound healing requires a moist wound environment; hence it is important that exudate is adequately balanced by appropriate dressings. However, ischaemic wounds with low healing potential should be kept dry. Purulent exudate provides evidence of infection and a greenish discharge suggests colonization or infection by Pseudomonas aeruginosa.

After evaluation of the DFU as described above, it then needs to be classified to facilitate management planning and prognosis. The Wagner Ulcer Classification system is commonly used and is based on the depth of the DFU, but does not provide for categorising infection and ischaemia. Hence, TTSH Podiatry prefers the University of Texas Diabetic Wound Classification (table 2).

Management of DFUs

The TIME principle for wound bed preparation is applied to managing DFUs. The acronym stands for:

- **T**issue management
- Control of **I**nfection
- **M**oisture balance
- Advancement of the epithelial **E**dge of the wound

Tissue management refers to the debridement of the wound bed. This is routinely performed for DFUs if there are no contraindications like ischaemia. A sharp scalpel is used to remove overlying slough, biofilm and necrotic tissue from the wound bed to reduce the bioburden on the wound. Maggot debridement therapy may be used but is not frequently utilised due to inconvenience. Callus build-up is often observed with DFUs on the plantar aspect of the foot, hence it is also important to debride them to reduce pressure on the wound and allow the edges to epithelialise.

The next two principles, control of infection and moisture balance, are addressed with wound dressing.

Exudate level	No infection or ischaemia (University of Texas Stage A)	Infection without ischaemia (Includes chronic colonised ulcers) (University of Texas Stage B)	Ischaemia without infection (University of Texas Stage C)	Infection and ischaemia (University of Texas Stage D)
Superficial, clean (University of Texas Grade 0 and 1)				
Nil	Simple gauze dressing (protection)	Providone iodine with gauze dressing	Spirit dressing Providone iodine / Alcohol iodine	Providone iodine / Alcohol iodine with gauze dressing
+	Simple gauze dressing Urgotul/Jelonet (TG) Collagen particles	Iodosorb ointment / powder Acticoat Mesalt	Providone iodine with gauze dressing Providone iodine impregnated dressing Iodosorb powder	Iodosorb powder
++	Foam dressing Alginate/Hydrofibre ± foam	Iodosorb powder ± foam Acticoat ± foam Silver alginate/hydrofibre ± foam Iodosorb powder with foam	Iodosorb powder ± foam	Iodosorb powder ± foam Silver alginate / hydrofibre ± foam
+++	Alginate with foam	Silver alginate/hydrofibre with foam	Alginate with foam	Iodosorb powder with foam Silver alginate/ hydrofibre with foam
Superficial, sloughy (University of Texas Grade 0 and 1)				
Nil	Hydrogel	Silver gel	Spirit dressing Providone iodine/ Alcohol iodine	Providone iodine/ Alcohol iodine with gauze dressing
+	Hydrogel Mesalt Collagen particles	Silver gel Iodosorb ointment / powder Mesalt	Providone iodine impregnated dressing Iodosorb powder	Iodosorb powder
++	Foam dressing Hydrofibre ± foam	Iodosorb powder ± foam	Iodosorb powder ± foam	Iodosorb powder ± foam Silver alginate/ hydrofibre ± foam
+++	Hydrofibre with foam	Iodosorb powder with foam	Alginate with foam	Iodosorb powder with foam Silver alginate/ hydrofibre with foam
Tunnelling / Sinus / Cavity (University of Texas Grade 2 and 3)				
+	Pack alginate	Pack Acticoat Pack silver alginate	Pack alginate	Pack Acticoat
++	Pack alginate ± foam	As above ± foam	Pack alginate ± foam	Pack silver alginate As above ± foam
+++	Pack alginate with foam	Pack silver alginate with foam	Pack alginate with foam	Pack silver alginate with foam

Table 3. Podiatry wound care algorithm.

Key pointers:
- **Iodine sensitivity for patients with thyroid issues**
- **Mesalt not to be used on wounds with exposed tendons or with active bleeding**
- **For bleeding wounds, alginate is preferred over hydrofibre as it has haemostatic properties**
- **Hydrofibre ribbon (with reinforcement) can also be used in place of silver alginate**

Pressure relief interventions

Pressure relief interventions, like offloading devices, are most often indicated for plantar DFUs. The aetiology of plantar DFUs are insensate feet (neuropathy) and high mechanical stresses making it imperative to address these underlying factors when planning intervention strategies.

Types of offloading devices

Offloading devices provide pressure relief to the area of high pressure on the foot, through redistributing pressure across a wider surface area. This is usually achieved by increasing the contact area with the foot interface, and, for some devices, on the leg as well. These devices can come in the form of a knee-length cast, shoes, insoles and paddings.

KNEE-LENGTH CASTS

Knee-length casts can either be made removable or non-removable. Non-removable casts include the total contact cast (TCC) and instant total contact cast (iTCC). TCC is made of fiberglass, similar to the cast that is used to immobilise fractures. iTCC on the other hand, is a removable long walker (RLW) that is made non-removable by applying a layer of fiberglass on the outer shell (figure 1). As the cast extends to the leg, it provides a greater surface area for pressure re-distribution. Studies have shown that up to 30% of the load is transferred to the leg with TCC. The cast also locks the ankle joint and prevents plantar flexion of the foot, which makes it an excellent device to offload plantar forefoot ulcers. Clinicians have to adopt a cautious approach when considering the device on patients with falls risk, lower limb oedema and underlying peripheral vascular disease.

This device is usually indicated in superficial non-infected DFUs as the cast will be left on for a week and the wound inspected only upon cast removal. When using a TCC for DFUs that are infected or that extend to deeper structures like tendon or bone but require a high level of pressure relief, modifications to the TCC can be made by creating a window over the ulcer area to allow for regular wound inspection and dressing changes. Another alternative is the use of a removable cast device such as the RLW incorporated with total contact insoles. A study that looked into the offloading properties of TCC and RLW found that both had similar offloading profiles, while others have shown that non-removable casts are superior to the removable devices in optimising DFU healing. A follow-up study found that patients on removable devices only wore the device during 28% of their daily activities. Therefore, the superiority of the non-removable device is attributed to the forced compliance aspect that increases the effectiveness of the intervention.

SHOES

Types of offloading shoes include: (1) stiff-sole post-op sandals, (2) heelwedge sandal, (3) orthowedge sandals, and (4) rocker-bottom shoes (figure 2). The stiff-sole post-op sandals prevent dorsiflexion of the toes, ensuring even redistribution of forces across the metatarsal heads. The heelwedge and orthowedge sandals are thicker at one end to allow increased load on that end and reduced load at the other. The heelwedge sandals is used to offload the heel, with the sandals thicker from the midfoot and forefoot end, while the orthowedge is used to offload the forefoot, with the sandal being thicker

Figure 1. Knee-length devices (from left to right): Total contact cast, instant total contact cast, removable long walker.

Figure 2. Custom offloading insoles.

at the heel and midfoot end. The disadvantage of these two sandals is that they are unstable, making them unsuitable for patients who are liable to fall. As the sandals have thicker ends, they create a functional limb length discrepancy against the contralateral limb and may cause back pain with prolonged use. Therefore, they are mainly used as a temporary measure where offloading is quickly required or in the interim period while awaiting a long-term customised device. Rocker bottom shoes are meant to facilitate propulsion of the foot, that is, accelerating the propulsion phase of gait and reducing plantar forefoot pressures. Shoes with extra width and extra depth are also often used to accommodate foot deformities, such as clawed toes and bunions, and are often prescribed along with customised insoles.

INSOLES

Customised insoles are devices customised to the patient's feet and increase contact surface across the entire foot so as to reduce pressure at the ulceration site (figure 3). A soft material is commonly used to reduce peak plantar pressures. It is commonly fitted into an extra depth and extra wide shoe for use.

PADDING

Padding is probably the most commonly used offloading intervention by podiatrists (figure 4). It is quick and easy to manufacture. Felt is the most common material used and is cut in shapes with an aperture around the ulceration site to aid in pressure relief. The disadvantage is that it needs to be changed when the dressing is changed. It can be made removable to prevent wastage of material but it also loses its offloading capacity quickly.

Figure 3. Custom offloading insoles.

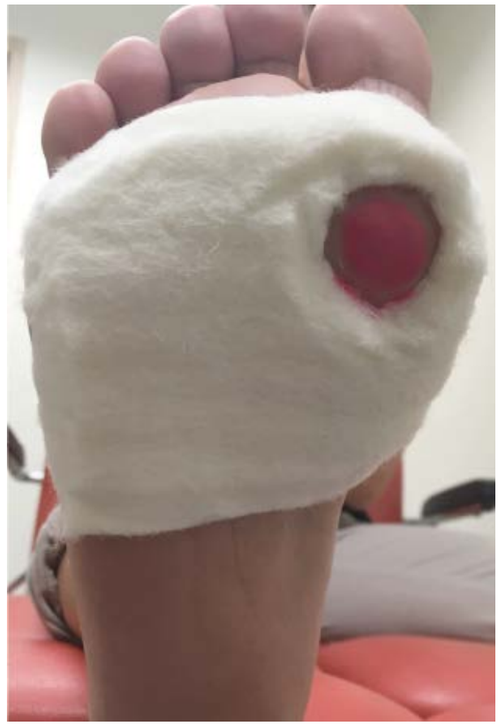

Figure 4. Felt padding.

Conclusion

In conclusion, podiatric management of DFUs involves a complex web of interweaving factors that impact management considerations. In addition to wound classification and TIME principles for wound management (including offloading strategies), individual patient factors such as degree of foot deformity, activity levels, psychosocial issues and financial constraints also need to be addressed when deciding on the appropriate management plan.
In order to optimise care delivery to this group of high-risk patients, TTSH Podiatry capitalises on the synergistic interactions with the other members of the multi-disciplinary team involved in the care of this patient group to deliver the most appropriate care.

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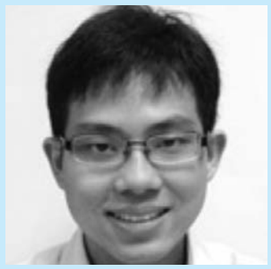

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Orthotic Management of Charcot Arthropathy

The role of the orthotist in the management of patients with Charcot arthropathy

As detailed above, the effects of Charcot arthropathy can be debilitating; disrupting the integrity of the foot and ankle complex, and inhibiting functional locomotion. In order to facilitate healing and return to mobility, the joints must first be protected from continual trauma. Orthoses are used throughout the condition's progression from immobilisation during the acute phase to supporting residual structures post-resolution.

The broader term of orthoses refers to devices applied externally to a body segment affected by neuromuscular and skeletal conditions. They act to modify the structural and functional characteristics of these systems to compensate for their impairments. An orthotist is the healthcare professional who specialises in the assessment, prescription, design, fitting and monitoring of orthoses.

Common orthoses used for Charcot arthropathy and their functions

There are a large variety of devices available for Charcot arthropathy, however each type is highly specific to the user's presentation at a certain point in time. The goals of orthotic treatment will change as the disease improves or deteriorates, and the patient will often progress through several devices. Generally, the treatment goals should be to maintain or achieve structural stability of the foot and ankle, prevent ulceration, and to preserve a plantigrade foot.
A summary of orthoses frequently prescribed and their purpose at each stage is illustrated in table 1.

It is recommended for all patients with acute stage 0-I Charcot arthropathy to be fitted with a non-removable device unless contraindicated. This aggressive immobilisation approach has been shown to be the most effective in both total contact casts (TCCs) and instant total contact casts (iTCCs) for treating and shortening time to resolution by encouraging compliance. Exclusion criteria for non-removable devices include the presence of active skin disease, severe fluctuating lower limb oedema, active infection, high exudate, wound probing to tendon or bone, wound with deep sinus tracking, ischaemia (Ankle-Brachial Index <0.65), severe peripheral arterial disease, high falls risk, blindness, known non-compliance and inability to attend regular follow-up reviews. However, some of these risks may be managed at the discretion of the clinician by alternative methods of application and arranging additional healthcare support.

Multi-disciplinary approach in optimising orthotic outcomes

It has been well established that Charcot arthropathy is a complex condition associated with increased morbidity, mortality and risk of amputations. Consequently, appropriate management requires the expertise from a network of healthcare workers. Efficacy of orthotic intervention can be maximised by engaging with this wider network; from polyclinic physicians to endocrinologists, and from diabetes nurse educators to dieticians. Table 2 summarises some simple steps all healthcare professionals can take in giving their patients the best chance of recovering with a stable and functional foot.

First, it is critical that a referral be initiated to a foot and ankle specialist at the first signs of Charcot arthropathy regardless of whether the diagnosis has or has not yet been confirmed. All suspected cases require immediate immobilisation and are usually treated as acute stage 0-I while awaiting definitive test results. However, timely management of the acute phase continues to be a challenge. Literature reports that diagnosis is missed in 25 to 79% of cases, with an average 29-week delay for accurate diagnosis. A delay of approximately 8 weeks after initial Charcot arthropathy onset was significantly associated with increased risk of ulcer formation and infection compared to patients diagnosed within 4 weeks. Similarly another study found that only 9% of patients developed gross foot deformity when managed within 4 weeks of onset, compared to 92.3% when managed within 3 months of onset. Therefore it is evident that early intervention enabled through early referral is the key to breaking the cycle of repetitive trauma and

	Orthotic aims and functions	Orthotic device
Stage I	• Immediate and aggressive short-term immobilisation • Prevent further deformity • Protect from additional trauma • Reduce plantar pressures and oedema • Minimise weight-bearing	**TOTAL CONTACT CAST (TCC)** Custom cast commonly moulded with plaster of Paris or fibreglass to maintain total contact with all surfaces of the foot and leg Effective for moderate to severe deformities when applied by a highly skilled clinician **INSTANT TOTAL CONTACT CAST (ITCC)** Prefabricated cast walker with custom insole converted into a non-removable device by securing fibreglass or other reinforcement materials around straps Effective for nil to mild deformities where minimal time and clinical training is available 
Stage II	• Continued immobilisation, protection and pressure distribution • Gradually re-introduce weight bearing	**REMOVABLE CAST WALKER (RCW) WITH INSOLE*** Prefabricated cast walker with custom insole Effective for nil to mild deformities when patient can operate device themselves or with carer, and adheres to management plan 
Stage III	• Long-term management to maintain foot and ankle support • Maintain even plantar pressure distribution to avoid ulceration • Accommodate fixed deformities if present	**CHARCOT RESTRAINT ORTHOTIC WALKER (CROW)†** Custom-made walker with soft inner lining, rigid front and back shell, and rocker bottom sole Effective for severe deformities or chronic instability **FOOTWEAR AND INSOLE** Supportive footwear commonly with rigid sole, rocker bottom, firm heel counter and extra depth to accommodate custom moulded insole. Custom/modified footwear may be necessary depending on the severity of deformity. Effective for nil to moderate deformities. 

Table 1. Common orthotic devices used to manage Charcot arthropathy

***RCW may be used during Stage 0-I as a less aggressive form of immobilisation if patient conditions are not suitable for non-removable device.**

†CROW may be used for all stages of Charcot arthropathy if patient conditions are not suitable for non-removable device and/or there is severe deformity which cannot fit into a prefabricated device.

Before/beginning	• Know the red flags for Charcot arthropathy: Red, hot and swollen foot • Refer immediately to foot and ankle orthopaedic surgeon, orthotist or podiatrist for all suspected cases
During	• Encourage patient compliance • Contact orthosis provider or foot and ankle specialist if complications arise
After	• Look out for return of clinical signs and symptoms indicative of relapse • Refer back foot and ankle orthopaedic surgeon, orthotist or podiatrist accordingly

Table 2. Recommended actions for healthcare professionals to maximise efficacy of orthotic treatment before, during and after an acute Charcot arthropathy episode

preventing secondary complications.
Second, educating patients, their family and carers is essential for gaining patient compliance. The more healthcare professionals can facilitate patient understanding towards the nature of their limb-threatening condition and necessity of immobilisation, the more likely patients will adhere to their orthotic management plan. During orthotic consultation, care is also taken to further explain instructions for orthotic use, expected length of treatment and outcomes, and the importance of attending regular follow-up appointments. It is understandable that patient motivation may wane through the course of orthotic treatment, especially with the pressures of work and family life – an acute Charcot arthropathy episode can last from 2 to 12 months, with an average of 6 months most commonly reported. However if healthcare workers consistently reinforce the same messages, patient adherence can be significantly improved.

Third, healthcare workers should be aware of Charcot arthropathy signs and symptoms returning after the consolidation stage, and refer accordingly if this occurs. Recurrence is reported in 15-30% of patients with a history of Charcot arthropathy. Ensuring the patient has routine podiatric appointments for foot care, involving the patient and carers in self-detection, and providing education about the risk factors of neuroarthropathy are all valuable components of care for this demographic. Whilst risk of relapse cannot be eliminated, it can be mitigated at each client interaction.

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PHARMACY

SURGICAL ANTIBIOTIC PROPHYLAXIS IN ELECTIVE SURGERIES: MORE IS LESS

A patient was admitted for an elective right total hip replacement surgery and was prescribed IV cefazolin peri-operatively as prophylaxis against post-operative infections. The surgery was successful and IV cefazolin was administered for three more days in the general ward. The pharmacist queried the need for prolonged antimicrobial prophylaxis but the surgical team was concerned of the risk of surgical site infection as the surgical drains were still in-situ.

Surgical site infection (SSI) is the most common nosocomial infection in post-surgery patients, leading to increased hospitalisation and costs.[1] International guidelines have emphasised the role of appropriate antimicrobial prophylaxis, hair removal by clipping as needed, and avoidance of hypothermia, in addition to the maintenance of normoglycaemia for diabetic patients, to reduce SSI rates.[2,3]

A pilot project performed in Tan Tock Seng Hospital from 2006 to 2007 on elective gastrointestinal surgeries focusing on these four interventions reduced SSI rates from 3.1% to 0.5% with an estimated cost saving of S$205,562.[4] A subsequent 3-month audit performed in 2008 on 216 elective general, neurological and orthopaedic surgical procedures identified a mean of 1.4 antibiotic prophylaxis errors per surgery with correct antibiotic type identified in 64%, appropriate antibiotic timing in 83%, supplemental antibiotic dosing in 34%, and antibiotic duration of less than 24 hours in 44%.

Normothermia was present in 79% of surgeries and normoglycaemia was present in 17%. Multivariate analysis showed that the presence of more than two antimicrobial prophylaxis errors per surgery significantly predicted SSI (odds ratio, 4.030; 95% confidence interval 1.02-15.96).[5]

It is important for healthcare professionals to be aware of the critical steps needed to ensure appropriate antimicrobial prophylaxis to prevent SSI.

A "Take 5" Model To Guide The Use Of Surgical Antibiotic Prophylaxis

The following points must be considered when deciding on surgical antibiotic prophylaxis:

1) Is antibiotic prophylaxis indicated?
2) Which antibiotic should I use?
3) When should I administer to achieve adequate antibiotic tissue concentration?
4) How do I maintain adequate tissue concentration for the duration of the surgery?
5) Do I continue antibiotic after surgery?

(1) Is Antibiotic Prophylaxis Indicated?
(2) Which Antibiotic Should I Use?

Surgical wounds can be classified according to the scheme in table 1.[6] There is increased bacterial contamination and risk of SSI in contaminated and dirty wounds. The use of antimicrobial agents for contaminated or dirty wounds is considered treatment and not prophylaxis. Antibiotic prophylaxis is generally recommended for most clean-contaminated procedures and in certain clean procedures where there can be severe consequences if infection occurs, for example implantation of prostheses.[6] International guidelines provide antibiotic recommendations for different types of surgeries.[2,3,6] These recommendations should be adapted to local epidemiology of antimicrobial resistance.

WOUND CLASSIFICATION	DEFINITIONS
Clean	Uninfected operative wounds in which no inflammation is encountered and the respiratory, alimentary, genital or uninfected urinary tracts are not entered. Wounds are primarily closed.
Clean-contaminated	Operative wounds in which the respiratory, alimentary, genital or urinary tracts are entered under controlled conditions and without unusual contamination.
Contaminated	Open, fresh, accidental wounds. Include operations with major breaks in sterile techniques or gross spillage from viscus and incisions in which acute, non-purulent inflammation is encountered.
Dirty	Old traumatic wounds with retained devitalised tissue and those that involve existing clinical infection or perforated viscera.

Table 1. Wound Classification System to inform the decision about prophylactic antibiotics.[6]

(3) When Should I Administer To Achieve Adequate Antibiotic Tissue Concentration?

Most antibiotics should be administered not longer than 1 hour before skin incision.[6] Patients who receive prophylactic antibiotics within 1-2 hours prior to initial incision have lower rates of SSI than patients who receive antibiotics sooner or later than this window period.[7-8] However, other agents like vancomycin and fluoroquinolones should be administered 2 hours before skin incision. The prolonged infusion times are required to reduce the risk of red-man syndrome and venous irritation. Because these drugs have long half-lives, administering them 1 hour early should not compromise the antibiotic tissue concentrations.

(4) How Do I Maintain Adequate Tissue Concentration For The Duration Of The Surgery?

One dose of antibiotics is usually sufficient for pre-operative prophylaxis.[2] Re-dosing of prophylactic antibiotics during operations are only required if the duration of operation is extended to beyond two half-lives of the antibiotics or if there is excessive loss of blood (more than 1500 ml) to ensure adequate concentrations of drugs in body.[6]

(5) Do I Continue Antibiotic After Surgery?

Single dose antibiotic prophylaxis is recommended for most surgical cases except for cardiothoracic surgery, which may require up to 48 hours based on expert consensus.[2] It may be intuitive to continue antibiotic prophylaxis post-surgery especially when surgical drains are in-situ post-operatively. However, prolonged duration of prophylaxis does not reduce SSI rates, and can lead to antimicrobial resistance and unnecessary nosocomial infections.

Single dose antibiotic prophylaxis is recommended for most surgical cases except for cardiothoracic surgery, which may require up to 48 hours based on expert consensus.

A systematic review concluded there was no difference in rates of SSI with single dose compared with multiple dose antibiotic regimens.[9] The risk of SSI was not reduced when antibiotic prophylaxis was extended beyond 48 hours in patients undergoing coronary artery bypass graft surgery.[10] There were no differences in SSI rates among patients with open fractures when comparing a variety of surgical antibiotic prophylaxis duration (1 day, 2-3 days, 4-5 days and >5 days).[11] Similar results were observed in a study of lumbar arthrodesis surgery.[12]

The use of antibiotics can alter the individual and institutional bacterial flora, leading to changes in colonisation rates and increased bacterial resistance. Prolonged duration of antibiotic prophylaxis increases the risk of acquired antimicrobial resistance (cephalosporin-resistant *Enterobacteriaceae* and vancomycin-resistant *Enterococcus*).[10] Prolonged duration of antibiotic prophylaxis following excision of head and neck lesions (5 days) resulted in significantly more patients with wounds infected by MRSA when compared to the short term group (1 day).[14] Even a single dose of antibiotic can increase the risk of *C. difficile* carriage and prolonged duration of antibiotic prophylaxis is a risk factor of *C. difficile*-associated colitis.[15] Limiting antimicrobial prophylaxis to a single pre-operative dose can reduce risk of *C. difficile*-associated colitis. In a study involving more than 1,800 patients undergoing surgery for hip fracture, the use of a single dose of cefuroxime with gentamicin instead of three doses of cefuroxime resulted in a decrease of *C. difficile* infection from 4.2% to 1.6%.[16]

In the light of these evidence, international guidelines recommend that there is no sufficient data to support

the continuation of antimicrobial prophylaxis until indwelling drains and intravascular catheters are removed.[2,3,6,13] Other than cardiothoracic surgeries, repeat dosing of antibiotics after wound closure is not necessary and may result in antimicrobial resistance.

Tan Tock Seng Hospital has a set of antimicrobial prophylaxis guidelines available in the intranet which is accessible via the Antimicrobial Stewardship Programme microsite or the Pharmacy notice board. Our guidelines provide the clinicians useful information to address the "Take 5" points.

Conclusion

Appropriate surgical antimicrobial prophylaxis is crucial in reducing SSI rates. The "Take 5" model to surgical antibiotic prophylaxis together with guidance from an institutional guideline can be used. Locally, emphasis should be given to improve selection of appropriate antibiotics and limit duration of prophylaxis.

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PHARMACY:

PERI-OPERATIVE MANAGEMENT OF ANTICOAGULATION AND ANTIPLATELET THERAPY

CASE STUDY

Mr Tan is a 65-year-old male on warfarin for atrial fibrillation (AF) and moderate rheumatic mitral valve stenosis. He is scheduled for a laparoscopic cholecystectomy on 7 July. He weighs 55 kg and has an estimated creatinine clearance (CrCl) of 56 ml/min. How should his peri-operative management of warfarin be carried out?

The management of anticoagulation and antiplatelet therapy for patients undergoing elective operation or procedure is frequently encountered in clinical practice. Optimal management depends on an accurate assessment of the patient's risk of thromboembolism and the risk of bleeding from the procedure.

Bridging anticoagulation is initiated when oral anticoagulation is held off and the international normalised ratio (INR) falls below the therapeutic range. It involves administering a short-acting anticoagulant, such as subcutaneous (SC) low-molecular-weight heparin (LMWH) or intravenous (IV) unfractionated heparin (UFH), and its necessity is dependent on the patient's thromboembolic risk.

Risk Of Thromboembolism

The American College of Chest Physicians (ACCP) 2012 guidelines on Perioperative Management of Antithrombotic Therapy proposes a three-tiered thrombotic risk classification, where high-risk patients receive bridging anticoagulation during interruption of warfarin and low-risk patients do not (table 1). For patients at moderate risk, the decision on bridging anticoagulation is left to the physician-in-charge based on individual patient and surgery-related factors.[1]

The Tan Tock Seng Hospital (TTSH) Anticoagulation and Antiplatelet Peri-Operative Management Guidelines recommend a two-tiered risk categorisation, in which ACCP moderate risk indications are re-classified as either high or low risk (table 2). Similar to the ACCP guidelines, high-risk patients receive bridging anticoagulation while low-risk patients do not.[2]

Pre-Operative Management Of Anticoagulation

WARFARIN

Warfarin is stopped 5 days before surgery. Four days before surgery, patients at high risk for thromboembolism start bridging with SC LMWH, of which SC enoxaparin (Clexane®) is most commonly used. The last dose of SC enoxaparin is given in the morning 1 day, approximately 24 hours, before surgery (table 2). SC enoxaparin and warfarin are withheld on the day of surgery.[1,2]

The pharmacist from the TTSH Anticoagulation Service (ACC) can be contacted to review the patient at the Pre-Admission Counselling and Evaluation (PACE) Clinic and advise the patient on the peri-operative plans. Alternatively, the surgeon can refer the patient to the outpatient ACC clinic at least 1 week before surgery for peri-operative planning. The pharmacist will instruct the patient on the date to hold off warfarin, as well as the self-injection of SC enoxaparin, if required.

The INR is measured 1 day before surgery to ensure that it has returned to baseline. Blood tests can be done at the PACE Clinic, as part of panel of blood tests ordered by the surgeon, or during an ACC appointment. If the INR is >1.5, the PACE Medical Officer or pharmacist should alert the surgeon that further INR correction is needed. Failure to assay the INR prior to surgery denies the doctor the option to prescribe Vitamin K to correct a suboptimal result and may lead to postponement of procedure or forcing the surgeon to modify the procedure, such as performing endoscopy without biopsy.

For patients with a mechanical heart valve, either SC enoxaparin or IV UFH may be used for bridging. However, IV UFH is preferred in patients with more than one mechanical heart valve and in mechanical heart valve patients with CrCl below 30 ml/min. Warfarin is omitted 5 days before surgery and the patient hospitalised 3 days before surgery to start IV UFH when INR is <2, titrated according to the heparin protocol with the last dose 4-6 hours before surgery.[1]

RISK STRATUM	INDICATION FOR VITAMIN K ANTAGONIST THERAPY		
	MECHANICAL HEART VALVE	ATRIAL FIBRILLATION (AF)	VENOUS THROMBOEMBOLISM (VTE)
High (>10% annual risk)	• Any mitral valve prosthesis • Any caged-ball or tilting disc aortic valve prosthesis • Recent (within 6 months) stroke or transient ischaemic attack (TIA)	• $CHADS_2$ score of 5 or 6 • Recent (within 3 months) stroke or TIA • Rheumatic valvular heart disease	• Recent (within 3 months) VTE • Severe thrombophilia (eg, deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies; multiple abnormalities)
Moderate (5 to 10%)	Bileaflet aortic valve prosthesis and one or more of the following risk factors: AF, prior stroke or TIA, hypertension, diabetes, congestive heart failure, age >75 years	$CHADS_2$ score of 3 or 4	• VTE within the past 3-12 months • Non-severe thrombophilia (e.g. heterozygous factor V Leiden or prothrombin gene mutation) • Recurrent VTE • Active cancer (treated within 6 months or palliative)
Low (<5%)	Bileaflet aortic valve prosthesis without AF and no other risk factors	$CHADS_2$ score of 0 to 2 (no prior stroke or TIA)	VTE >12 months previous and no other risk factors for stroke

High-risk patients may include:
- prior stroke or TIA occurring >3 months before planned surgery and $CHADS_2$ score <5,
- prior thromboembolism during temporary interruption of Vitamin K antagonists,
- certain types of surgery associated with an increased risk for stroke or other thromboembolism (e.g. cardiac valve replacement, carotid endarterectomy, major vascular surgery).

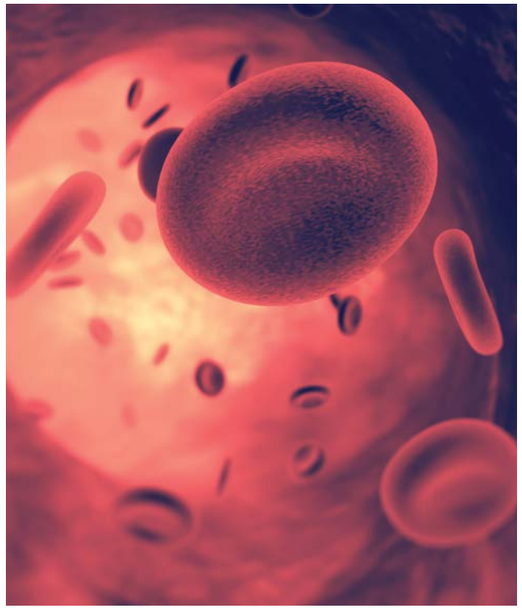
Table 1. Suggested risk stratification for peri-operative thromboembolism by ACCP 2012 Guidelines on Peri-operative Management of Antithrombotic Therapy.

	HIGH RISK FOR THROMBOEMBOLISM	LOW RISK FOR THROMBOEMBOLISM
Indication for Warfarin	• Known hypercoagulable state as documented by a thromboembolic event and one of the following: - Antiphospholipid syndrome - Antithrombin III deficiency - Factor V Leiden mutation - Protein C deficiency - Protein S deficiency • AF with history of stroke/TIA • Mechanical valve replacement • Intracardiac thrombus ≤3 months • Rheumatic mitral stenosis • Recurrent stroke or stroke/TIA ≤3 months without AF • Venous thromboembolism ≤3 months • Arterial thromboembolism or artificial bypass graft (by vascular surgeons)	• Non-valvular AF without history of stroke/TIA • Intracardiac thrombus >3 months • Stroke/TIA >3 months without AF • Venous thromboembolism >3 months
Peri-Operative Management	Omit warfarin 5 days before surgery. Inject SC enoxaparin 4 days before surgery WITH last dose in the morning one day before day of surgery. (50% of dose if once daily dose) *Dosage of enoxaparin is usually 1 mg/kg bd, or 1.5 mg/kg daily if patient unable to self-inject, or 1 mg/kg daily in renal impairment (CrCl <30 ml/min)*	Omit warfarin 5 days before surgery

Table 2. Risk categories for thromboembolism and peri-operative management according to the TTSH Anticoagulation and Antiplatelet Peri-Operative Management Guidelines.

RENAL FUNCTION (CrCl, ml/min)	DABIGATRAN		RIVAROXABAN AND APIXABAN	
	High risk for bleeding	Low risk for bleeding	High risk for bleeding	Low risk for bleeding
>50	2 days / 48 hours	1 day / 24 hours	2 days / 48 hours	1 day / 24 hours
30-50	4 days / 96 hours	2 days / 48 hours	2 days / 48 hours	1 day / 24 hours
<30	6 days / 144 hours	4 days / 96 hours	4 days / 96 hours	2 days / 48 hours

Table 3: Recommended duration for discontinuation of NOACs prior to surgery or invasive procedures.



NOVEL ORAL ANTICOAGULANTS

As drug clearance of the novel oral anticoagulants (NOACs) is dependent on the patient's renal function, the duration to withhold NOACs pre-procedure depends on the surgical team's assessment of the patient's bleeding risk and renal function. Table 3 summarises the duration for NOAC discontinuation prior to surgery recommended by the TTSH guidelines and the Chapter of Haematologists, College of Physicians, Singapore.[2,3]

Pre-Operative Management Of Antiplatelet Therapy

Whether to withhold antiplatelet therapy before surgery depends on the doctor's assessment of the cardiac risk.[1,2]

In the treatment of patients who require surgery within 6 weeks of placement of a bare-metal stent (BMS) or within 6 months of placement of a drug-eluting stent (DES), both ACCP and TTSH recommend continuing dual antiplatelet therapy in the peri-operative period and seeking a cardiology consult.[1,2]

In patients with moderate to high risk of cardiovascular events (e.g. severe coronary artery disease who have declined CABG or PCI) and patients with BMS >6 weeks or DES >6 months, it is recommended to continue aspirin if surgery allows. Patients on dual antiplatelet combination of aspirin plus clopidogrel or prasugrel will stop clopidogrel or prasugrel 5 days before surgery.[1,2]

For patients not at high risk of cardiac events, antiplatelet therapy can be withheld prior to surgical procedure according to the following guidelines:[1] Patients receiving aspirin, clopidogrel, dipyridamole and prasugrel should be instructed to discontinue the drug 7 days before the procedure. For those on ticagrelor and ticlopidine, it is 5 and 14 days respectively.

DENTAL PROCEDURES

Outpatient dental procedures including simple or multiple tooth extractions and endodontic (root canal) procedures generally do not require interruption of oral anticoagulation or antiplatelet therapy.[1,2] The dental surgeon can consider checking the INR approximately 72 hours before the procedure.

Studies suggest that prescribing a prohaemostatic agent, e.g. tranexamic acid mouthwash, for a patient on warfarin ensures a low (<5%) risk of clinically relevant non-major bleeding following dental procedures. Other local measures such as applying pressure or suturing can control bleeding after the procedure. Alternatively, partial interruption of warfarin by stopping 2-3 days before the dental procedure can be considered.

Patients should be informed that minor bleeding or oozing from the gingival mucosa may occur. They should apply local pressure and continue tranexamic acid mouthwash to control this bleeding.[2]

RISK OF BLEEDING

The bleeding risk of the surgery is assessed by the surgeon based on surgery type and individual patient factors. Anticoagulation and/or antiplatelet therapy can be restarted 48-72 hours after procedures with high bleeding risk, or 24 hours after procedures with low bleeding risk.[1,2]

Tan Tock Seng HOSPITAL

Sticky label (includes name, registration number and address)

Peri-operative Management of Anticoagulation

Patient Counselling Form

Scheduled date of Surgery: _____

Dose of enoxaparin (Clexane®): Before surgery _____ for 3 days, then _____ for 1 day

After surgery _____ for _____ days till ACC appt

Date	With reference to surgery	Action	Anticoagulation
	Day –5		Stop warfarin
	Day –4		Inject enoxaparin at 8am & 8pm
	Day –3		Inject enoxaparin at 8am & 8pm
	Day –2		Inject enoxaparin at 8am & 8pm
	Day –1	Check INR. Dr to inform surgeon if INR > 1.5	Inject enoxaparin at 8am **ONLY**
	D-Day (Date) _____	Day of surgery	- Surgical team to confirm restart of anticoagulation post-surgery. - If for inpatient admission, inform Anticoagulation Service for review and warfarin restart dose.
	Day +1		Restart warfarin (at 6pm) _____ Restart enoxaparin (from 8pm onwards) _____
	Follow up appointment		TCU CVM / NNI / GMD ACC _____ PT-INR OA

Dear Doctor / Nurse,

The above mentioned patient is scheduled for surgery and has been instructed to stop warfarin. Please administer enoxaparin (Clexane®) subcutaneously as stated while he / she is not on warfarin / waiting for warfarin to take effect post-surgery.

Thank you for your assistance.

_____ *(sign, name, designation, date)*

Anticoagulation Service / Pre-Admission Counselling & Evaluation
Tan Tock Seng Hospital
Tel: 6357 2220

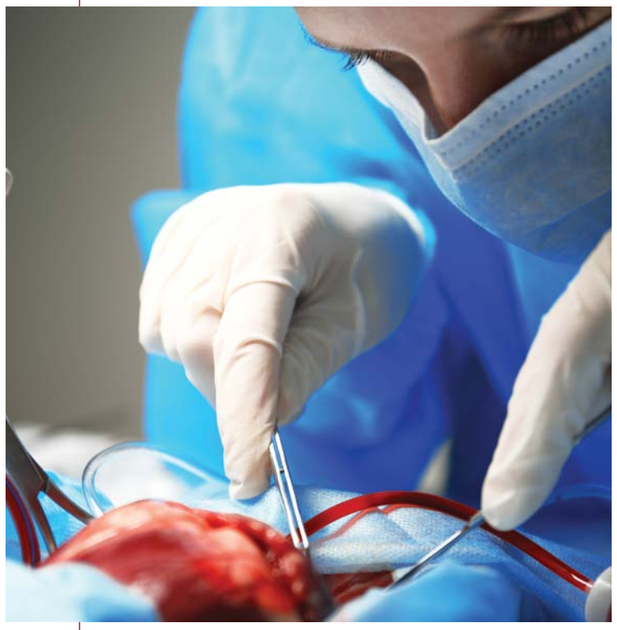
PHA-ACC-04-02

Figure 1: Peri-operative management of anticoagulation - Patient Counselling Form.

Post-Operative Management Of Anticoagulation And Antiplatelet Therapy

WARFARIN

For patients at low risk of thromboembolism, warfarin can generally be restarted at the previous stable maintenance dose when deemed safe by the surgeon and haemostasis is secured.[1] For patients at high risk of thromboembolism, warfarin and SC enoxaparin or IV UFH may be restarted together when the patient is haemodynamically stable. IV UFH should be restarted without a loading bolus dose at least 12 hours after surgery.[1] For Day Surgery or Next Day Discharge cases, the surgeon is to assess when it is safe to restart anticoagulation and to instruct the patient accordingly. If haemostasis is secured, the patient can follow the post-operative anticoagulation plans suggested by the pharmacist during PACE/ACC consult. ACC can be contacted for inputs if suggested post-operative anticoagulation plans require adjustment, e.g. if restarting of anticoagulation needs to be delayed or when re-operation is indicated.



For patients admitted to inpatient wards, the surgical team confirms that the patient can be restarted on warfarin before contacting ACC for inpatient review. If re-initiation of anticoagulation has to be postponed, surgeons are to state this specifically in the case records and order forms.

If the patient does not have unresolved surgical or medical issues and is fit for discharge, bridging anticoagulation can be managed in the outpatient setting with SC enoxaparin. The pharmacist can advise on the warfarin dose and outpatient ACC appointment.

NOACs

The surgeon can restart NOAC at the usual dose when haemostasis has been achieved and the patient is deemed safe to restart anticoagulation.[1]

ANTIPLATELET AGENTS

ACCP does not offer concrete recommendations on antiplatelet therapy after procedures. Resumption of antiplatelet therapy may be determined by the surgical team based on individual thrombosis risk and security of haemostasis.

PRACTICAL TIPS AND REMINDERS

1. When referring patients to ACC for peri-operative management, surgeons should indicate the date of procedure, estimated length of stay, and expected restart date of anticoagulation post-operation.

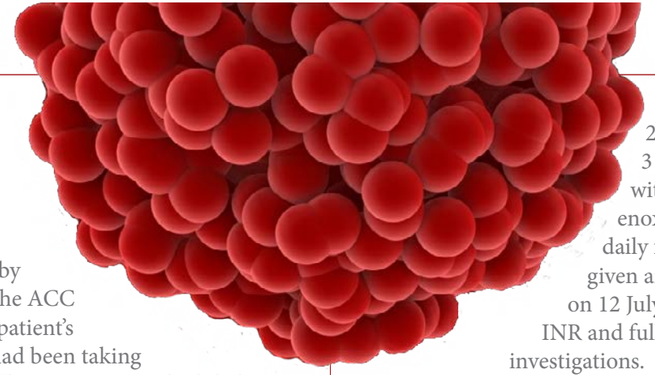
2. The surgeon or the doctor in charge of the anticoagulation or antiplatelet management must ensure that INR is checked 1 day before procedure.

3. Surgeons must assess if it is safe for patients to resume anticoagulation therapy. Pharmacists at ACC will then assist in the titration of warfarin, as well as the dosing and counselling of SC enoxaparin self-injection.

4. After surgery, if warfarin has to be withheld for a longer period, the surgical team can re-initiate treatment at the outpatient surgical clinic or determine a pre-specified date for the patient to restart at home, with an ACC appointment a week after the start date. There is no need to refer patients to ACC merely to restart warfarin.

5. An assessment form (table 2) and patient counselling form (figure 1) for peri-operative management of anticoagulation are available in the Pharmacy Notice Board in the TTSH Intranet (only available to doctors working there). ACC can be contacted for clarification if needed.

6. There is no need to refer patients on NOACs to ACC for peri-operative management.



Conclusion To The Case Discussion

Mr Tan was referred by the surgical team to the ACC clinic. On 1 July, the patient's INR was 2.4 and he had been taking warfarin 3 mg daily. The patient was scheduled for laparoscopic cholecystectomy on 7 July.

The pharmacist advised him to withhold warfarin from 2 July and start SC enoxaparin from 3 July. As the SC enoxaparin dose is 1 mg/kg twice daily and the patient weighed 55 kg, he was prescribed 60 mg (0.6 ml) twice daily. The last dose of SC enoxaparin before surgery was on the morning of 6 July.

To re-initiate anticoagulation, the pharmacist proposed the warfarin dose of 5 mg daily for 2 days (loading), then 3 mg for 2-3 days, with simultaneous SC enoxaparin 60 mg twice daily for 5 days. He was given an ACC appointment on 12 July with prothrombin-INR and full blood count investigations.

The surgical team arranged for INR check at PACE on 6 July to ensure that INR had normalised so that the procedure may proceed safely. Post-surgery, if there are no complications and haemostasis is secured, the surgeon has to advise the patient on the exact restart date for warfarin and SC enoxaparin. The post-operative plans for warfarin, SC enoxaparin and ACC appointment can be accessed from the ACC C-Doc entry. If complications arise and the post-operative plan has to be modified, the team can contact ACC for discussion.

> For patients not at high risk of cardiac events, antiplatelet therapy can be withheld prior to surgical procedure according to the following guidelines: Patients receiving aspirin, clopidogrel, dipyridamole and prasugrel should be instructed to discontinue the drug 7 days before the procedure. For those on ticagrelor and ticlopidine, it is 5 and 14 days respectively.

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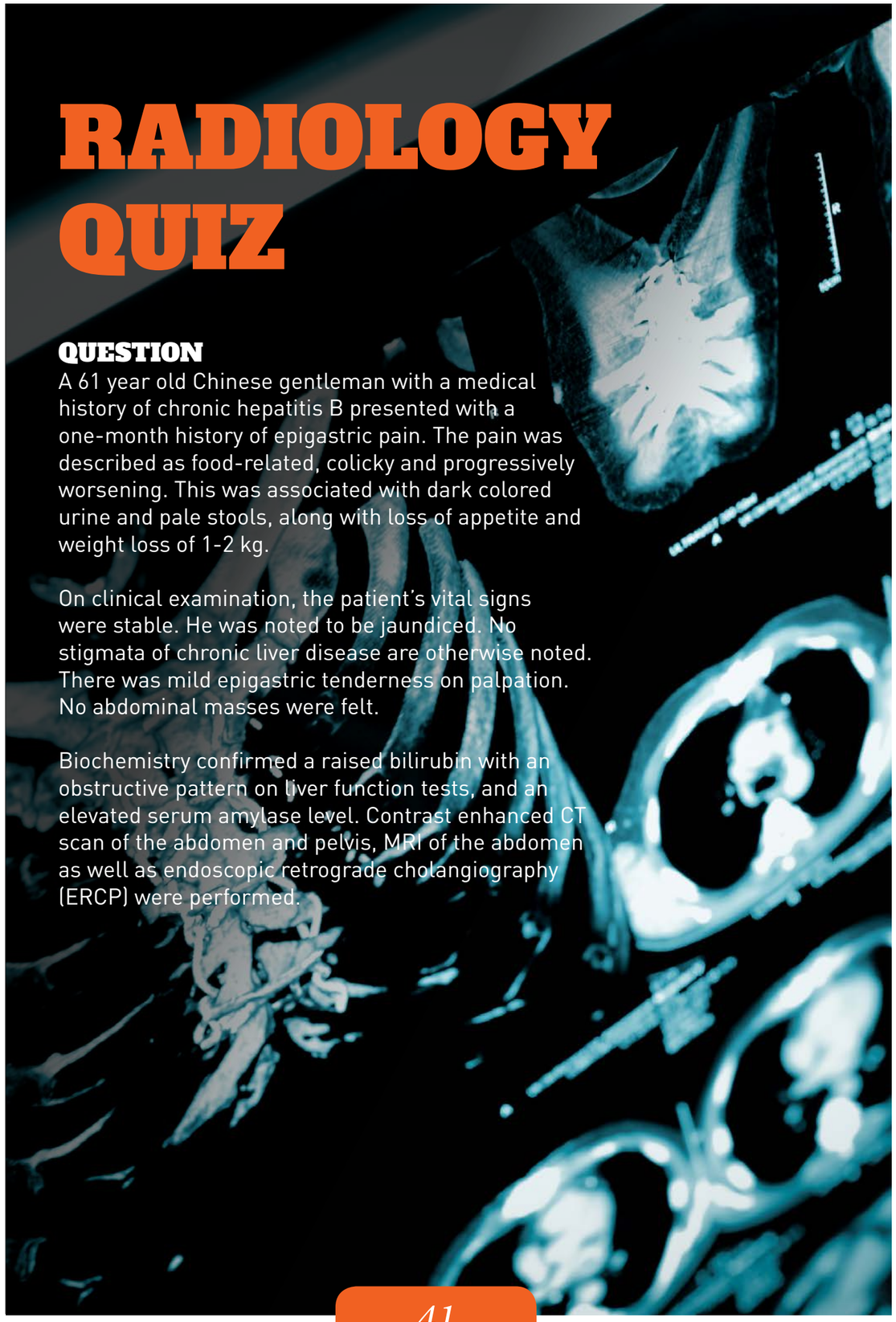
RADIOLOGY QUIZ



QUESTION

A 61 year old Chinese gentleman with a medical history of chronic hepatitis B presented with a one-month history of epigastric pain. The pain was described as food-related, colicky and progressively worsening. This was associated with dark colored urine and pale stools, along with loss of appetite and weight loss of 1-2 kg.

On clinical examination, the patient's vital signs were stable. He was noted to be jaundiced. No stigmata of chronic liver disease are otherwise noted. There was mild epigastric tenderness on palpation. No abdominal masses were felt.

Biochemistry confirmed a raised bilirubin with an obstructive pattern on liver function tests, and an elevated serum amylase level. Contrast enhanced CT scan of the abdomen and pelvis, MRI of the abdomen as well as endoscopic retrograde cholangiography (ERCP) were performed.

What abnormalities on these images are indicated by the arrows?

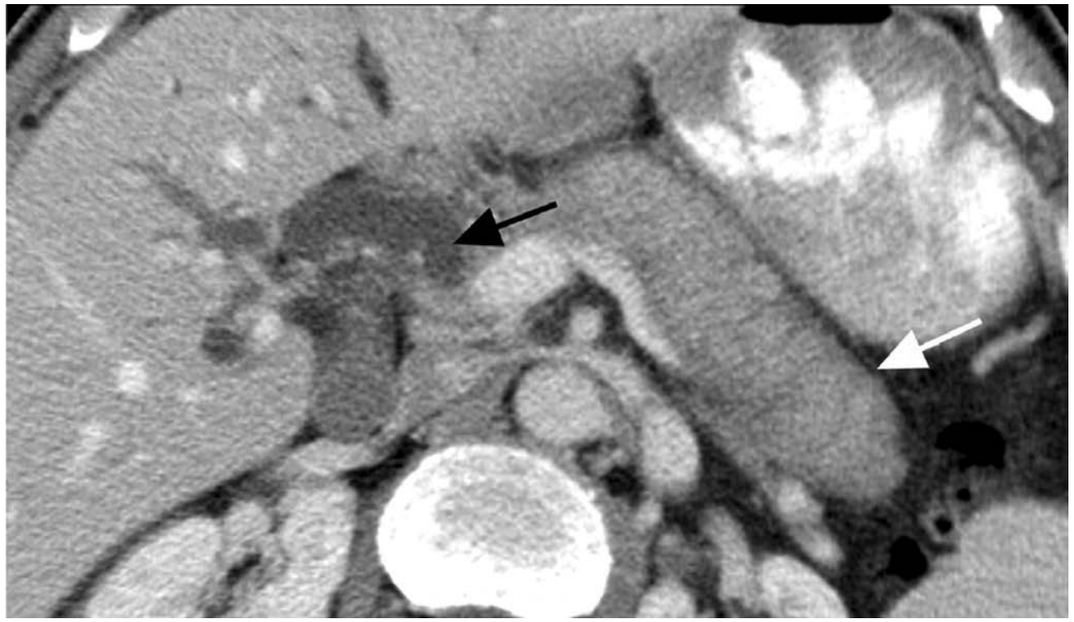


Figure 1. Axial CT scans of the abdomen.

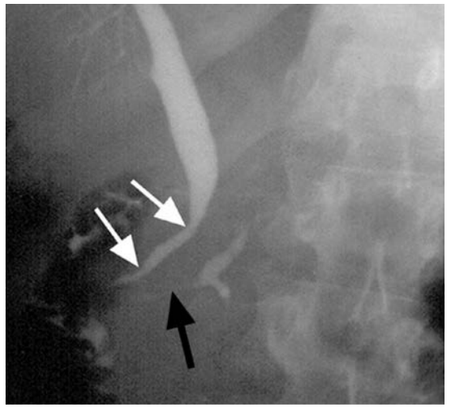


Figure 2. Endoscopic retrograde cholangiography demonstrating narrowing of the distal common bile duct (white arrows) and pancreatic duct (black arrow).

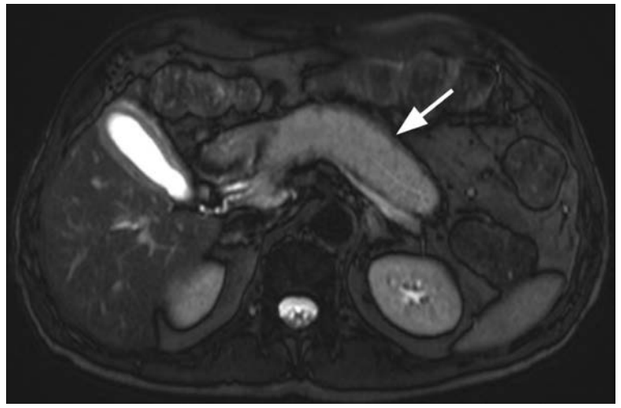


Figure 3. Axial MRI image of the upper abdomen.

ANSWER:

Figure 1 shows dilatation of the common bile duct (black arrow) and intrahepatic biliary ducts. The pancreas is enlarged with effacement of the pancreatic clefts and no significant surrounding fat stranding (white arrow). Figure 2 shows narrowing of the distal common bile duct (white arrows) and pancreatic duct (black arrow), but no evidence of intra-ductal calculi. Figure 3 shows diffuse swelling of the pancreas (white arrow) with effacement of the pancreatic clefts and vague soft tissue surrounding the pancreas, otherwise known as a 'halo'. No discrete obstructive mass in the pancreatic head was identified.

Imaging findings are in keeping with a diffuse pancreatic pathology causing obstruction of the biliary tree. Pancreatitis is the main differential, although the mild clinical symptoms and lack of peri-pancreatic oedema are atypical. Malignant causes such as diffuse infiltrative pancreatic adenocarcinoma, lymphoma and metastases to the pancreas should also therefore be considered.

The patient underwent a pylorus preserving pancreatico-duodenectomy in view of possible malignancy. Histology revealed pancreatitis, of likely auto-immune aetiology. A serum IgG level was performed and was found to be elevated.

Discussion

Auto-immune pancreatitis is a chronic pancreatitis that is characterised by an autoimmune inflammatory process with lymphocytic infiltration with subsequent pancreatic fibrosis that causes organ dysfunction. It accounts for 5-11% of chronic pancreatitis cases with a predilection for the male gender. Patients may present with chronic/recurrent abdominal pain, focal enlarging mass, obstructive jaundice, weight loss, new onset diabetes and extra-pancreatic manifestations.

There are two classifications. Type I is the most common and is associated with extra-pancreatic manifestations (best seen on imaging: peri-pancreatic or mesenteric lymphadenopathy, inflammatory pseudotumours involving the kidney, retroperitoneal fibrosis and pleural effusions.) with raised serum IgG4. Type II is characterised by serum IgG4 paucity and disease that primarily involves the pancreas, making it difficult to distinguish from other causes of pancreatitis. Severe abdominal pain and acute pancreatitis are unusual presentations. When present, these are more commonly seen in Type II disease. Serum amylase/lipase and ALP may also be elevated. Serum IgG and ANA levels are elevated in more than 50% of cases.

Steroids are effective treatment in up to 98% of patients with resolution of both morphologic changes and organ function. Remission is seen in 98% of cases. Some studies report that 2 weeks is sufficient to determine response, especially important in differentiating AIP from CA. Relapse rates are unfortunately high and may be seen in up to 24% of patients treated with steroids, with higher rates in untreated patients and in patients with Type I disease. The disease may also have a self-limiting course, with spontaneous resolution seen in up to 74% of cases.

Pancreatic adenocarcinoma is a worrying cause for biliary obstruction, but usually occurs as a focal mass in pancreatic head. While autoimmune pancreatitis may mimic this on imaging, the tumour displays delayed enhancement on contrast enhanced imaging.

Lymphoma is a cause for diffuse involvement of the pancreas with biliary obstruction, seen in up to 40% of patients. It may be primary disease, which is rare and represents only 2% of extra-nodal lymphoma, or secondary disease where it is seen in up to 30% of cases. Findings are associated with lymphadenopathy and homogeneous hypoenhancement on imaging.

Metastatic disease to the pancreas is only seen in 3-12% of patients with widespread metastatic disease, most commonly with renal cell carcinoma and melanoma.

In conclusion, we should be mindful of the entity of autoimmune pancreatitis when evaluating pancreatic pathology. This should be suspected in patients with atypical presentation and patients with imaging findings supportive of AIP. Serum IgG4 levels are helpful. Further evaluation with an ERCP with ampullary biopsy or endoscopic ultrasound with core biopsy may be considered in equivocal cases. Trial of steroids is often the treatment for such patients.

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ECG QUIZ

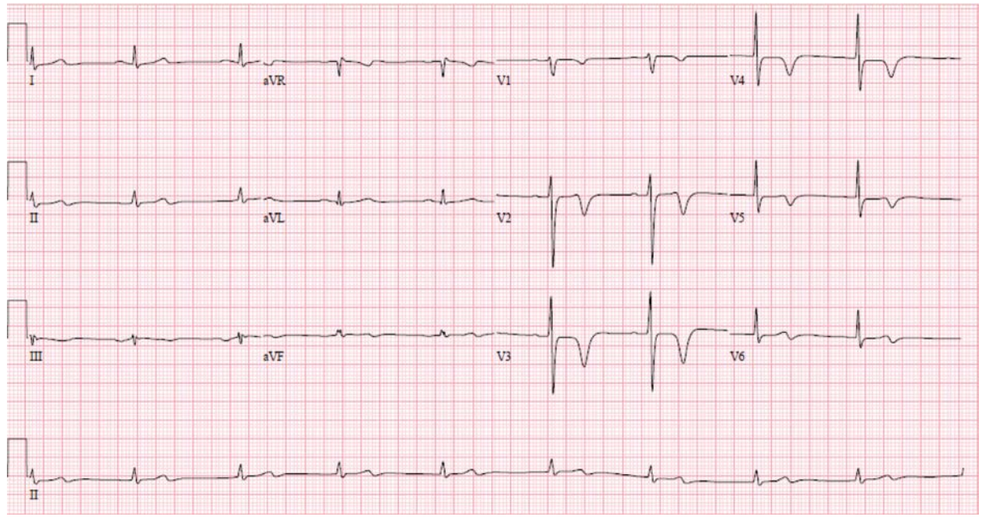
QUESTION

A 60 year old male with hypertension and dyslipidemia presented to the Emergency Department (ED) for chest pain. The chest pain started 8 hours prior to the ED visit and was described to be centrally located and crushing in nature. The episode lasted 20 minutes and resolved spontaneously.

His pain had completely subsided by the time he reached the ED. His heart rate, blood pressure and oxygen saturations were within normal limits. Physical examination was unremarkable. His serum Troponin level is 0.01ug/L (normal <0.5ug/L). His 12 lead resting electrocardiogram (ECG) is shown.

Q1: What is the name given to this ECG abnormality?

Q2: How should this patient be managed subsequently?



Patient's 12 lead resting ECG taken at the ED.

ANSWERS

A1: Wellens Syndrome

A2: Antiplatelet therapy
Early invasive coronary angiogram

Discussion

This 12 lead ECG taken while the patient is completely asymptomatic reveals sinus rhythm with deep symmetrical T wave inversions over V1-V5. Together with the history of chest pain suggestive of unstable angina, the patient was immediately sent for an invasive coronary angiogram. The angiogram revealed triple vessel coronary artery disease with severe stenoses involving the distal left main coronary artery and the proximal left anterior descending artery (LAD). He was referred to the cardiothoracic surgeon for early coronary bypass surgery.

In 1982, de Zwann et al studied ECGs of patients admitted with unstable angina. They identified characteristic ECG abnormalities in the precordial leads that predicted the presence of a critical stenosis in the proximal LAD. These patients had either biphasic T waves or symmetrical deep T wave inversions over leads V2-V3 (may also extend to other precordial leads). These 2 ECGs patterns were subsequently named after the corresponding author Dr H.J Wellens.

A Wellens ECG is often captured in a pain free patient with a history of preceding chest pain. Besides indicating the presence of a significant proximal LAD stenosis, it is also a harbinger of an impending massive anterior myocardial infarction. In the same paper, de Zwann reported that 75% of medically treated patients with a Wellens ECG went on to develop an extensive anterior myocardial infarction within a few weeks after admission.

In summary, an asymptomatic patient with a Wellens ECG deserves early Cardiology referral and further assessment, especially if there is a history of preceding angina.

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REFERENCE
De Zwaan C, Bär FW, Wellens HJ. Characteristic electrocardiographic pattern indicating a critical stenosis high in left anterior descending coronary artery in patients admitted because of impending myocardial infarction. Am Heart J. 1982 Apr;103(4 Pt 2):730-6.