

TAN TOCK SENG HOSPITAL

MEDICAL DIGEST

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

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FROM THE EDITOR

On 7 March 2017, Nicholas Barber published a piece entitled *Why the Silence of the Lambs is a Feminist Fable* on BBC Culture. He argued that Anthony Hopkins's portrayal of Hannibal Lecter as a brilliant, mad and suave character hoarded all the attention, spawned many imitators and excited many people, but he was only a cartoon monster. He was more intrigued with Jodie Foster's Clarice Starling. Starling was a police officer sent to interview the jailed Lecter in the hope that he could provide some clues to apprehending the perpetrator of a kidnapping.

He wrote, 'But Silence of the Lambs has a deep respect for the FBI's methods, and so does Starling. She isn't a rebel. She doesn't rely on intuition or luck. She is a clever, dedicated professional who succeeds by doing everything by the book and with the encouragement of her superiors. How many other Hollywood heroines – or heroes – are anything like her?'

Billionaire Elon Musk offered to build a mini-submarine for the rescue of the 13 people trapped in the cave in Chiang Rai. When the people were rescued using good old-fashioned skill and courage, he was irritated that his technology was not deployed. In a New York Times article published on 14 July 2018, Dr Zeynep Tukekci wrote 'But what got the children and their coach out of the cave was a different model: a slower, more methodical, more narrowly specialised approach to problems, one that has turned many risky enterprises into safe endeavours ... This "safety culture" is neither stilted nor uncreative. On the contrary, deep expertise, lengthy training and the ability to learn from experience (and to incorporate the lessons of those experiences into future practices) are a valuable form of ingenuity.'

Do not be enthralled by people and things that are bright and loud but ultimately specious. They are a distraction. We have been remiss because we do not celebrate those among us who do their work quietly and effectively. They improve the system incrementally. They write protocols and work instructions. They ensure that we practice good medicine, that we do not waste and that we do not harm. They keep the machinery running. They are the heroes. Nicholas Barber laments 'Today, you can see versions of Hannibal Lecter every time you switch on the television. But there's still only one Clarice Starling.'

Dr Leong Khai Pang
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Medical Digest

MEDICAL DIGEST

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RESEARCH

TTSH RESEARCH NEWS

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

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MEDICAL DIGEST

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RESEARCH EXCERPT 1

Clinical impact of non-antibiotic recommendations by a multi-disciplinary antimicrobial stewardship team

Ng TM, Phang VY, Young B, Tan SH, Tay HL, Tan MW, Ling LM, Ang BS, Teng CB, Lye DC. Int J Antimicrob Agents 2017; 50(2):166-170.

The TTSH multi-disciplinary Antimicrobial Stewardship Team conducts prospective review all inpatient orders of piperacillin-tazobactam and carbapenems. The team, which includes trained pharmacists, also provides non-antibiotic recommendations such as suggestions of additional investigations and input for infectious disease management. This study describes the impact of these recommendations on patient outcomes when they are accepted by the managing physicians.

We included 166 patients on carbapenem and piperacillin-tazobactam who received at least one non-antibiotic recommendation between January 2012 and August 2014. Acceptance and rejection of non-antibiotic recommendations by the managing physician were compared. The primary outcome was 30-day mortality.

The baseline characteristics between patients for whom recommendations were accepted or rejected were similar. Thirty-day mortality (18.0 vs. 34.5%, $p=0.02$) was significantly lower in patients who had at least one non-antibiotic recommendation accepted. In multivariate analysis, 30-day mortality was independently associated with Charlson's comorbidity score [odds ratio (OR) 1.20, 95% confidence interval (CI) 1.03-1.42, $p=0.03$], APACHE II score (OR 1.10, 95% CI 1.01-1.19, $p<0.01$), hepatobiliary source of infection (OR 10.19, 95% CI 1.44-72.13, $p=0.02$), and acceptance of at least one non-antibiotic recommendation (OR 0.39, 95% CI 0.17-0.88, $p=0.02$).



IMPORTANCE IN CLINICAL PRACTICE

Traditional prospective audit has concentrated on the impact of antibiotic recommendations on dosing and de-escalation. Non-antibiotic recommendations typically concern the duration of antibiotic therapy, or the diagnosis of infection-related complications and non-infectious conditions. Our review found that acceptance of non-antibiotic recommendations was associated with a reduction in 30-day mortality.

The data suggest that trained pharmacists play an integral role in the team and are able to provide independent recommendations in many instances, and summarise the case for review with the infectious disease physicians. The study also highlights the importance of the continued evolution of our multi-disciplinary team contributing not only to therapeutics but also diagnostics.

This summary was prepared by Dr Ng Tat Ming, a principal pharmacist (clinical) in the Department of Pharmacy, Tan Tock Seng Hospital.

RESEARCH EXCERPT 2

Comparison of elderly- and young-onset rheumatoid arthritis in an Asian cohort

Tan TC, Gao X, Thong BY, Leong KP, Lian TY, Law WG, Kong KO, Howe HS, Chng HH, Koh ET; TTSH Rheumatoid Arthritis Study Group. Int J Rheum Dis. 2017;20(6):737-745.

This study described and compared the demographics, clinical features, quality of life (SF-36) and functioning (DAS28) scores in patients with elderly-onset (EORA) rheumatoid arthritis (RA) vs younger-onset RA. Individuals with RA attending the outpatient clinic of the Department of Rheumatology, Allergy and Immunology at Tan Tock Seng Hospital from September 2001 to December 2012 were invited to participate in the study. Patients fulfilled the 1987 American College of Rheumatology (ACR) revised criteria for RA.

Among 1,206 patients who completed the questionnaire at the first study visit, 178 (14.5%) had EORA. For EORA, the mean age of onset was 66.7 ± 5.6 years while for YORA it was 41.4 ± 10.6 years. The time between onset of disease and the first study visit was 39.2 months in the EORA group and 90.8 months in the YORA group. There were more males in the EORA group compared to the YORA group. Individuals with EORA achieved lower education levels and were mostly retirees (45%) or housewives (45%). There were no significant differences in the DAS28 scores, and physicians' and patients' assessments of disease activity. EORA patients were less likely to be rheumatoid factor positive. They had higher erythrocyte sedimentation rate and lower haemoglobin concentrations, which are characteristic of chronic diseases in the elderly.

EORA patients are treated less intensively and have more RA-related comorbidities associated with poorer physical function. However, they may be coping better emotionally and mentally than YORA patients reflected by higher SF-36 scores in these domains

This excerpt was written by Dr Leong Khai Pang, senior consultant in the Department of Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital.

IMPORTANCE IN CLINICAL PRACTICE

The management of EORA is challenging. Optimal treatment should be guided by clinical experience and cohort studies such as this because randomised controlled clinical trials often exclude the elderly due to the presence of significant comorbidities. This study found that there are differences in demographic characteristics and clinical features between EORA and YORA patients. Although EORA patients may have poorer physical function, our results showed that they are coping better emotionally and mentally. Unfortunately, we are less aggressive in treating RA in the elderly than in the younger patients which partly explains the acquisition of disease-related complications.

Therefore, we should be alert to the presence of RA in the elderly as the rheumatoid factor test may be negative and the raised ESR attributed to other causes. In addition, we should treat these patients appropriately so that complications are minimised.



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

ELECTROMAGNETIC NAVIGATION BRONCHOSCOPY – A GPS SYSTEM TO LOCATE DISEASE IN THE LUNG

Lung cancer is the number one killer among all cancers.^{1,2} The high mortality rate of lung cancer among all cancers is because it is often diagnosed late. Hence, lung cancer presenting as a nodule lends the best opportunity for cure. The currently practiced non-surgical approaches for sampling peripheral lung nodules are computed tomography (CT)-guided percutaneous biopsy, conventional transbronchial biopsy, and guided bronchoscopy with the aid of virtual bronchoscopy (VB), radial probe endobronchial ultrasound (radial-probe EBUS), or electromagnetic navigation bronchoscopy (ENB).

The diagnostic yield of CT-guided biopsy is as high as 90% (range, 76–90%).³ The pooled sensitivity, specificity, diagnostic odds ratio, positive likelihood ratio, and negative likelihood ratio in a meta-analysis of 21 studies are reported as 0.95, 0.99, 54.72, 0.06, and 821.90 respectively.⁴ The pneumothorax rate and bleeding rate ranges from 14.8–50%, and 4.1–18%, respectively.⁵⁻⁷

The diagnostic yield (sensitivity) of conventional transbronchial biopsy for peripheral lesions is 53%. When stratified by size, the sensitivity of this diagnostic procedure for nodules smaller than 2 cm is 34% and larger than 2 cm is 63%.⁸ Based on distance from the hilum by lesion size, lesions ≤ 2 cm have a diagnostic yield of 14% when located in the peripheral third versus 31% when located in the inner two-thirds of the lung.⁹

The pooled diagnostic yield of guided bronchoscopy (virtual bronchoscopy, radial-probe EBUS, and ENB) in a meta-analysis of 39 studies is reported as 70%, much higher than yields reported using conventional bronchoscopy.³ When stratified based on the individual technique, the diagnostic yields for VB and radial-probe EBUS are 72.0% and 71.1% respectively.³

ENB-guided biopsies have been shown to have a higher diagnostic yield in the evaluation of peripheral lung nodules than flexible bronchoscopy alone, with diagnostic yields ranging from 62–85% compared with 36–86%, respectively.^{8,9} Recently the American College of Chest Physicians (ACCP) guidelines concerning the diagnosis and management of lung cancer recommended ENB for the evaluation of peripheral lung lesions that cannot be reached by conventional bronchoscopy.¹⁰

What is ENB? As an analogy, when we arrive in an unfamiliar foreign country, we could rent a car and drive to the hotel. But what do we do if there is no one to offer directions, and we have no city map or GPS? The drive to the hotel will be challenging. Respiratory physicians face the same problem every day when they perform bronchoscopic biopsies to diagnose lung diseases. It is even more challenging when the diseased area is smaller than 2 cm or located in the periphery of the lungs.

The airways are the roads to the diseased area. But like the roads, different bronchioles lead to different areas of the lungs. Following a certain path at the outset does not guarantee that it will lead to the area of interest. Correspondingly, the diagnostic accuracy of bronchoscopy for peripheral lesions has traditionally been no better than 30–50%. Due to this, many respiratory physicians choose the alternative methods of CT-guided biopsy or surgery. The physicians and

patients who agree on bronchoscopy to evaluate such lesions have to be prepared for an inconclusive result and a repeat procedure.

Although CT-guided biopsy has high detection rates, it carries high risk (25–50%) of complications such as pneumothorax. This increases the hospital resource utilisation by adding to the cost of diagnosis. Surgery, on the other hand, is invasive.

Recently, a technological advance in miniaturisation has adapted the GPS technology of terrestrial navigation to help physicians find their way to abnormal areas in the lungs. This is called Electromagnetic Navigation Bronchoscopy. It uses virtual reality and a GPS-guided system to locate and obtain suspected diseased cells in the lungs. In the procedure, a 3D ‘road map’ is created in which the physician has a choice of a number of bronchioles to approach the target site with the suspected diseased or cancerous cells. The onscreen map guides the procedure, showing the proximity of the instrument – in centimetres – to the site. Once the target is reached, tissue samples can be obtained using biopsy forceps or a triple needle brush. The map makes the bronchoscopy safer and more precise. If the area is shown to be cancerous, a dye can be injected to mark the site, making it easy for the surgeon to remove the cancer subsequently.

This technology has improved the reach and accuracy of bronchoscopy over the conventional approach, favourably impacting patient care. This procedure has been performed on 35 patients with no complications in Tan Tock Seng Hospital so far. For ENB, the pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio in a meta-analysis of 17 studies have been reported as 82%, 100%, 18.75, 0.22 and 97.36%, respectively.¹¹ ENB has been used in the US and Europe for more than 10 years. Elsewhere in Asia, it is also available in Hong Kong and Malaysia.

There are several factors that affect the success of ENB-guided biopsy. This success correlates positively with the size of the lesion, the use of needle for collecting the specimen, availability of rapid onsite evaluation (ROSE) of the specimen to ascertain tissue quality and adequacy, radial-probe EBUS to locate the lesion, and thinner CT slice for constructing virtual pathways to the lesion.

Some investigators have reported diagnostic yield of 89% for nodules >3 cm compared to 61% for nodules <2 cm ($p=0.03$) with ENB.¹² Despite making sense intuitively, several other studies have paradoxically reported lack of association between the yield and the size of the lesion.¹³⁻¹⁶

The use of needle for obtaining tissue has been reported to give better yield than with forceps as the former penetrates the tissue deeply whereas the latter may only sample the surface of the nodule.¹⁷ Correspondingly, some investigators reported the yield with ENB of 70% with needle technique.¹⁸ However, in Singapore we only use forceps or brush biopsy, followed by bronchoalveolar lavage. The practice of using the needle for bronchoscopic biopsy of parenchymal lesions is underutilised globally. This is because the small nodules are not visible on fluoroscopy, making real time visualisation of the lesion and needle position difficult thereby increasing the risk of pneumothorax.

The use of ROSE with ENB has been consistently shown by several investigators to improve the yield. Twenty-five of 36 patients were diagnosed with malignancy by ENB, yielding a sensitivity for malignancy of 69.4% when ROSE was used in one study.¹⁹ Another study reported improved yields when ENB was combined with ROSE.¹⁸ This could be one reason for the lower yield in our hands as we did not use ROSE for the bronchoscopic biopsy.

In a randomised controlled trial of 118 patients, the investigators reported an improvement in overall yield and yield for malignancy, from 59% to 88% and 55% to 90% respectively, by addition of radial-probe EBUS to ENB.²⁰

The success of ENB is inversely related to the thickness of the slice of the CT scan used for constructing virtual pathways to the lesion. Planning and pathway construction using 1-mm slices is associated with better yield. Investigators in the past have reported better yield with slices of 1 mm thickness compared to those of 3 or 5 mm.²¹

Despite the above factors associated with the success of ENB-guided biopsy, we have experienced encouraging yields for diagnosing lung cancer with ENB alone under fluoroscopy, without thin CT slice, needle technique, ROSE, or radial-probe EBUS, compared to conventional bronchoscopy. The addition of the above techniques will improve the diagnostic yield of ENB with reduced risk of complications.

Tan Tock Seng Hospital is the first and, up to now, the only hospital to offer this service Singapore.

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Adjunct ASSISTANT PROFESSOR AKASH VERMA is a senior consultant in the Department of Respiratory and Critical Care Medicine, Tan Tock Seng Hospital.

CRANIAL ORTHOTIC (HELMET) MANAGEMENT OF DEFORMATIONAL PLAGIOCEPHALY



Deformational plagiocephaly is cranial deformity with flattening of one side of the occiput due to external forces. This occurs in newborns as their cranial bones are soft and malleable. The first 4 months of life is the critical period for developing this deformity.

It commonly leads to craniofacial changes such as ipsilateral frontal bossing, contralateral occipital bossing and anterior shift of the ipsilateral ear and cheek (figure 1). However, deformational plagiocephaly is mainly an aesthetic problem with little evidence of developmental delay.¹

There are pre-natal, peri-natal and post-natal causes of deformational plagiocephaly.² Pre-natal causes are related to tight intrauterine environments, for examples, with breech or transverse intrauterine presentations, or in multiple gestation pregnancies. The forces exerted on the infant's head as it moves through the birth canal with vacuum- or forceps-assisted deliveries constitute the peri-natal cause. Peri-natal deformations are usually temporary and spontaneously resolve within six weeks in healthy infants. Post-natal causes are the most common, due to prolonged supine sleeping positions, especially with a preference to lying on one side. This can be related to torticollis in the infant. Other risk factors include low gestational age, small size in relation to gestation age, prematurity, low activity levels, assuming the same position during bottle or breast feeding, infrequent adoption of the prone position, and limitation of neck function. Male infants are prone to acquire deformational plagiocephaly compared with female ones.

Quantification of severity

The cranial vault asymmetry index (CVAI) is widely used to quantify the severity of the deformity. Two measurements are taken. The short diagonal measurement is taken in a strictly horizontal plane from the ipsilateral frontal-temporal point to the contralateral lambdaoideal point while the long diagonal uses the same landmarks on the opposite side (figure 2).³ Diagonal measurements are approximately 30° from the vertical in the transverse

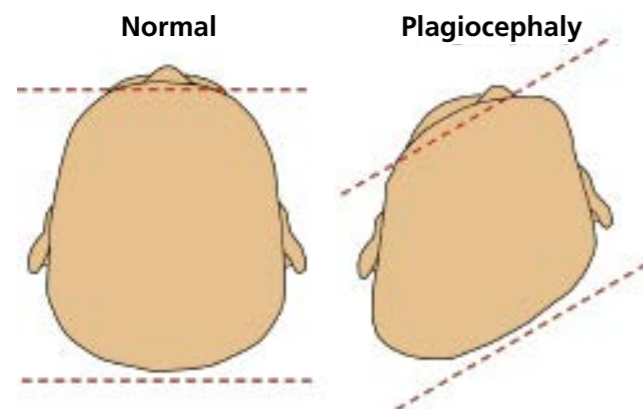


Figure 1. Comparison of a normal and plagiocephalic head shape.

plane. From the diagonal measurements, the CVAI can be calculated with the following formula:

$$\text{Cranial vault asymmetry index} = \left[\frac{\text{Long transcranial diagonal} - \text{Short transcranial diagonal}}{\text{Short transcranial diagonal}} \right] \times 100$$

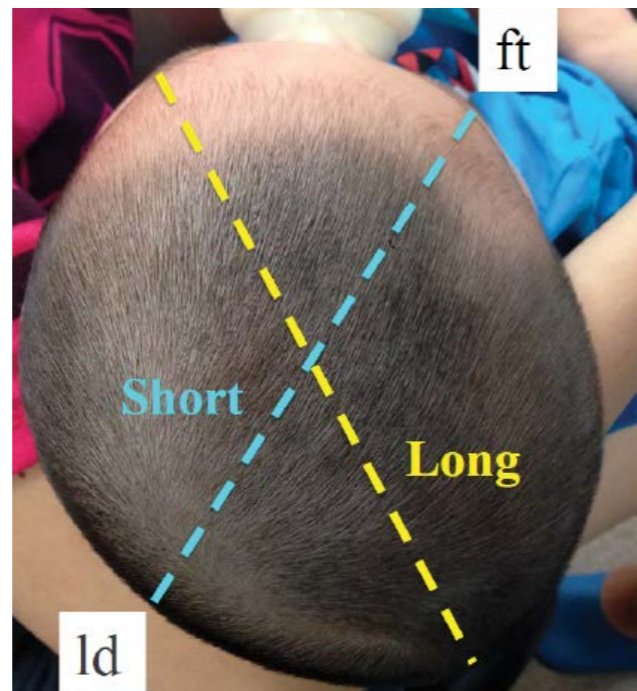


Figure 2. Short diagonal measurement taken from the ipsilateral fronto-temporal point (ft) to the contralateral lambdaoideal point (ld), with the long diagonal measurement taken from the opposite corresponding points.

The CVAI will show the percentage of diagonal asymmetry of the skull; 0% CVAI represents a completely symmetric skull. CVAI of 0–3% is normal, 3–7% indicates mild asymmetry, 7–12% moderate and >12% severe.⁴

There are two ways of taking measurements of the infant's head – two-dimensional direct anthropometry and three-dimensional scanning. Direct anthropometry using tape measure and callipers is simple, low-cost and easy to use. Scanning allows a three-dimensional analysis of the deformity, and also allows the measurement of quadrant volume symmetry ratios.

Cranial orthotic treatment

Cranial orthotics, or helmets, are custom-made moulds used to remodel the shape of the skull by allowing the head to grow symmetrically (figure 3). Regions of free spaces guide the growth of the cranial bones to the flattened regions (figure 4). The orthosis does not interfere with head growth as it does not apply any compressive forces. Compared to repositioning, the effect of cranial orthotic treatment is

usually more consistent and allows a greater degree of correction. Repositioning treatment requires constant diligence from the parents to ensure that the infant avoids sleeping on the flattened portion of its head, which can be very tedious for them. After 4 months of age, repositioning becomes very challenging.



Figure 3. Cranial orthosis with 12-mm foam lining.

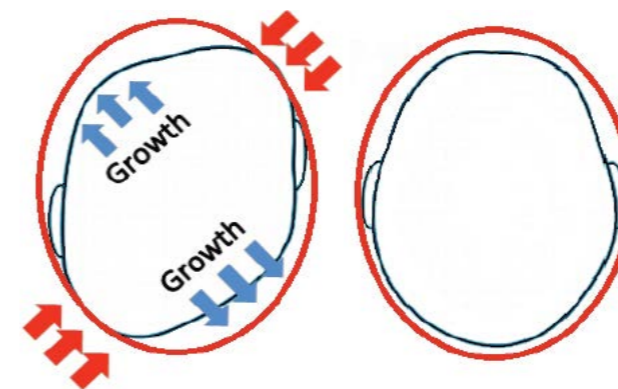


Figure 4. Cranial orthosis restricting growth on pointed areas and allowing growth on flattened areas.

Cranial orthotic treatment is usually initiated when repositioning efforts have demonstrated insufficient correction of cranial asymmetry of the infant. Cranial orthotic treatment should be initiated between 4 to 6 months of age to achieve the best outcomes. Starting treatment at a later age leads to reduced correction and extended treatment durations, as the infant's cranial bones become firmer and rate of growth decreases. Cranial orthotic treatment implemented after one year of age has minimal effectiveness and reduced compliance as the infant can remove the orthosis on its own. Strict compliance to 23 hours of wear time per day is highly essential, to ensure that the shape of the skull grows into the shape of the orthosis. Shorter wear time not only leads to reduced effectiveness, but also

fitting issues as the skull growth does not conform to the intended shape of the orthosis.

Skin complications can occur during cranial orthotic treatment in some cases, but they resolve with skin care and maintenance of helmet cleanliness.

Effectiveness of cranial orthotic treatment

There is an increasing demand for cranial orthotics in the treatment of deformational plagiocephaly (figure 5). At the Prosthetics and Orthotics Service, Tan Tock Seng Hospital, 108 cranial orthoses were fitted in the past 4 years for the treatment of deformational plagiocephaly, including 35 in the past year. These exclude cranial orthoses fitted for other head deformities such as brachycephaly. Table 1 shows the patient demographics and treatment outcomes. Mean CVAI improved from 9.7% to 3.0% after cranial orthotic treatment, with an overall 69% correction at an average treatment period of 2.9 months. At baseline, 1.2% of patients had normal CVAI, 19.0% had mild CVAI, 47.6% moderate, and 32.1% severe. After treatment, 61.9% had normal CVAI, 34.5% had mild, 3.8% moderate and 0% severe (figure 6). Most patients experienced a high degree of correction, such that their eventual head deformities were none or mild, supporting the notion that cranial orthotics are effective in the management of deformational plagiocephaly. We do not have a comparator group as many parents who wanted to monitor the condition without orthotic intervention decided to accept treatment in the end. This was mainly due to poor outcomes from repositioning efforts as many of these infants were becoming too active to benefit from this method.



Figure 5. Clinical review session with senior prosthetist/orthotist Rie Nagai and her patient with plagiocephaly.

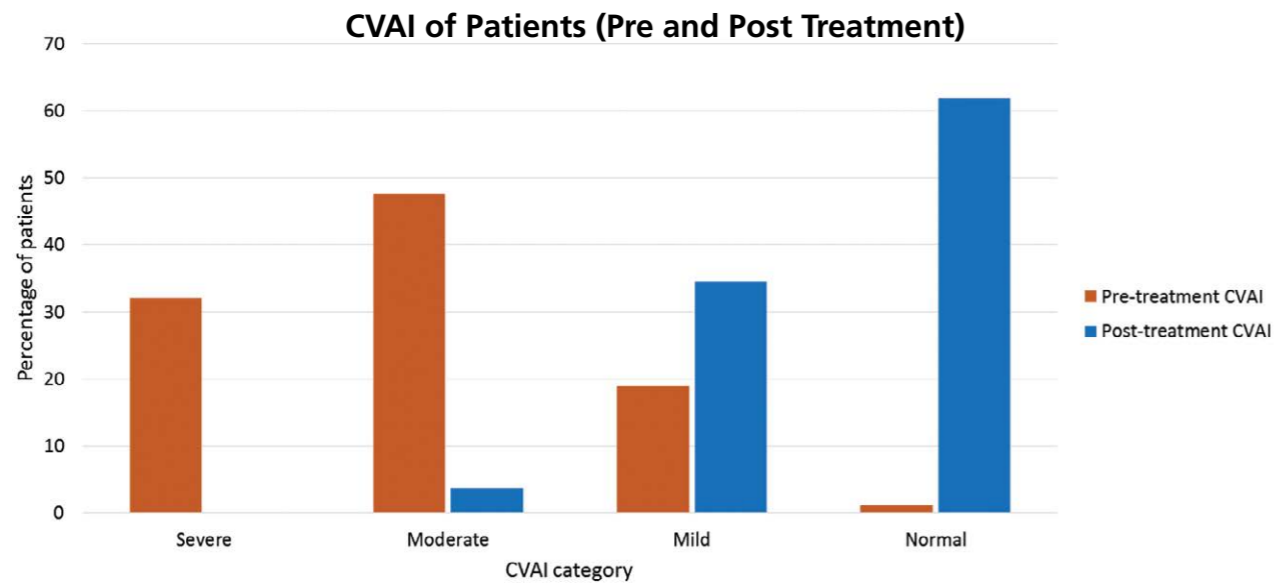


Figure 6. Cranial vault asymmetry index (CVAI) of patients before and after orthotic treatment.

We can predict good response if cranial orthotic management is initiated at an early age (4 to 6 months), and the treatment period can be short because of rapid cranial growth (figures 7 to 9). Infants are more amenable to the orthosis at younger age. Hence we recommend that cranial orthotic treatment to be initiated as early as possible (4 months old) if an infant presents with severe plagiocephaly. For mild cases, the initiation of orthotic treatment can be delayed till 6 months of age if parents are keen to observe if the deformity resolves with repositioning efforts.

Summary

Deformational plagiocephaly is a flat head deformity commonly occurring during early months of life due to prolonged one-sided sleeping positions. Repositioning treatment is most effective before 4 months of age, after which cranial orthotic management is more effective in correcting the deformity. Early orthotic intervention, starting at 4 to 6 months of age, leads to greater success rates and shorter treatment periods.

	%	Range
Gender (male)	72.2	
Mean age (months)	7.3	3.4–28.7
Associated torticollis	38.5	
Associated brachycephaly	19.4	
Pre-treatment CVAI	9.7	2.3–19.7
Post-treatment CVAI	3.0	0–9.0
Percentage correction	69.0	31–100
Mean treatment length (months)	2.9	0.2–14.0

Table 1. Demographic and treatment outcomes of patients fitted with cranial orthosis from 2014 to present (N=108).



Figure 7. Photographs of patient A showing skull deformity pre- (CVAI 12.5%, severe, on the left) and post-orthotic treatment (CVAI 2.3%, mild), with 82% correction and 2-month treatment period.



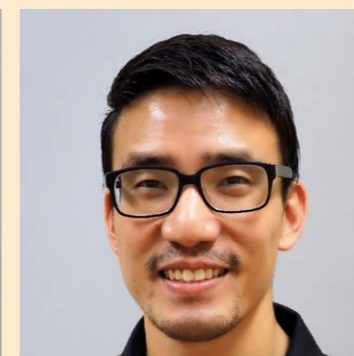
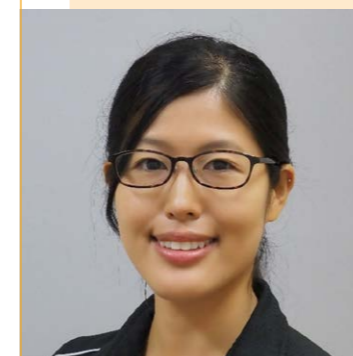
Figure 8. Photograph of Patient B before (CVAI 12%, severe) and during orthotic treatment (CVAI 6.9%, mild), with 42% correction and 1 month of treatment thus far.



Figure 9. Photographs of Patient C before (CVAI 13.5%, severe) and after (CVAI 3.8%, mild) orthotic treatment, with 72% correction and 2.4 months treatment period.

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AUGMENTATIVE AND ALTERNATIVE COMMUNICATION

Mr Tan has motor neurone disease (MND). Due to the progressive nature of the disease, he is tracheostomised and requires a ventilator to support his breathing. Unable to talk, walk or move his hands, he spends most of his time lying in bed. He can only move his eyes and count the minutes and seconds ticking by. He tries to blink his eyes to express what he wants and needs, or even to communicate his thoughts to his family. Communicating this way was often challenging as the ideas he was trying to convey were beyond just a simple blink.

One day, a group of healthcare professionals visited him and introduced an eye gaze device. Now, Mr Tan can send text messages to his nurse to arrange for appointments, inform his helper to assist in repositioning his hand, surf the internet, and even type a birthday message for his son. This is the power of Augmentative and Alternative Communication (AAC).

What is Augmentative and Alternative Communication?

Augmentative and Alternative Communication refers to alternative ways of communication besides talking.^{1,2,3} Communication may be affected in people with certain medical conditions (e.g. stroke, Parkinson's disease and MND) or from medical interventions (e.g. oral surgery and tracheostomy). People with severe speech or language impairment may require AAC to support communication.¹

The speech therapist's role is to assess the individual's speech and language difficulties and determine the most suitable form of AAC. There are many different types of AACs. They include unaided methods (i.e. using only the body such as sign language, gestures, facial expressions, and body language) or aided methods (i.e. use of low technology communication books, alphabet charts or high technology software).^{1,2,3}

This article focuses on the use of eye gaze technology as a form of AAC device. It provides information on the eye gaze device, its uses, the referral process, and costs and funding.

Eye gaze AAC devices – Its components

There are many different brands of eye gaze AAC devices, of which Tobii Dynavox is one of the major brands.⁴ In Tan Tock Seng hospital, we mainly use the Tobii eye tracker device combined with a Windows Surface Pro tablet. Through calibration, the eye tracker is able to detect the user's eye movements when navigating the tablet (figure 1). This allows the user to use programmes on the tablet by simply using eye movements. Essentially, it is similar to using the computer via the control of eye movements.

Uses of the eye gaze device

The eye gaze device is suitable for people who are unable to speak clearly and are unable to use their upper and lower limbs to support communication

(e.g. through writing or pointing to picture communication charts). This may include people with MND or medical conditions such as brainstem strokes or cervical spine injuries.

To support communication, programmes like the 'Communicator 5' or 'Grid Player' are installed in the device (figures 2 and 3).

Through assessment, the speech therapist will determine the suitable communication programme for the person. A series of training sessions will be required for both the user and the carer in order to maximise communication potential through the use of the eye gaze device.

For some people, the eye gaze device is not only used for communication, but also to maintain some form of independence, especially so for people with MND. Very often, the person starts losing independence with the progressive loss of upper



Figure 1. Tobii – calibration of the eye gaze tracker device. The Tobii eye gaze device is connected to the tablet. On the screen, the two white dots indicate the detection of the user's eyes.



Figure 2. 'Communicator 5' programme in Mandarin. Users can use eye gaze to indicate their thoughts and feelings with a communication chart installed in the programme.

DIABETES AMPUTEE PROGRAMME

Singapore has one of the highest rates of diabetes-related lower extremity amputation in the world.¹ The age-sex standardised rate for major lower extremity amputation is 13.3 per 100,000 people.² The number of such amputations stood at 1,500 in 2016. The length of stay of patients with major amputations is 53 days, which is 6.5 times that of non-operatively treated patients.³ The journey of these patients does not end at hospital discharge but stretches over many months thereafter, requiring multi-disciplinary rehabilitative care.

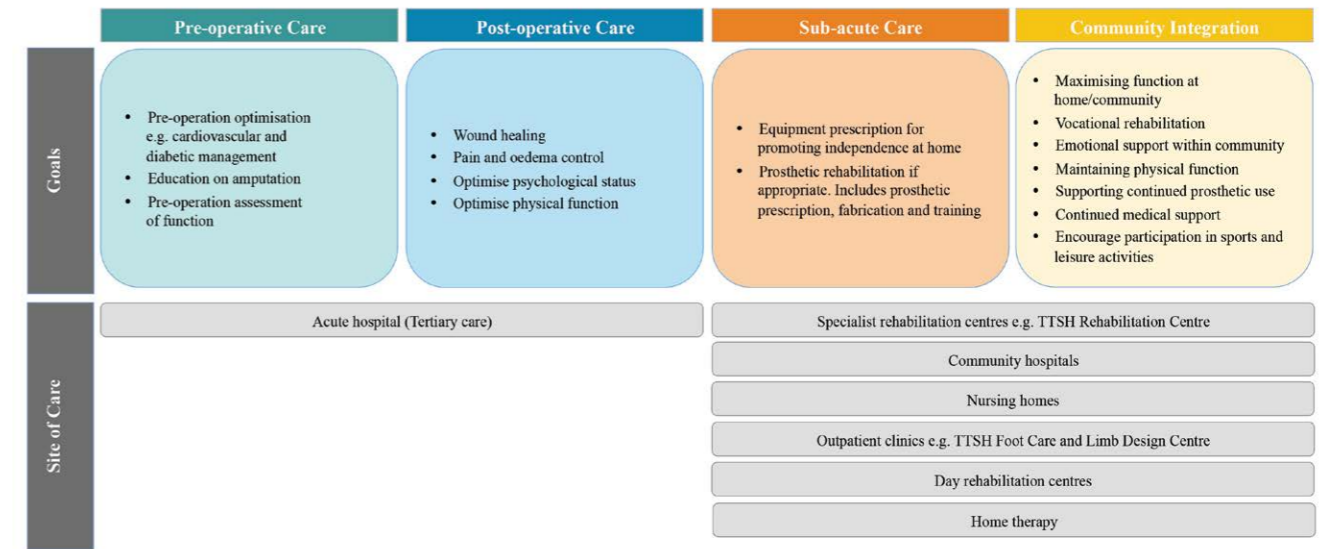


Figure 1. Continuum of care and goals of different phases of rehabilitation of a person with amputation. These goals can be achieved at the different sites of care.

In a casual conversation between a few therapists looking after amputee patients, the complex journey of amputee patients was discussed. They shared that despite the good work done by each healthcare professional for amputee patients, the care provided remains variable. The differences are due to the multi-dimensional care these patients require, and the resultant numerous and varied touch points involved in its provision. Care often cuts across different settings, ranging from the acute hospital (tertiary care) to intermediate and longer-term care in the community. The journey of care can be fraught with challenges and difficulties not just because their illness but also the barriers from the fragmentation of service. This care journey should be optimised so that patients can be better supported through this life-changing event.

The conversation led to the start of the Amputee Care Stream comprising members from various departments and professions involved in the management of an amputee. The overall objective is to facilitate her members to work together to integrate the care journey and optimise the experience of amputee patients. The group consists of physiotherapists, occupational therapists, prosthetists and orthotists, medical social workers, psychologists, and case managers. These allied health professionals (AHPs) come from a variety of care settings including acute care hospitals, specialised rehabilitation centres, and community rehabilitation centres. The team is supported by Dr Tjan Soon Yin, Head of Rehabilitation Medicine, TTSH, who guides the medical aspects of the amputee patient's care.

The objectives of the Amputee Care Stream

The Amputee Care Stream started with the vision of creating an optimal rehabilitative journey for a person after a major lower extremity amputation. The following steps were undertaken:

1. Mapping out the care journey of an amputee patient (figure 1);
2. Evaluating current practice to tease out good practices and identify gaps;
3. Understanding the role of each allied health discipline in the care of the amputee patient;
4. Identifying overlapping and differing interventions between professions;
5. Aligning clinical goals and standardising clinical interventions;
6. Collaboration between allied health and medical professionals to optimise patient care; and
7. Transforming care by leveraging on research and technology to optimise care delivery.

The first step was to examine current practice to evaluate good clinical practice and understand the gaps of current interventions. This allowed different clinicians to identify areas where there may be differing interventions between professions and understand the clinical thought processes behind them. Thereafter, the team looked into the services that the patient needs in the whole continuum of care right from the acute post-operative phase all the way to community reintegration (figure 1). The team believes that the care that the patient receives should be evidence-based and which has demonstrated favourable outcomes. There should be standardised clinical

The first step was to examine current practice to evaluate good clinical practice and understand the gaps of current interventions. This allowed different clinicians to identify areas where there may be differing interventions between professions and understand the clinical thought processes behind them.

practice to ensure that all patients have access to appropriate care. Collaboration between the AHPs and the medical team should be cohesive to cover all aspects of care. Care transformation of current practice by incorporating new research and technology can further benefit this group of patients.

Pre-operation	Post-operation	Rehabilitation	Level of function upon discharge
<ul style="list-style-type: none"> Not provided with adequate emotional support prior to amputation 	<ul style="list-style-type: none"> Not provided with sufficient information/education immediately after amputation 	<ul style="list-style-type: none"> Generally satisfied 	<ul style="list-style-type: none"> Generally satisfied, comments include: unable to return to work or sports after rehabilitation

Figure 2. Results of patient survey.

Pre-operation	Post-operation	Rehabilitation	Reintegration
<ul style="list-style-type: none"> Not provided with adequate emotional support prior to amputation Not provided with sufficient information/education 	<ul style="list-style-type: none"> Not provided with sufficient information/education immediately after amputation 	<ul style="list-style-type: none"> Time taken to deliver prosthesis is not ideal Time between each appointment is not ideal 	<ul style="list-style-type: none"> Insufficient knowledge and resources to facilitate return to sports

Figure 3. Results of clinician (allied health professionals) survey.

From envisioning the ideal care for our patients, the team came up with the following guiding principles:
Safe and sustainable care
Uniform standardised care
Practice that is efficacious
Patient's voice at the heart of things
Outcome focused that is meaningful to patient and staff
Resource building through staff development
Trans-disciplinary and transformational

Through this, the Amputee Care Stream intends to build a 'SUPPORT' care network that works together, works for, and works with our patients so that their journey from hospital to home and community can be well supported and optimised, incorporating transformed models of care where appropriate.

The journey of the Amputee Care Stream Workgroup

The AHPs within the care stream highlighted the challenges that the patients and clinicians face during the post-amputation period. They felt that it was important to truly understand the views of the patients and clinicians directly involved in their care. The Amputee Care Stream Workgroup surveyed patients about their experiences regarding their amputation and rehabilitation process. They also surveyed AHPs about their views on the

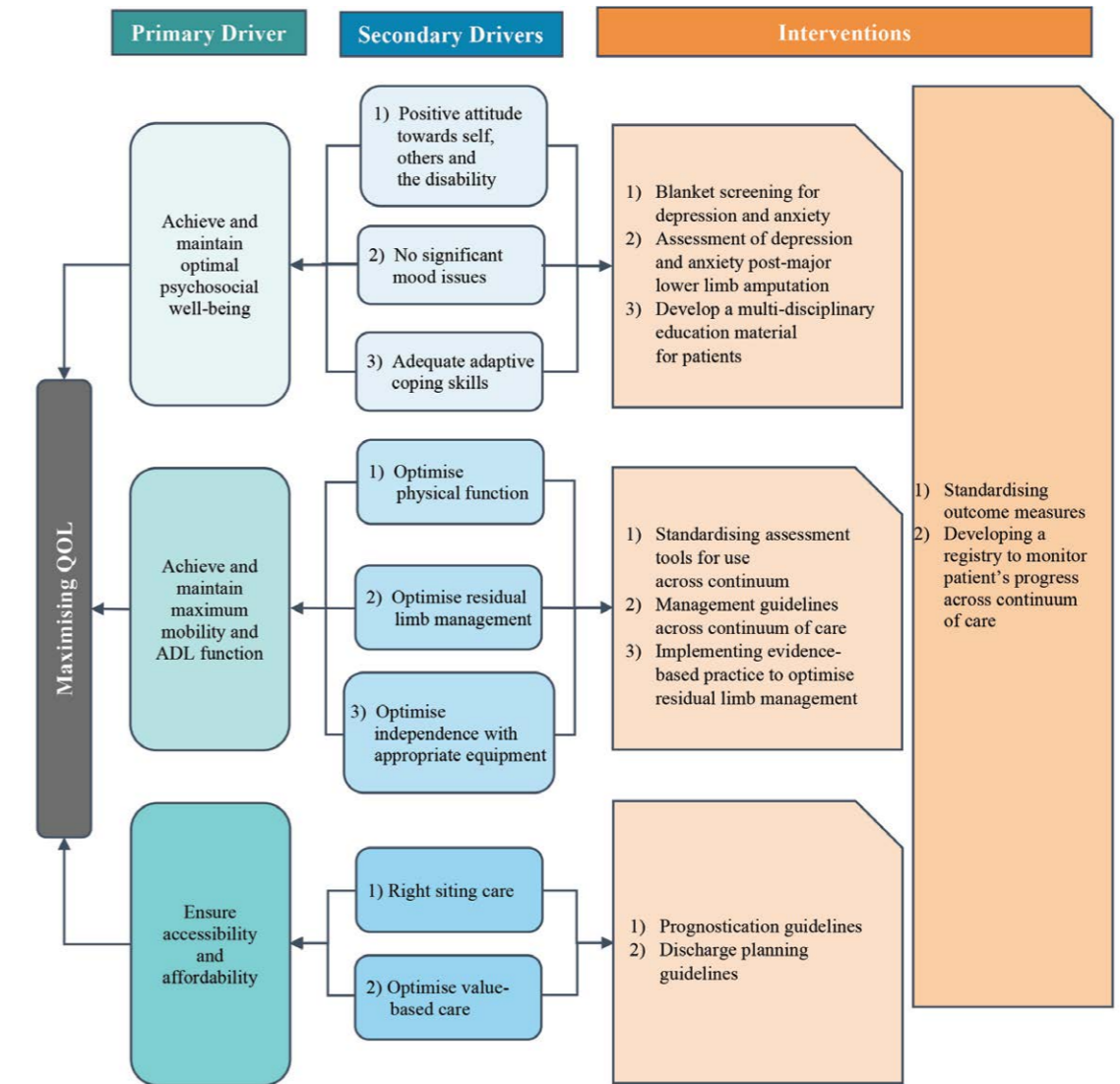


Figure 4. Primary and secondary drivers that will drive the team towards maximising quality of life for patients post-amputation.

care delivered to patients. Key findings common to both patients and healthcare providers were the lack of emotional support and the scant information provided to patients and their families. Patients found it difficult to return to work or sports. Healthcare providers reflected something similar but tended towards lack of knowledge in enabling patients to return to sports or hobbies. The detailed results of the surveys are found in figures 2 and 3.

The desire to maximise the quality of life of patients with amputation emerged as a common broad theme in both surveys. The team brainstormed ways of addressing this (figure 4) and the following priorities were identified:

1. Achieving and maintaining optimal psycho-social well-being

This key priority was identified through the patient and AHP surveys, that is, a lack of emotional and psychological support for patients before amputation

and during the recovery process. A review of the literature shows that there is high prevalence of depression and anxiety in people with major lower limb amputations that can persist for up to 2 years.⁴⁻⁶ However, there is little information on how local patients fare psychologically. The workgroup thought that it would be worthwhile to investigate this, so that appropriate care can be planned for, should there be a demonstrated clinical need. The psychologists in the team secured funding through the TTSH Pitch-for-Fund grant to conduct a research on this, entitled "Assessment of depression and anxiety post-major lower limb amputation in Tan Tock Seng Hospital".

It was also uncovered during the survey that patients felt that insufficient information and education was provided before and after amputation. In addition, information provided to patients by different clinicians was variable but also often overlapped. Therefore, to reduce repetition from AHPs and confusion for the patients, a set of patient education

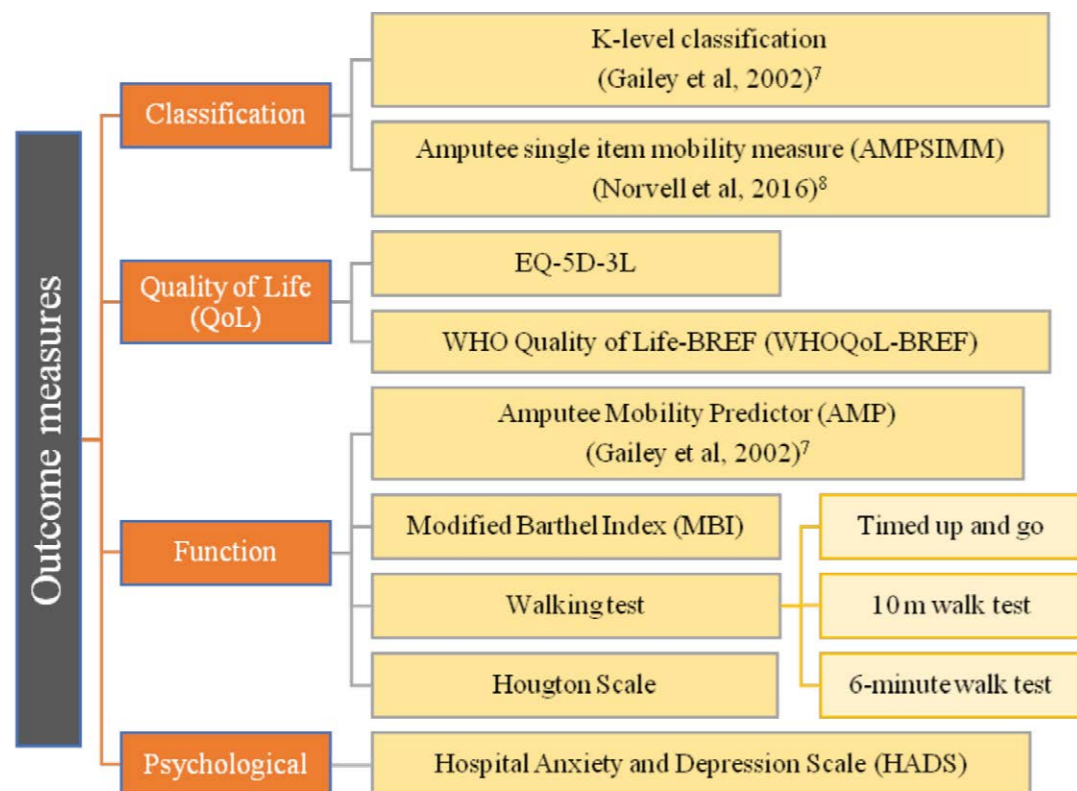


Figure 4. Primary and secondary drivers that will drive the team towards maximising quality of life for patients post-amputation.

booklets was created to advise patients on the process of recovery in both inpatient and outpatient settings. The booklets contain information from the whole multidisciplinary team. This allows patients to understand the rehabilitation process clearly and holistically and helps them cope with life after amputation. The team is currently finalising the education materials and will be obtaining patients' feedback before they are disseminated within the institution.

2. Achieving and maintaining maximum mobility and function for activities of daily living

In order to achieve and maintain maximum mobility and functional ability, the team believes that it is essential to optimise physical function, residual limb management and independence with appropriate equipment. Therefore, it set out to develop a local rehabilitation intervention guideline for managing patients after major lower limb amputation. The aim of this guideline is to standardise management across the continuum of care and to guide AHPs to develop the ideal treatment plans for their patients with amputations in the local context. This guideline is driven by evidence-based practice from research done within the amputee population and includes information that is relevant to the multi-disciplinary team. The team is currently compiling the rehabilitation intervention guidelines which will

be made readily available for all healthcare professionals that are directly involved in the care of people with amputations.

3. Ensuring accessibility and affordability of care

To ensure accessibility to rehabilitation services post-amputation, patients must be right-sited to the most appropriate setting based on their rehabilitation needs. To determine their rehabilitation needs and to plan for discharge from acute care, accurate prognostication in the acute phase is important. However, prognostication can be challenging as patients are not homogenous and many factors can affect rehabilitation outcomes. Through extensive background review of available research on prognostication of amputees, the team developed a guideline to assist clinicians in this difficult task. The guideline advocates a holistic view of the patient including medical, functional and psychological factors. Within the guideline is a discharge planning flow chart for use in the inpatient setting. The flow chart was shared with medical teams, nurses and other AHPs who work with amputees and is currently being adopted.

To ensure affordability of care, the team will embark on further projects to look at care transformation to optimise value-based care.



Figure 6. Return to driving training with an occupational therapist.



Figure 7. Prosthetic training in the community under the Community Rehabilitation Programme (CRP).



Figure 8. Adaptive climbing event with the amputee support group. Left: A transfemoral amputee rock climbing during an amputee support group event. Right: A bilateral transtibial amputee rock climbing during the event.



Figure 9. Review of prosthesis with a prosthetist & orthotist at the TTSH Foot Care and Limb Design Centre.



Figure 10. Prosthetic rehabilitation with a physiotherapist at the TTSH Foot Care and Limb Design Centre.

4. Outcome measures and registry

The team did an extensive literature review on a wide array of outcome measures that have been used in the amputee rehabilitation setting. These include outcome measures for mobility, activities of daily living, quality of life measures, and psychological well-being (figure 5). The feasibility of using these outcome measures in the local context was

considered. The team then trialed a set of outcome measures across different settings and phases of rehabilitation. The results of the trial allowed the team to select the most appropriate quality of life, functional, psychological, and patient-reported measures for the patients. These outcome measures have now been implemented across various settings in TTSH.

A registry allows the team to monitor the cohort of patients across the continuum of care and continually analyse the changes to the population. This also enables the study of the effects of new guideline implementation or new interventions. An ongoing evaluation of the amputee population will allow the team to analyse the impact of the care stream on the care of patients so that continual improvements to be made. A registry also provides large-scale data that enables future research on the amputee population. Figures 6 to 10 depict some of the activities the Amputee Care Stream members hold with individuals with amputation.

Future directions

The team has started to engage various clinicians such as Endocrine, Vascular and Orthopaedic doctors. A potential area for collaboration is to look at prevention of higher level amputations or bilateral amputations. We hope to work even more closely with fellow doctors in our day-to-day practice and to carry out projects to improve the care of patients.

Further down the road, we plan to involve partners such as the community hospitals and day rehabilitation centres to ensure smooth transition of these patients from tertiary care to the community. Valuable information and learning experiences that the workgroup has gained can be shared with the

partners so that the lessons benefit not just TTSH patients but all persons with amputations living in the community. The pinnacle of community integration for persons with amputation is their involvement in activities that the average person engages in, including community centres activities, sports and even volunteerism. This will be an eventual target that the healthcare community may like to explore.

Care transformation projects should make the process of rehabilitation smoother for all patients by optimising value-based care. Care transformation will, for examples, improve wait times for outpatient services and maximise medical and therapy services to the patients.

Research and technology are areas that the team will increasingly focus on. Research will ensure that there is constant improvement for rehabilitation of amputees. The team believes that advancement in technology can greatly contribute to the rehabilitation of amputees.

The Amputee Care Stream Workgroup has invested considerable effort to ensure that people with amputations achieve the best care that they deserve. There are diverse projects that target different areas of patient care and the team is making improvements gradually but surely.

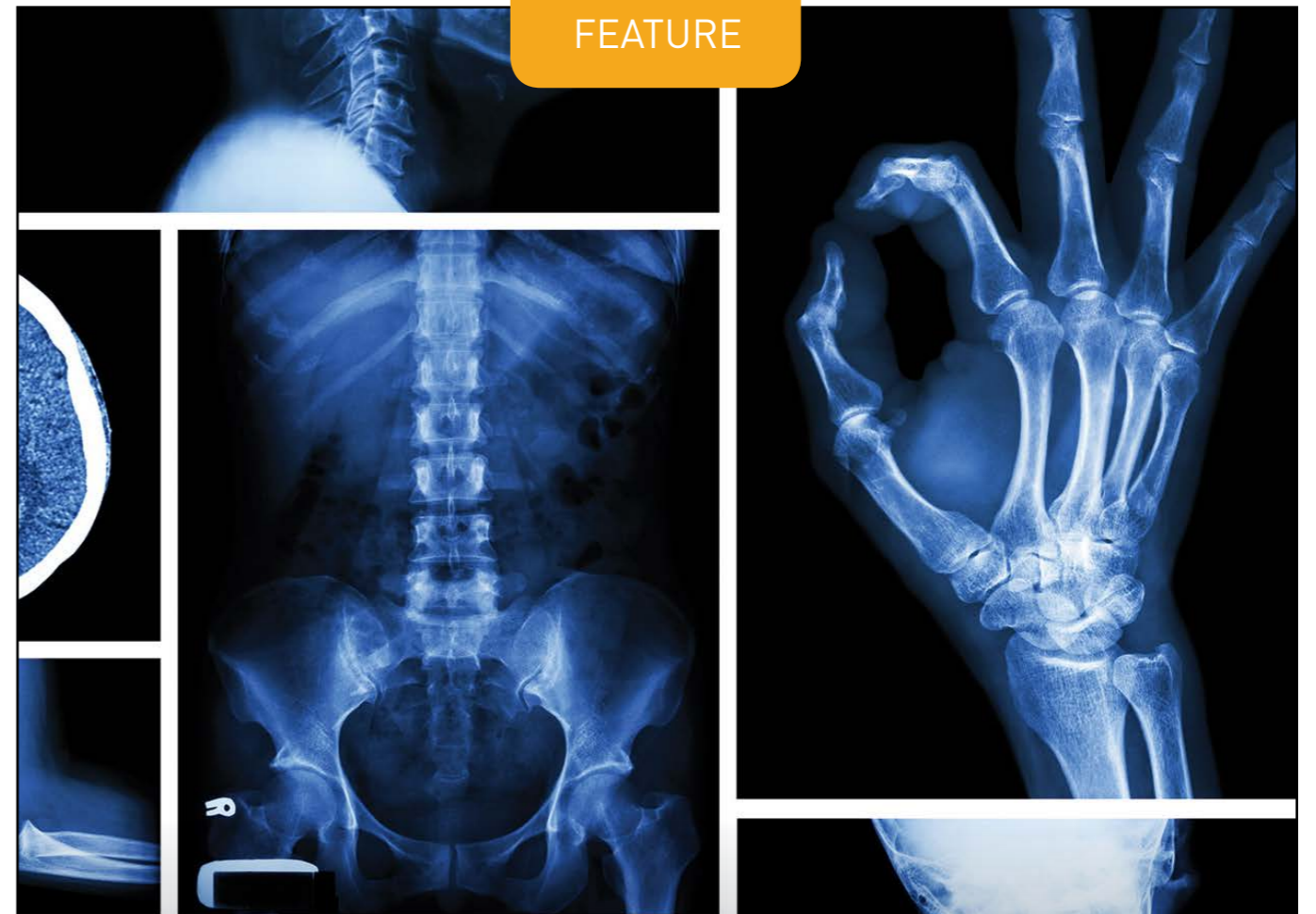
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FEATURE



JOINT CONDITIONS THAT NO ONE TOLD YOU ABOUT WHICH YOU SHOULD KNOW

We are not talking about gout, rheumatoid arthritis, tennis elbow or frozen shoulder here. We want to bring to your attention some uncommon conditions that occasionally present to primary care physicians. For various reasons, these are not taught in medical school or in postgraduate courses. Some of these diseases can be mistaken for more serious ones, leading to undue investigations and anxiety. In this article, we will lift the lid and expose these, so that any doctor can diagnose these conditions and refer the patients to the specialist, if necessary.

I shall start with vignettes of the patients' history and discuss the conditions in a subsequent section.

Case presentations

Patient 1

A 45-year-old man presented with episodes of unilateral knee swelling of a year's duration. The episodes start fairly suddenly and the knee would become visibly swollen. Usually he could ambulate in spite of the pain but there has been one incident in which the intensity was so severe that he had to seek medical attention.

The attacks are not associated with fever or constitutional symptoms. They usually occur spontaneously, but on the occasion in which the pain was maximal, he was cycling the day prior to the attack. Milder attacks respond to rest and NSAIDs but major ones require joint aspiration and intra-articular triamcinolone injection.

The left knee was initially affected, but over time, the right was also involved. The attacks have always involved one knee at a time. No other joints were involved.

Though the acute phase reactants are mildly raised during attacks, the serum uric acid was normal. The joint aspirate showed 350 red cells per ul, 4,950 leucocytes per ul with a differential count of neutrophils 52%, lymphocytes 18%, monocytes 30%, eosinophils 0%, and basophils 0%. Crystals were not found. He was well between episodes.

Patient 2

This patient was first discussed in our Apr–Jun 2011 issue. A 61-year-old man complains of episodes of right wrist pain for the past 10 years. There was no trauma at any time. The episodes occurred once every few months and could be precipitated by unaccustomed activity. The blood investigations, especially the acute phase reactants, were normal. His doctor diagnosed gout, though the wrist was the only joint ever affected and the serum uric acid had been persistently normal. The knowledge that Dr Jerome E. Groopman's difficult-to-diagnose condition had a similar presentation (described in his book *How Doctors Think*¹) helped in the management. The hand X-ray confirmed the diagnosis (figure 1).



Figure 1. Hand X-ray of a man with episodic right wrist pain. Please disregard the old injury of the right little finger.

Patient 3

A 42-year-old lady presented to the rheumatology clinic with intermittent pain of the metacarpophalangeal joint of the right middle finger for a few years. Figure 2 shows the shifting and changing nature of her disease. On 15 November, inflammation was found over the metacarpophalangeal joint of the right middle finger. However, on 1 December, the right hand is perfectly normal but the right knee is swollen. On 15 December, no synovitis was found. On the next visit, dactylitis was recorded on the right index finger plus swelling of the right lateral malleolus. On 26 January, the dactylitis had disappeared and right posterior tibialis tendonitis was found. On 16 February, erythema was detected over the right metacarpophalangeal joint and swelling of the left second metatarsophalangeal joint.

The patient recovers fully from each episode and no permanent joint deformity was found. She cannot recall any event that can provoke the joint swelling. The blood investigations have generally been unremarkable.

Because of the various types of rheumatic manifestations, diagnoses of undifferentiated connected tissue disease and psoriatic arthritis sine psoriasis were entertained. Finally a diagnosis was made and sulphasalazine was prescribed.

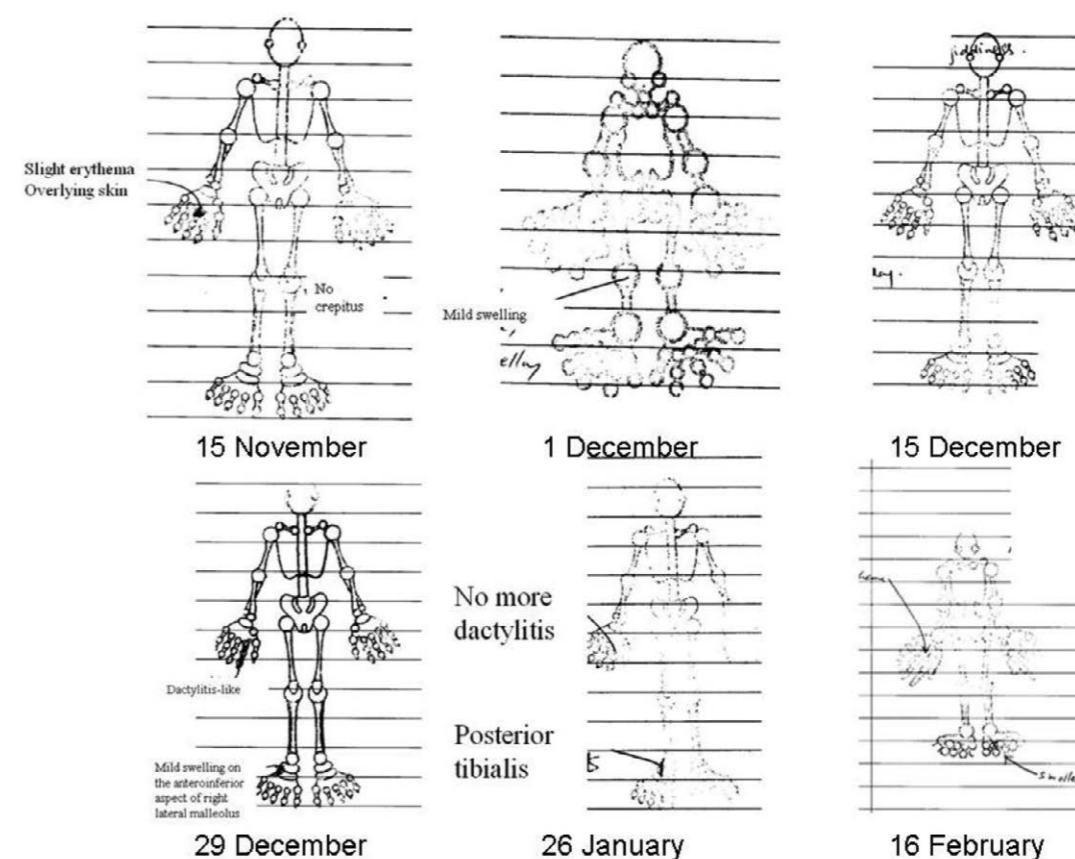


Figure 2. Diagrams taken from the patient's medical record showing the shifting nature of the joint and tendon inflammation.

Patient 4

We had presented this patient in our Jan–Mar 2012 issue, but the lesson bears repeating. This 60-year-old lady complains of pain over the left heel, just below the insertion of the tendoachilles, for the past two years. There was no trauma. She was finding it hard to wear court shoes or pumps.

Clinically, there was a firm swelling over the calcaneum just superior to the insertion of the tendoachilles but the tendon itself was normal (figure 3). The patient had no problems walking or standing on the ball of her foot. There were no other joint complaints. The erythrocyte sedimentation rate (ESR) was 15 mm per hour.



Figure 3. Picture of the left foot showing the prominent bony swelling at the posterior heel. An X-ray of the hind foot is shown on the right.

Patient 5

A 50-year-old lady complains of pain over the metacarpophalangeal joint of the left second toe for two years. There is pain when she walks but she is otherwise quite well. The ESR and C-reactive protein (CRP) were normal. We discussed this patient in our Oct 2015–Mar 2016 issue.

The X-ray shows narrowing of the tarsometatarsal joint of the same digit (figure 4). The patient was diagnosed to have spondyloarthritis and initiated on sulphasalazine therapy. She did not feel that the medication was effective.



Figure 4. X-ray of the left foot of a lady with pain over the base of the second toe. There is narrowing and flattening of the base of the second metatarsal bone and narrowing of the joint space of the metatarsophalangeal joint.

The conditions

Patient 1 – Intermittent hydrarthrosis

Intermittent hydrarthrosis was first reported in 1845 by Perrin.² The condition is uncommon and there are only 38 hits in PubMed using the keyword ‘intermittent hydrarthrosis’. Patients develop episodes of knee swelling or effusion without marked rise in the ESR or CRP. Unlike palindromic rheumatism, only the knees are affected. Early writers stress the regular periodicity of the attacks,³ but I do not think that the intervals are as uniform as believed.

The family physician or orthopaedic surgeon may occasionally see patients with recurrent knee effusion which does not appear to be inflammatory. Of course, infection, gout, osteoarthritis, and pseudogout have to be excluded. There is no established treatment for intermittent hydrarthrosis though colchicine (2 cases) and hydroxychloroquine (1 case) have anecdotally been reported to be effective. I have used sulphasalazine (2 cases) with benefit.

Patient 2 – Scapholunate dissociation

Dr Groopman’s book was about the cognitive reasoning of doctors and he wrote of the difficulty of managing his own wrist pain. After seeing many doctors, including some cavalier ones, he was finally correctly diagnosed.

Étienne Destot (1864–1918) was the first to report scapholunate disability in wrist injuries. He was one of the earliest adopters of X-rays in medical practice. We can read his 1926 report describing the first cases of scapholunate disability as it is republished in a modern journal.⁴

The X-ray shows that the scaphoid is anteverted (the superior end of the bone is nearer the viewer than the inferior pole) and appears foreshortened (arrow), as if the bone is bowing to the viewer. The space between the scaphoid and the lunate is widened (indicated by a star in figure 5). The diagnosis is scapholunate dissociation. These findings were confirmed in the MRI of the right wrist (figure 6). Another instance of scapholunate dissociation is shown in figure 7.



Figure 5. This is a magnified view of the right wrist from figure 3. The scaphoid is anteverted (arrow) and the scapholunate distance is widened (star). The radioulnar distance is also widened incidentally (dotted arrow).

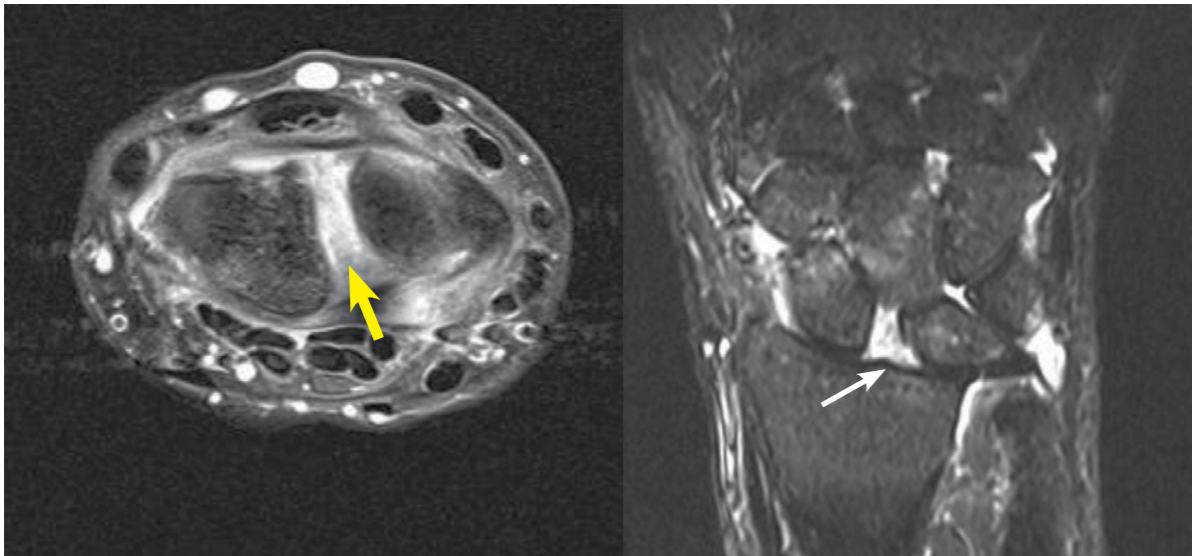


Figure 6. MRI of the right wrist showing the increased distance between the scaphoid and lunate (arrows).



Figure 7. X-ray of the left wrist of another patient with scapholunate dissociation. Note the dorsal tilt of the scaphoid and the widened space between that bone and the lunate.

Patient 3 – Palindromic rheumatism

Palindromic rheumatism is a disease that was described in 1944 by Dr Philip Showalter Hench of the Mayo Clinic.⁵ Patients experience self-limited episodes of arthritis or peri-articular inflammation that resolve without leaving residual damage clinically and radiologically. In each episode, one to three joints (and not more) are affected simultaneously. The attack lasts a few days to weeks, and resolves fully. The next attack occurs after an unpredictable interval, which could be days or weeks or months. The acute phase reactants can be raised during an attack. Perhaps a quarter to half of these patients eventually develop rheumatoid arthritis, so some authorities believe that palindromic rheumatism is a subset of rheumatoid arthritis.⁶

In my encounters with patients, I find that palindromic rheumatism is often mistaken for gout because of the episodic nature. However, the inflammation in gout is usually more intense and the onset is more rapid. The metatarsophalangeal joint of the big toe is the initial articulation affected most of the time in gout, but there is no such predilection in palindromic rheumatism. Patients with palindromic rheumatism usually do not need to miss work because of the pain. It is also mistaken for rheumatoid arthritis because of the prolonged history of inflammatory joint pain. Invariably, patients do not develop joint deformities in spite of the absence of definitive treatment over years of disease.

Mattingly extracted these diagnostic features from Hench's paper:⁷

1. Recurrent attacks of joint pain and swelling at variable and irregular intervals lasting a few hours or a few days.
2. Any joint affected but especially fingers, wrists, shoulders, and knees.
3. Para-articular attacks and transient nodules.
4. Good health; normal blood tests and X-rays.
5. Good prognosis: no effective treatment.

I prescribe the less toxic anti-rheumatic agents sulphasalazine or hydroxychloroquine to patients with palindromic rheumatism manifesting frequent attacks. Antimalarial drugs such as chloroquine and hydroxychloroquine may prevent the evolution to rheumatoid arthritis.⁸

Patient 4 – Haglund's syndrome

There are a few structures near the lower end of the tendoachilles that can be diseased. The tendon itself can be inflamed, especially if the patient is suffering from one of the spondyloarthritides. Superficial to the tendon, just beneath the skin, is the retro-achilles bursa. Between the tendon and the calcaneum is the retrocalcaneal bursa. Both these bursae can be inflamed, and careful examination of the hindfoot usually allows us to locate the offending structure. The tendon can rupture, due to sporting activity or, rarely, subsequent to the use of quinolones.

The tendon goes around the posterior aspect of the calcaneum, separated from the bone by the retrocalcaneal bursa, before inserting into the tuberosity. Our patient has a soft tissue swelling at the insertion of the Achilles tendon at the heel; she has Haglund's syndrome.

Patrik Haglund (1870–1937) was a professor of Orthopaedic Surgery at Stockholm's Karolinska Institute. He described the disease that bears his name in 1928.⁹ It is due to retrocalcaneal bursitis due to rigid low-back shoes in people who happen to have prominent bursal projection. This is why the condition is also known as 'pump bump'. Persistent tendoachilles swelling can be misdiagnosed as spondyloarthritis and the patient subjected to unnecessary treatment. Figure 8 shows the prominent postero-superior calcaneal (bursal) projection and the swelling of the retro-Achilles bursa. The inferior calcaneal spur is incidental. There is calcification of the insertion of the Achilles tendon but it is not a requirement for diagnosis of Haglund's syndrome.

The treatment is conservative. I always send the patients to see the Podiatrist for advice.

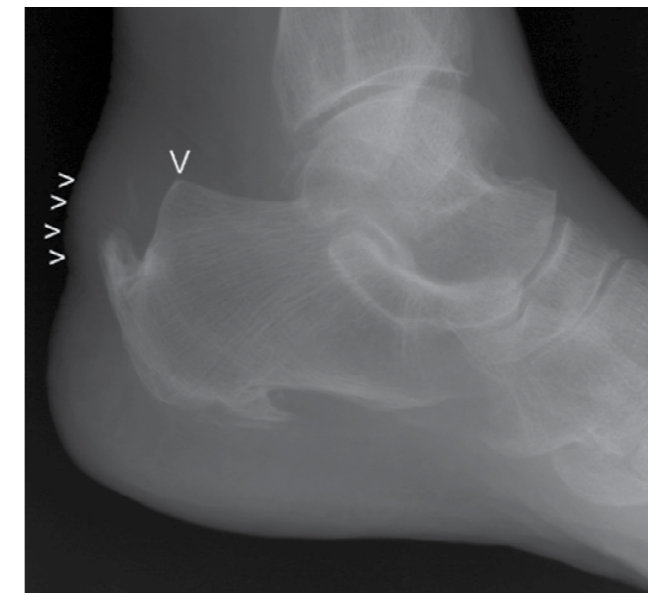


Figure 8. The lateral X-ray of the left calcaneum indicating the bursal calcaneal projection (V) and soft tissue swelling of the retroachilles region (horizontal V's).

Patient 5 – Freiberg’s infraction

Freiberg’s infraction is a non-inflammatory disease of the metatarsophalangeal joints, usually the second but the third may be involved. Dr Albert H. Freiberg of Cincinnati reported six cases of his disease in 1914.¹⁰ This is described as a condition of cartilage degeneration or osteonecrosis of the lesser metatarsal heads. The cause is unknown but genetic influence on the blood supply is postulated to play a role. Tarsal bones are also susceptible to osteonecrosis.

Dr Smillie described five stages in the progression of this condition.¹¹ There is fissure of the metatarsal head, followed by absorption of the bone, then further absorption and sinking of the head, loose body formation and finally flattening, deformity and arthrosis. Figure 9 shows the X-ray of the feet of another patient with Freiberg’s infraction, but with bilateral involvement of the second metatarsophalangeal joints. Both our patients are probably in Smillie stage 2.

The treatment is conservative and if surgery is indicated because of pain or disease progression, the joint should be preserved as much as possible.



Figure 9. X-ray of the feet of a patient with bilateral Freiberg’s infraction and hallux valgum.

Conclusion

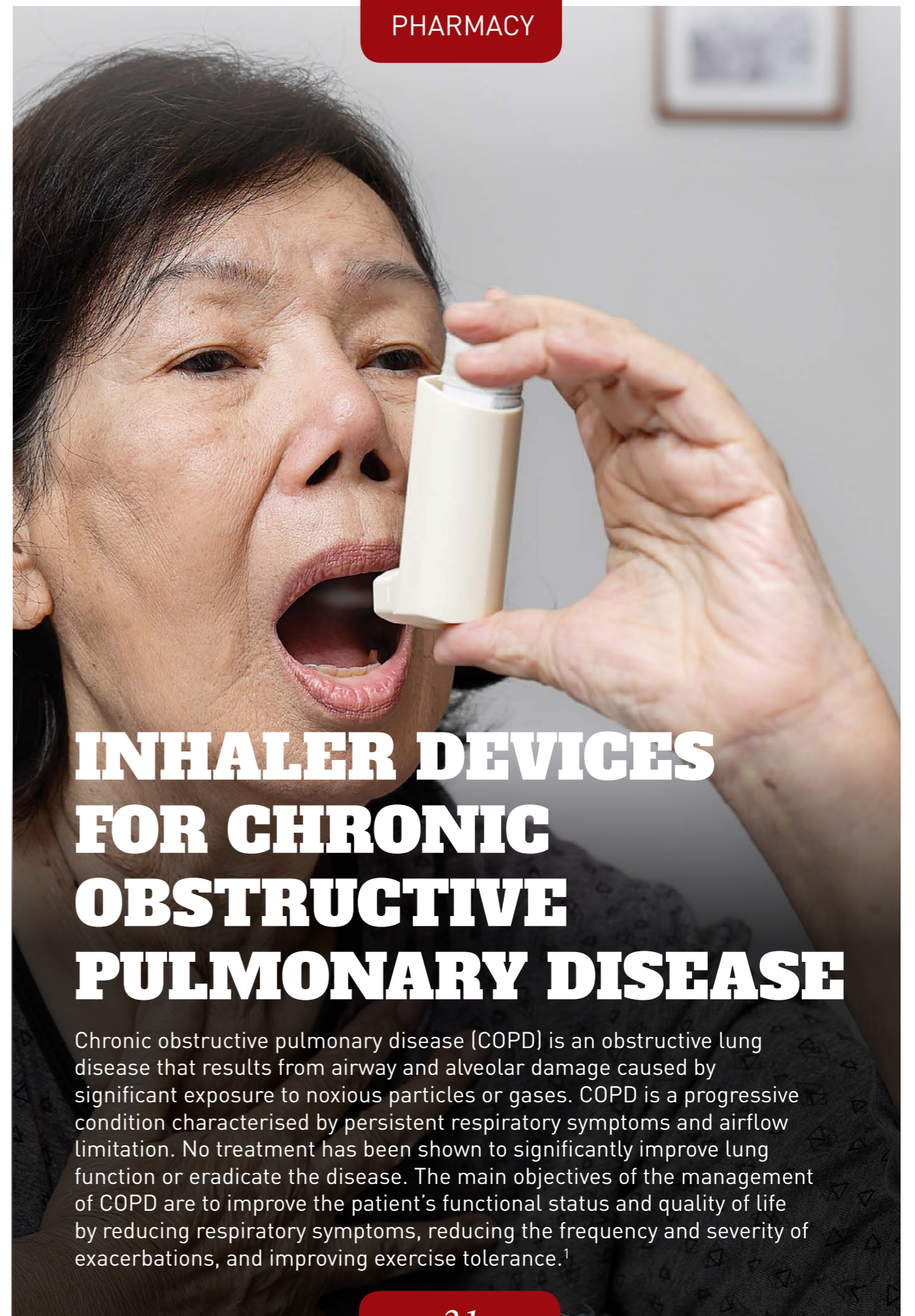
We have discussed a couple of uncommon conditions that were described many decades ago. As our patients demonstrate, they do occur on occasion and it is good to keep these diagnoses in mind.

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INHALER DEVICES FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease (COPD) is an obstructive lung disease that results from airway and alveolar damage caused by significant exposure to noxious particles or gases. COPD is a progressive condition characterised by persistent respiratory symptoms and airflow limitation. No treatment has been shown to significantly improve lung function or eradicate the disease. The main objectives of the management of COPD are to improve the patient’s functional status and quality of life by reducing respiratory symptoms, reducing the frequency and severity of exacerbations, and improving exercise tolerance.¹

Inhalation therapy forms the mainstay of pharmacological management of COPD. The main drug classes recommended by treatment guidelines to treat COPD include inhaled short- and long-acting beta-agonists (SABAs and LABAs), inhaled short- and long-acting muscarinic antagonists (SAMAs and LAMAs), as well as inhaled corticosteroids (ICS).¹ These pharmacological agents may be used either as monotherapy or as combination therapy, depending on the severity of respiratory symptoms and frequency of exacerbations. Devices used for inhalation therapy typically include pressurised metered-dose inhalers (pMDI), dry powder inhalers (DPI), and soft mist inhalers and nebulisers, of which inhalers are most commonly used.

Inhalation therapy is advantageous as it allows for the local delivery of therapeutic drug doses to the lungs where the pharmacological action is required. In addition, the large surface area of the alveoli, the abundant vasculature and thin air-blood barrier allow for fast absorption and rapid onset of action of the inhaled drug while minimising undesirable systemic side effects.²

In recent years, there has been an influx of new inhaler devices and drug formulations for the management of COPD, driven by innovation in inhaler design as well as development of inhaled bronchodilators with longer duration of action.

In this article, we review the characteristics of recent inhaler devices and inhaled bronchodilators developed for the management of COPD, and discuss how they influence inhaler selection.

Inhaler devices for treatment of COPD

1) Pressurised metered dose inhalers

Before the invention of the pMDI, hand-held, squeeze-bulb nebulisers were used to deliver inhaled drugs in the treatment of respiratory diseases. These nebulisers were fragile as they were mostly made of glass and the doses delivered were inconsistent as they vary with hand pressure. pMDIs – portable, multi-dose inhaler devices – were thus developed in the mid-1950s to provide convenient and consistent delivery of inhaled medications.³ The pMDI comprises a canister which contains the medication dispersed in a propellant, a metering valve that delivers a consistent amount of drug with each dose, and an actuator (or mouthpiece) that helps to direct

the medications into the patient's lungs (figure 1). The pMDI is designed to deliver a fixed amount of medication in aerosol form with the aid of the propellant with each actuation while the patient breathes in simultaneously.³



Figure 1. Pressurised metered dose inhalers.
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The pMDIs remain the most widely prescribed inhalation device for drug delivery to the respiratory tract. These devices are generally inexpensive, portable, multi-dose, and can be used with spacer devices to aid administration. However, the main drawback is that they generate an aerosol at a rate faster than what the patient can inhale and much of the dose may be deposited at the back of the throat rather than the lungs.³ Although newer pMDIs have switched to the use of warmer hydrofluoroalkane (HFA) propellants to generate the aerosol, the “cold Freon® effect” generated by the propellant can be uncomfortable and cause patients to stop inhaling prematurely once the propellants reach the back of the throat.⁴ In addition, drug delivery via the pMDI is highly dependent on the coordination of the inhaler actuation and the patient's inhalation, which can be difficult for children and the elderly.³ Poor inhalation technique results in the patient receiving little or no dose at all and in such cases the use of a spacer is necessary.

2) Dry powder inhalers

Dry powder inhalers (DPIs) are devices where medication, in the form of a dry fine powder, is inhaled to be delivered to the lungs (figure 2). DPIs differ from pMDIs as they are breath-actuated, which avoids the need for the breath-hand coordination that is required in the use of pMDIs. DPIs do not require propellants to generate the medication aerosol, but instead rely on the inhaled airstream of the patient to release and disperse the medication.⁵ Thus a sufficient inspiratory effort



Figure 2. Dry powder inhalers.
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to overcome the internal resistance of the DPI is required by the patient, which can be challenging for elderly patients or patients with poor lung function.⁶ Drug delivery can be suboptimal if inhalation is too slow or if the time to peak inspiratory flow is too long.³

DPIs can be classified into three categories based on their design.² The first generation DPIs are the single-dose DPIs, such as the Spiriva Handihaler® and Onbrez Breezhaler®. The medication is released from the capsule when the patient presses on a button in the device to pierce the capsule using a needle attached to the button. The second generation DPIs are the multiple-dose DPIs, such as the Turbuhaler®, Accuhaler® and Ellipta® inhalers. The second generation DPIs can be classified into two further categories, namely multi-dose DPI inhalers (where the dose is retrieved from a powder reservoir, e.g. Turbuhaler®) and multi-unit DPI inhalers (where individual doses are packaged into blisters or strips, e.g. Accuhaler® and Ellipta®). The third generation DPIs include active or power-assisted DPIs, which utilise a power source e.g. battery-driven impellers and vibrating piezo-electric crystals for aerosol production.

The Ellipta® inhaler is a second generation DPI with a dose counter integrated into the mechanism.⁷ It is used for the delivery of various once-daily medications developed by GlaxoSmithKline and can hold up to one month's supply of medications. Ellipta® is convenient for patients to use, as it only requires a single step to prepare the dose. Patients are only required to open the mouthpiece cover fully to activate the inhaler and load the dose for inhalation.

Characteristically, the Ellipta® inhaler has air vents which allow air to enter the inhaler and exit through the mouth piece, thus enabling the medication to be aerosolised and delivered to the patient. This feature allows the patient to inhale more slowly and with less force as compared with other devices, which is beneficial for patients with severe COPD. Thus, it is important for patients to not block the air vents while using the inhaler.⁷



Figure 3. The new category of inhaler devices – the soft mist inhaler.

Type of inhaler	Advantages	Disadvantages
Pressurised metered-dose inhalers E.g. Evohaler	<ul style="list-style-type: none"> Relatively inexpensive Portable Convenient to carry around and use Can be used with a spacer device to facilitate administration Pressurised canister is able to protect medication from external environment. 	<ul style="list-style-type: none"> Drug delivery is highly dependent on the patient's inhalation technique Require correct actuation and inhalation coordination – can be challenging for children and elderly patients Less suitable for patients with low dexterity and low cognitive ability, or those with difficulty actuating the inhaler mechanism Slow and steady inhalation is required, patient has to hold breath after inhalation Use of propellants can result in the "cold Freon® effect" – may result in low deposition of medication dose in the lungs, with most of the dose being deposited in the oropharynx.
First generation dry-powder inhalers (inhalation powder in hard capsule) E.g. Tiotropium Handihaler®, Indacaterol Breezhaler®	<ul style="list-style-type: none"> Portable Breath-actuated, hence the coordination between inhaler actuation and patient inhalation is not required Do not require the use of a propellant. 	<ul style="list-style-type: none"> Require sufficient inspiratory effort to deliver dose optimally, less suitable for young children or the elderly who are unable to breathe in strongly to inhale the dose Require dexterity to load the capsule into the inhaler and to press on the side button to pierce the capsule Quick, deep inhalation required, patient has to hold breath after inhalation May require patient to repeat inhalation for a few times to ensure that the capsule is emptied May be inconvenient as the capsule needs to be loaded before each use.
Second-generation dry-powder inhalers E.g. Accuhaler®, Turbohaler®, Ellipta® Inhaler	<ul style="list-style-type: none"> Portable Multi-dose Breath-actuated, hence the coordination between inhaler actuation and patient inhalation is not required Do not require the use of a propellant Presence of dosing counter Simple, one step actuation with the Ellipta® inhaler. 	<ul style="list-style-type: none"> Require sufficient inspiratory effort to deliver dose optimally, less suitable for young children or the elderly who are unable to breathe in strongly to inhale the dose.
Soft mist inhalers E.g. Respimat®	<ul style="list-style-type: none"> Portable Multi-dose Generate slow-moving mist and fine aerosol droplets Facilitate increased lung deposition Allow patients to take slow, deep breaths Presence of dosing counter. 	<ul style="list-style-type: none"> Complex loading Each new inhaler is required to be loaded with a medicine cartridge before use.

Table 1. Advantages and disadvantages of various inhaler devices for the treatment of COPD.

Inhalation therapy is advantageous as it allows for the local delivery of therapeutic drug doses to the lungs where the pharmacological action is required. In addition, the large surface area of the alveoli, the abundant vasculature and thin air-blood barrier allow for fast absorption and rapid onset of action of the inhaled drug while minimising undesirable systemic side effects.

3) Soft mist inhalers

The soft mist inhalers represent a new category of inhaler devices (figure 3). Marketed as the Respimat® inhaler, the soft mist inhaler does not utilise a propellant, but instead makes use of the energy released from a spring which is compressed when the base of the device is turned 180 degrees.⁸

The key characteristic of the soft mist inhaler is that the aerosol generated moves slower and lasts longer than the aerosol generated from other devices. In addition, it also produces an aerosol with finer particles which allows a higher proportion of the emitted dose to be delivered to the lungs with lesser oropharynx deposition.⁸ The combination of smaller particle size, and slower-moving and longer-lasting aerosol gives soft mist inhalers an edge over pMDIs. They also allow improved coordination of inhalation with actuation, higher lung deposition and lower oropharyngeal deposition.⁹ The soft mist inhaler is useful for patients with decreased lung function who cannot inhale deeply enough on their own to use traditional inhalers effectively. In addition, it is far less likely to cause voice hoarseness caused by deposition of medication at the back of the mouth and throat.

The first drug administered by Respimat® Soft Mist™ inhaler was tiotropium, where the change in drug delivery device allowed for a dose reduction from 18 micrograms daily with the HandiHaler® to 5 micrograms daily with the new inhaler.^{10, 11}

The main drawback of the soft mist inhaler is the need to load a new cartridge each time a new inhaler is used; this step can be complex for patients and is done by removing the transparent base and pushing the cartridge into the inhaler until it clicks into place.⁸ Thus, it is essential to demonstrate and ensure patient competence in loading a new cartridge when he is newly initiated on the soft mist inhaler to enable optimal use.

Pharmacological agents for the treatment of COPD

The pharmacological treatment algorithm indicates that the choice of agent used for treatment is dependent on individualised assessment of symptoms and exacerbation risk.¹ It is recommended for patients with high symptom severity and low exacerbation risk (Global Initiative for Chronic Obstructive Lung Disease (GOLD), Group B) to receive a long-acting bronchodilator, either a long-acting beta-agonist (LABA) or a long-acting anti-muscarinic agent (LAMA). Patients with persistent breathlessness should be escalated to a LABA/LAMA combination. Patients with minimal symptoms but frequent exacerbations (GOLD Group C) should receive a LAMA as first line treatment. If further exacerbations occur, treatment should preferably be escalated to a LAMA/LABA combination; alternatively, a LABA/ICS combination can also be used. Patients with persistent symptoms and frequent exacerbations (GOLD Group D) should be started first on a LABA/LAMA combination and therapy can be further escalated depending on further exacerbations and symptoms.

1) Long-acting beta-agonists

LABAs directly induce bronchodilation by relaxing airway smooth muscle through stimulation of β_2 -adrenergic receptors. Formoterol and salmeterol were the first two LABAs used for the treatment of COPD. Both formoterol and salmeterol have bronchodilating effects lasting for at least 12 hours after a single administration and are administered twice daily.¹² Formoterol, a full β_2 agonist, has a significantly faster onset of action compared to salmeterol.¹³ Formoterol and salmeterol have been shown to significantly improve forced expiratory

volume in 1 second (FEV₁) and lung volumes, dyspnoea, health status, exacerbation rate, and number of hospitalisations, but have no effect on mortality or rate of decline of lung function.^{14, 15}

Over the past decade, several newer β₂-agonists known as ultra-long acting beta-agonists or very long acting beta-agonists (VLABAs) have been developed. VLABAs include indacaterol, olodaterol and vilanterol. Their main advantage over traditional LABAs is that they have a rapid onset of action and can be dosed once-daily which greatly aids in adherence to therapy.¹⁶

Indacaterol was the first VLABA approved by the US Food and Drug Administration (FDA) (on 1 July 2011) for once-daily treatment of COPD. Once-daily indacaterol has been shown to significantly improve lung function in terms of increase in FEV₁, improved health status and dyspnea compared with formoterol and salmeterol.^{17,18} In a blinded 12-week comparison against tiotropium 18 micrograms once daily, indacaterol 150 micrograms daily also provided greater improvement in dyspnoea and health status, although the overall effects on the trough FEV₁ were similar in both groups.¹⁹

Olodaterol is the second VLABA approved by the FDA on 31 July 2014. It is available as monotherapy or in combination with tiotropium.²⁰ Olodaterol has been shown to improve lung function, exercise capacity and health status when compared against placebo. Improvements in lung



function seen with olodaterol were comparable to that with formoterol. However, statistically significant improvements in the St George's Respiratory Questionnaire (SGRQ) scores were seen with olodaterol but not formoterol.²¹

The available VLABAs, such as indacaterol and olodaterol, have not been compared in head-to-head trials with other agents in the same drug class. Vilanterol is only available in combination with umeclidinium or fluticasone.²⁰

In an indirect network meta-analysis conducted by Roskell et al., olodaterol and indacaterol appeared to show similar efficacy in terms of change from baseline in trough FEV₁.²² However, it was also acknowledged that comparisons were hampered by considerable heterogeneity in studies in terms of severity of COPD in the patients enrolled, as well as concomitant maintenance bronchodilator use.

2) Long-acting muscarinic agents

LAMAs prevent acetylcholine-induced bronchoconstriction by acting as competitive antagonists on muscarinic receptors. The currently available LAMAs for the maintenance therapy of COPD are tiotropium, glycopyrronium bromide, aclidinium bromide, and umeclidinium.¹

Tiotropium was the first LAMA introduced for the treatment of COPD. It was first developed as a dry powder capsule to be inhaled via a Handihaler®. Tiotropium has been associated with improvement in lung function and quality of life, and reduction in risk of exacerbations during a 4-year study period, but did not significantly reduce the rate of decline in FEV₁ or mortality when compared to placebo. Tiotropium appears to be more effective than LABAs in preventing COPD exacerbations and disease-related hospitalisations.²³

In terms of the other available LAMAs, aclidinium has a twice-daily dosing, while glycopyrronium and umeclidinium are dosed once daily. However in terms of comparative efficacy, randomised controlled head-to-head trials providing this evidence among the available LAMAs are few. A network meta-analysis of LAMAs versus placebo concluded that available LAMAs, namely aclidinium, glycopyrronium, tiotropium, and umeclidinium showed better efficacy compared to placebo. The efficacy profile of newer LAMAs was also comparable to tiotropium, the traditionally used LAMA.²⁴

3) Long-acting beta-agonist/Long-acting muscarinic agent combination

The fixed dose combination inhalers available for the treatment of COPD include aclidinium/formoterol, glycopyrronium/indacaterol, tiotropium/olodaterol, and umeclidinium/vilanterol.

LABA/LAMA combinations have been shown to improve lung function, and reduce symptoms and frequency of exacerbations when compared to placebo. A network meta-analysis which compared LAMA/LABA combinations with LAMA and LABA monotherapies found that fixed dose combinations provided benefits in lung function, symptoms and quality of life compared to their individual components. Combination therapy reduced moderate to severe exacerbations compared with LABA monotherapy but not when compared with LAMA monotherapy.²⁵

In the first direct comparison of the once-daily fixed-dose LAMA/LABA combinations umeclidinium/vilanterol and tiotropium/olodaterol in patients

with COPD, umeclidinium/vilanterol was shown to be superior in terms of trough FEV₁ at week 8, with an FEV₁ change from baseline 180 mL vs 128 mL; difference 52 mL (95% CI 28–77 mL); p<0.001. However, it is important to note that this was an open-label study with a limited study duration of 8 weeks, which is too short to detect longer-term efficacy differences.²⁶

Conclusion

The data for the comparative efficacy of long-acting bronchodilators within each drug class is mostly limited to indirect comparisons via network meta-analyses. Current data show that long-acting bronchodilators within each drug class have comparable efficacy, hence the choice of long-acting bronchodilators and inhaler device depends on the patient, clinician and cost preferences. Patient factors, such as good breath-hand coordination, type of inspiration, inspiration effort, and dexterity, have to be carefully considered when selecting an inhaler that the patient can use optimally.

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RADIOLOGY QUIZ

This 22-year-old lady presented to the Emergency Department with right iliac fossa pain for 2 days associated with fever Tmax 38 °C. She has no past medical history. The initial impression was acute appendicitis and the patient was referred for a CT scan to confirm the diagnosis.

The CT scan did not show any evidence of acute appendicitis although there was an abnormality noted in the pelvis. Below are selected axial and coronal CT images.

QUESTION 1

1) What pelvic organ do you think the yellow arrows pointing to (figures 1 and 2)?



Figure 1. Axial image of pelvic CT scan.

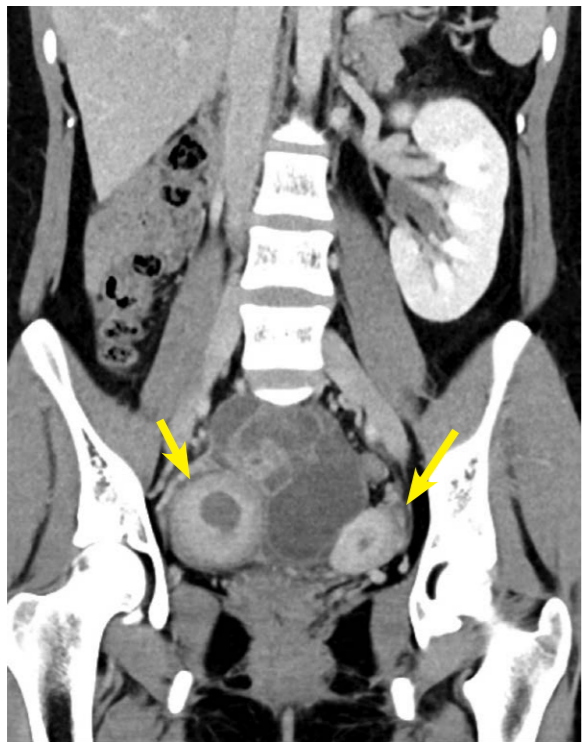


Figure 2. Coronal image of CT scan.

QUESTION 2

2) What do you think is the cause for patient's pain?

QUESTION 3

3) On this other selected coronal CT image (figure 3), what other incidental extra-pelvic finding do you note?



Figure 3. Coronal CT image showing extra-pelvic finding.

QUESTION 4

What spectrum of abnormalities does this patient have and what are the implications?

ANSWERS

- 1) The yellow arrows are pointing to the separate, right and left horns (cornu) of the uterus. This patient has a complete bicornuate uterus.
- 2) When comparing the right and left horns, the endometrial cavity of the right cornu is clearly distended with a small amount of fluid seen around the uterine wall. As such, there are indirect signs that there is obstruction of the right horn with secondary superimposed inflammation/infection, likely accounting for the patient's right iliac fossa pain as well as the fever. This is also further supported by an adjacent, enlarged tubular structure (figure 4, red arrow) which is compatible with right hydrosalpinx.
- 3) The right kidney is absent compatible with right renal agenesis. There is compensatory hypertrophy of the left kidney.
- 4) The constellation of findings is compatible with Müllerian duct anomalies (MDAs). MDAs are congenital abnormalities that occur when the Müllerian ducts do not develop correctly. This may be because of complete agenesis, defective vertical or lateral fusion or resorption failure.



Discussion

MDAs are estimated to occur in 1–5% of all women and despite these anomalies being common, the majority are asymptomatic or detected upon screening. Obstruction of the Müllerian duct may occur, and patients may present with superimposed infection, an abdominal mass and/or dysmenorrhea. Delayed treatment may result in severe consequences and potential infertility. Patients may also present with recurrent miscarriages and infertility.

Renal anomalies are frequently associated, most commonly renal agenesis but also crossed fused renal ectopia and duplex kidney.

Many patients are asymptomatic and require no treatment. However, where obstruction occurs, surgical intervention is usually required and may result in permanent infertility.



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ECG QUIZ

A 60-year-old lady with a history of triple vessel coronary artery disease treated with multi-vessel percutaneous coronary intervention (PCI) presented with an episode of acute breathlessness and chest discomfort. On review, she was pain-free and was not in respiratory distress. Physical examination was unremarkable. Her temperature, blood pressure and heart rate were within normal limits. Serum troponins were normal. Her resting 12-lead electrocardiogram (ECG) is shown in figure 1. An older ECG taken a year ago is shown in figure 2.

QUESTION

What is the ECG abnormality in figure 1?

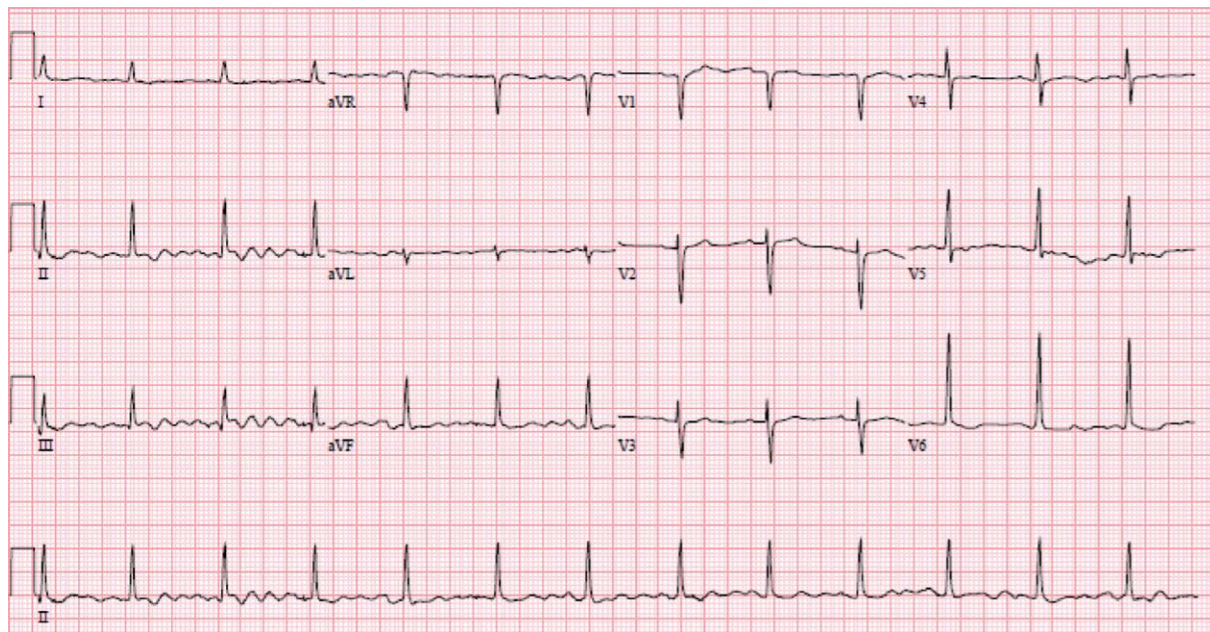


Figure 1. Resting 12-lead ECG recorded on presentation for breathlessness and chest discomfort.

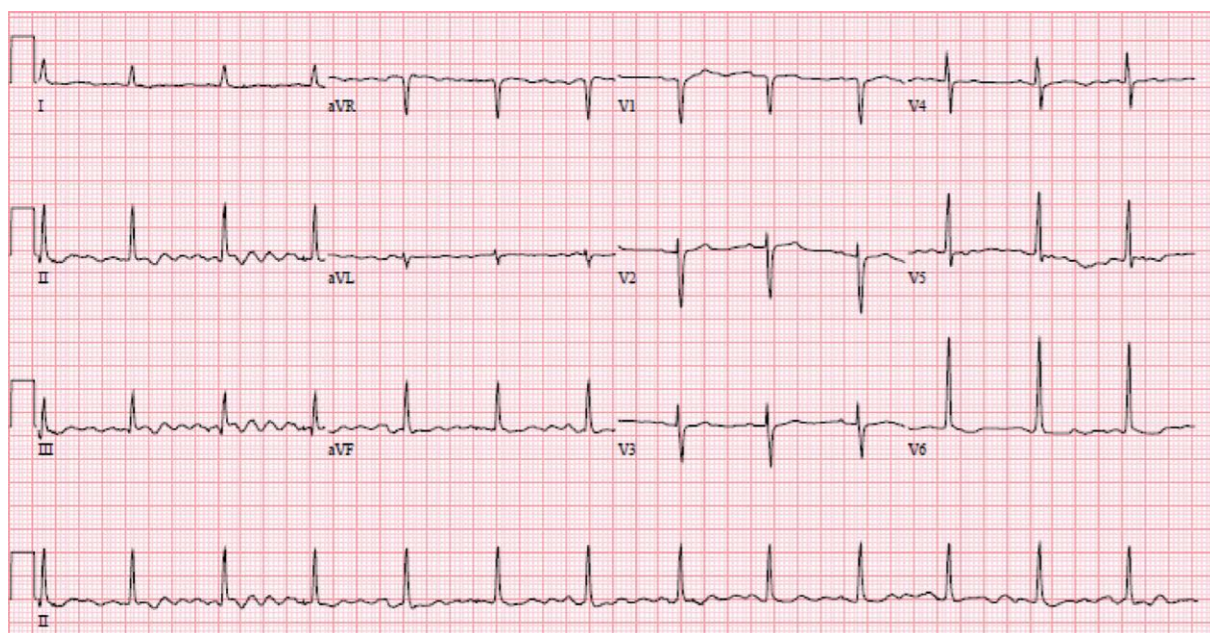


Figure 2. 12-lead ECG recorded one year ago.

ANSWER

ECG artefacts.

Discussion

The ECG shown in figure 1 was initially interpreted as atrial flutter by the attending doctor. Indeed, there are small 'saw-tooth' like complexes seen between the QRS complexes in leads II, III and aVF. Based on this ECG, the doctor explained the diagnosis of atrial flutter to the patient and recommended rate control and anticoagulation.

However, there are several features in the ECG that are inconsistent with atrial flutter. First, the 'saw-tooth waves' look different from one another and vary slightly in height and morphology. Second, these 'saw-tooth waves' are not seen in every lead, although flutter waves are known to be best seen in the inferior leads. Third, normal P waves and a normal isoelectric T-P interval can be clearly seen in leads V2 and V3 even though the long lead II continues to demonstrate the 'saw-tooth waves' in

the same corresponding time interval. These features suggest that these 'saw-tooth waves' are artefactual.

Atrial flutter is usually due to an intra-atrial re-entrant circuit and is characterised by 'saw-tooth' flutter waves typically occurring at a rate of 300 beats/min. These flutter waves should appear identical to one another as the impulses follow the exact same re-entrant circuit in the atrium. In the presence of a healthy atrio-ventricular node (AV node), a typical 2:1 block occurs resulting in a ventricular rate of approximately 150 beats/min. In the presence of rate lowering agents or a diseased AV node, higher grade blocks e.g. 4:1 can also occur. Figure 3 shows the ECG of a patient with atrial flutter.

For this patient, there were no arrhythmias detected on multiple repeat resting ECGs and telemetry. She was discharged after evaluation for cardiac ischaemia.

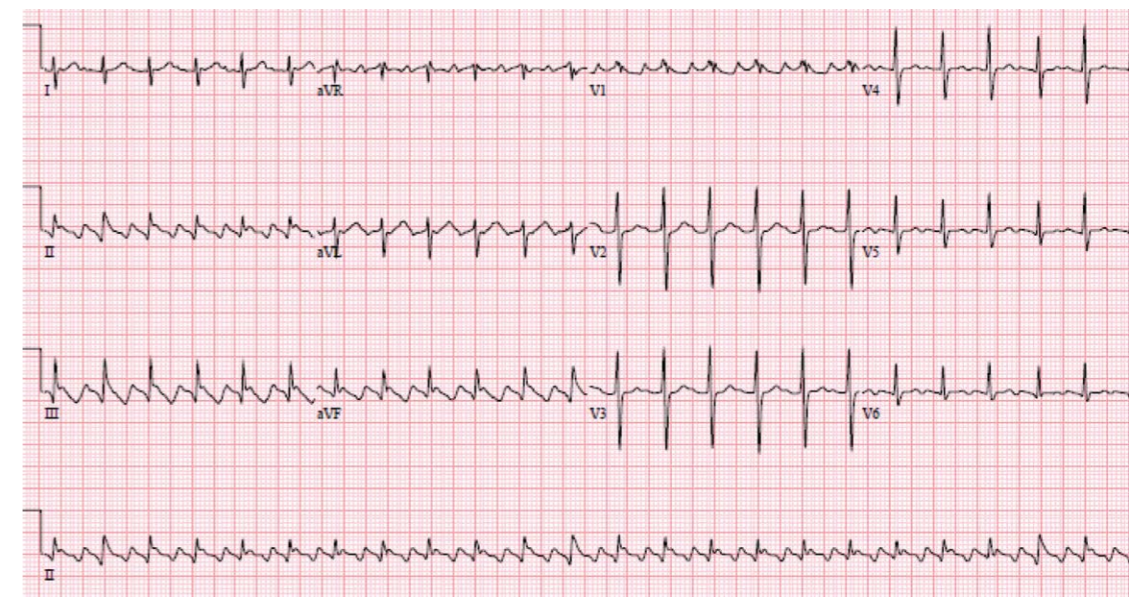


Figure 3. Atrial flutter with 2:1 block in a different patient. This ECG shows a narrow complex tachycardia at 140 beats/min with regular and identical saw-tooth complexes.



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