ANNALS
ACADEMY OF MEDICINE, SINGAPORE
COMMITTED TO SPECIALIST EDUCATION AND TRAINING SINCE 1957

VOLUME 50 | NUMBER 8 | FREE PAPERS | AUGUST 2021

MCI (P) 020/06/2021

Countries around the world are ramping up vaccination efforts with the hope of transitioning from a COVID-19 pandemic state to endemicity. A desired endemic state is characterised by a baseline prevalence of infections with a generally mild disease profile that can be sustainably managed by the healthcare system, together with the resumption of near normalcy in human activities.

A Singapore study examined evidence for a vaccine-driven COVID-19 exit strategy, and discussed how a transition can be made from a pandemic state to an endemic one. It weighed promising data around vaccine efficacy, together with uncertainties posed by emergent variants that may evade vaccine immunity.

One suggested calibrated approach is the lifting of non-pharmaceutical interventions in phases while ramping up vaccination coverage, with less restrictions imposed on vaccinated individuals. This may help to avoid spikes in COVID-19 infection rates, deaths and strain in healthcare capacity, which can derail progress to endemicity.

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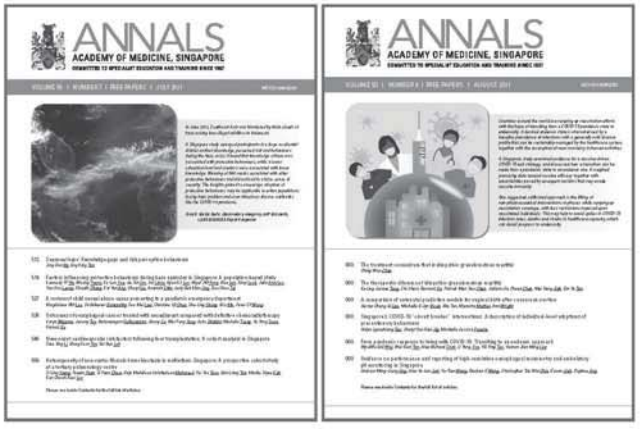

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Printed by Straits Printers (Pte) Ltd

ISSN 0304-4602

MCI (P) 020/06/2021

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EDITORIAL

Ann Acad Med Singap 2021;50:596-7
https://doi.org/10.47102/annals-acadmedsg.2021286

The treatment conundrum that is idiopathic granulomatous mastitis

Ching Wan Chan [1] *MBChB*

Mastitis—inflammation of breast tissue—is a benign, yet potentially debilitating condition that affects women of childbearing age, and its aetiology is usually infectious or autoimmune.

Judging from multiple publications in recent years, there has been increased interest in mastitis of autoimmune origin, of which idiopathic granulomatous mastitis (IGM) is a subset. However, evidence regarding the best treatment approach is still lacking as most reports are retrospective and hence skewed towards treatment bias of the service where patients are seen and managed. Despite this, no hard data regarding the incidence and prevalence of IGM as a medical condition are available from existing literature.

It is important to remember that IGM is a diagnosis of exclusion, and all other causes—such as tuberculosis, sarcoidosis, autoimmune conditions (Behçet's disease, Sjögren's syndrome and systemic lupus erythematosus), granulomatosis with polyangiitis (polyglandular autoimmune syndrome [PGA], formerly Wegener's granulomatosis), eosinophilic PGA (formerly Churg-Strauss syndrome), Crohn's disease, diabetic mastopathy and mammary duct ectasia—should be considered before starting treatment.[1] Needless to say, breast cancer should always be considered as one of the differentials.

IGM by definition is of unknown aetiology. However, based on its response to treatment (corticosteroids and immunosuppressants), and considering the postulated "known" triggers for the granulomatous response (contraceptive pills, hyperprolactinaemia, *Corynebacterium* infection, recent trauma and smoking) that gives rise to its symptoms, an autoimmune origin is the favoured underlying cause for now.[1]

The disease is benign, but can be locally aggressive, potentially causing widespread destruction of the breast, leaving patients with permanent scars. Scarring could be the result of severe inflammation that leads to sinus formation, skin ulceration, and cosmetic deformities from tissue loss. The condition is eventually self-limiting, burning out in the majority of patients within 1–2 years of onset.[2,3] However, a significant minority of patients do have a protracted course and suffer multiple relapses, which significantly impair quality of life[4] and leave a scarred, deformed breast that serves as a permanent reminder of the traumatic period in their lives.

Coupled with its symptoms and signs at presentation (hard, irregular masses, lymphadenopathy and irregular hypoechoic densities on ultrasound scans),[4] IGM may cause patients and their physicians continuous anxiety over the possibility of an underlying carcinoma, until there is complete resolution of the disease with no visible lesions on imaging. IGM commonly presents as a mass in the breast in mostly pre-menopausal women, and occasionally may be associated with pain, erythema and swelling.[5] Pus and abscess formation may be part of the acute presentation, whereas cases that present late often have mammary fistulae and ulceration of the skin on physical examination.[6]

The wide spectrum of therapeutic modalities recommended for this condition reflects the confusion concerning its aetiology, and can range from observation to prolonged use of antibiotics or immunosuppressants, and surgery (with certain patients opting for mastectomy to rid themselves of this disease).[4,6]

A recent study by Tang et al. in this issue of the *Annals* provides additional Singapore data regarding IGM in women.[7] Consistent with international evidence, the condition affects women with a history of breastfeeding in their pre-menopausal years. A positive *Corynebacterium* culture was found in a subset of patients and if present, symptoms were successfully abrogated with antibiotic therapy. However, while no modality of treatment offered superior outcomes, smoking was shown to increase relapse rates.

Thus, in light of the current literature, the following algorithm can be considered. Heightened awareness of IGM is necessary, and early core biopsy (fine needle aspiration is not diagnostic for this condition) of all masses should be performed. This not only excludes malignancy as a cause, but also provides histological

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proof of granulomatosis, which would then trigger the consideration of IGM as a diagnosis. Upon histological confirmation of the condition, patients can be offered observation (mild cases that present as a mass only, without any hallmarks of active inflammation, and patients are educated to detect when these become significant); a short course of steroids (high dose initially for control, and then tapering down as the disease resolves), unless there are active signs of infection (pus formation) that may necessitate antibiotic therapy; and/or surgical intervention. Patients should be reviewed regularly early on, and cases that are refractory to steroids can be referred to rheumatologists for consideration of immunosuppressant therapy (methotrexate or azathioprine) to avoid complications associated with long-term steroid use. The difficulty lies in discerning which patients require what treatment. Over-treatment could result in unwanted and unnecessary prolonged exposure to steroids, while late or inadequate treatment would fail to control the condition sufficiently and result in progressive scarring and deformity of the breast.

In any case, the principles of treatment would be to remove the triggering condition (such as oral contraceptive pill or infection) where possible, and to suppress the over-exuberant immune response (steroids or immunosuppressive therapy) once the initiating trigger has been controlled.

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ORIGINAL ARTICLE

Ann Acad Med Singap 2021;50:598-605
https://doi.org/10.47102/annals-acadmedsg.2020645

The therapeutic dilemma of idiopathic granulomatous mastitis

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ABSTRACT

Introduction: Idiopathic granulomatous mastitis (IGM) is a rare, benign, chronic breast condition that can cause repeated abscesses or mass formation in bilateral breasts. The condition can severely impact the quality of life of affected women. This study aims to evaluate effective treatment modalities, as well as understand the demographics and clinical presentation of patients with IGM.

Methods: An 11-year retrospective review was performed of patients diagnosed with IGM from 1 January 2008 to 31 December 2018 at a tertiary breast unit.

Results: A total of 77 patients were included in the study. The median age at presentation was 36 years old. IGM presented most commonly as a breast lump (98.1%). The median number of flares was 2 (1–12). Of the 77 patients, 68.8% (53) were treated with antibiotics, 50.6% (39) with steroids, and 44.2% (34) underwent surgery, in the course of their IGM treatment. Forty-five (59.2%) of the 76 patients with IGM required a multimodal treatment approach to achieve remission. There was no significant difference in the number of flares no matter the initial treatment (P=0.411), or subsequent treatment modality (P=0.343). Smokers had 10 times greater odds of having a "high flare" of IGM compared to those who did not smoke (P=0.031, odds ratio 10.444, 95% confidence interval 1.092–99.859).

Conclusion: IGM is a clinical diagnosis. It is a rare, relapsing breast inflammatory condition that affects young females with no superior treatment modality. Smoking is associated with higher number of flares of IGM and should be discouraged in IGM patients.

Ann Acad Med Singap 2021;50:598-605

Keywords: Breast inflammation, chronic mastitis, idiopathic granulomatous mastitis, recurrent breast abscess

INTRODUCTION

Idiopathic granulomatous mastitis (IGM) is a rare, benign, inflammatory breast condition that can cause repeated abscess or mass formation in bilateral breasts. It has a reported incidence of 2.4 per 100,000 women aged 20–40 years old.[1] Its aetiology is unclear, but various theories have been postulated, including autoimmune, inflammatory and hormonal causes.[2]

It is known to affect largely women of childbearing age (27–38 years old). Studies report up to 100% of patients presenting with palpable masses.[3] Patients may also present with breast pain, erythema, fistulae and ulceration.[1,4,5] IGM represents a diagnostic and therapeutic dilemma, as it mimics breast cancer and infectious mastitis clinically and radiologically. Diagnosis and management of the IGM may be delayed, as it is often a diagnosis of exclusion.[6]

IGM is known to recur frequently, with reported rates of 5–78% of IGM patients having at least 2 flares.[4,7] The protracted course of the disease has a significant effect on the quality of life for these women.[1]

Varied treatment modalities and successes have been reported, with no clearly superior management. The most common treatment options include antibiotics[8] and steroids.[3,5,9] Surgical options such as excisions, incision and drainage, and mastectomies have been performed,[10,11] while successful results with steroids and immunomodulators (such as azathioprine or methotrexate),[12] and observation[10] have been described.

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CLINICAL IMPACT

What is New

- Smoking increases the odds of having a high relapse of IGM by 10 times.
- There is no superior treatment modality for idiopathic granulomatous mastitis.

Clinical Implications

- This study demonstrates how idiopathic granulomatous mastitis is a clinical diagnosis. It should be considered when a young woman has 2 or more episodes of waxing and waning breast inflammation or breast lumps, in spite of treatment instituted.
- Women with IGM should be discouraged from smoking.

METHODS

This is a retrospective review in a tertiary breast unit in an Asian population. All patients diagnosed with granulomatous mastitis from 1 January 2008 to 31 December 2018 at the Breast Unit at Tan Tock Seng Hospital, a tertiary hospital in Singapore, were evaluated. A review of all patients with the histological diagnosis of "granulomatous mastitis", "xanthogranulomatous inflammation", "granulation inflammation", "inflamed granulation tissue", "chronic inflammation" and "granuloma" was also performed to evaluate for suitability for the study.

The clinical diagnosis of idiopathic granulomatous mastitis was based on recurrent inflammation of the breast in the absence of trauma, tumour and tuberculosis. These were guided by the clinical history, breast imaging results and histology report, if present.

Inclusion criteria were women diagnosed with an idiopathic cause of granulomatous mastitis. Exclusion criteria were other causes of granulomatous mastitis such as tuberculosis and foreign bodies. Periodic acid-Schiff stain and/or Grocott's methenamine silver stain were used to detect fungi on histology, while the Ziehl-Neelson stain was used to identify acid-fast bacilli. Demographic profile, histology results, treatment and recurrence rates were documented and evaluated.

Prednisolone was the steroidal agent used. Immunomodulators, where used, included azathioprine or methotrexate. Surgeries included incision and drainage, excision biopsy and mastectomy.

Any flare of IGM during, or after treatment, was considered a failure. A patient was determined to be in the "high flare" group with a high number of recurrences if she had 3 or more flares of IGM, and in "low flare" group if she had 2 or less flares of IGM. This was based on the mean of 2.3 flares in literature.[6] Patients were deemed "super-relapsers" if they were outliers who had more than 6 IGM flares.

This study aims to evaluate effective treatment modalities for IGM. The secondary aim is to understand the clinical presentation and demographics of patients with IGM.

The chi-square test, t-test, and one-way analysis of variance (ANOVA) were used as appropriate. Univariate analyses were performed with Graphpad Prism version 7 (GraphPad software Inc, San Diego, US). P values <0.05 were taken to be statistically significant. Ethics committee approval was granted by the National Healthcare Group Doman Specific Review Board (DSRB 2018/01157).

RESULTS

A total of 77 women were diagnosed with IGM in the Breast Unit at Tan Tock Seng Hospital over 11 years. The median follow-up was 18 (1–131) months.

The median age of the women was 36 (24–84) years. The racial distribution of the women was 57.1% Chinese, 29.9% Malay, 5.2% Indian and 7.8% other races (Table 1); 84.3% were parous. In 32 women with documented age of final pregnancy, the median time from pregnancy to onset of IGM was 4 years (1–28). Of the 77 IGM patients, 75.4% had breastfed previously, while 93.1% had never taken oral contraceptives. Prolactin levels were checked in 8 women; 3 women had hyperprolactinaemia, 2 of whom had pituitary adenomas.

There was a median of 2 flares (1–12) of IGM. IGM presented most commonly as a breast lump in 76 out of 77 patients (98.7%). The working diagnosis at presentation was breast cancer (36.4%) and breast abscess (36.4%). The initial breast imaging reporting and data system (BI-RADS) was ≥3.0 in 63.6% of patients with IGM. Radiological features described included "ill-defined mass" in 36.4% (28 of 77), "hypoechoic mass" in 61.0% (47 of 77), and "heterogeneous lesion" in 46.8% (36 of 77) of IGM patients.

The median duration to arrive at the diagnosis was 1 month (0.1–73). Seventy-two (93.5%) of the 77 women had histologically proven granulomatous mastitis, with the most common diagnosis being granulomatous inflammation (47.4%). Figs. 1 and 2 show characteristic histological findings of patients in the study.

The majority (65.2%) of breast tissue or pus cultured were sterile. The most common organism grown was *Corynebacterium*, found in 15.2% of patients (Table 1).

Steroids were used in the course of IGM treatment in 50.6% of patients (39 of 77), antibiotics in 68.8% (53 of 77), and surgery was performed in 44.2% (34 of 77). The median number of recurrences after initial

Table 1. Characteristics of patients with granulomatous mastitis

Median age (range), years	36 (24–84)
Mean age, years	38
Menopausal status, no. (%)	
No	66 (85.7)
Yes	11 (14.3)
Race, no. (%)	
Chinese	44 (57.1)
Malay	23 (29.9)
Indian	4 (5.2)
Others	6 (7.8)
Comorbidities, no.	
None	45
Diabetes	5
Hypertension	7
Asthma	2
Hyperlipidaemia	5
Psychiatric disorder	7
Others	10
Immunosuppressed, no. (%)	
Yes	4 (5.2)
No	73 (94.8)
Gave birth previously (n=70), no. (%)	
Yes	59 (84.3)
No	11 (15.7)
Oral contraceptive use (n=72), no. (%)	
Yes	5 (6.9)
No	67 (93.1)
Breastfeeding (n=61), no. (%)	
Yes	46 (75.4)
No	15 (24.6)
Obese (n=47), no. (%)	
BMI>25	14 (29.8)
BMI<25	33 (70.2)
Smoking (n=70), no. (%)	
Yes	5 (7.1)
No	65 (92.9)
Presenting complaint, no. (%)	
Breast lump	48 (62.3)
Breast pain	1 (1.3)
Painful breast lump	28 (36.4)
Initial diagnosis, no. (%)	
Breast cancer	28 (36.4)
Breast abscess	28 (36.4)
Granulomatous mastitis	4 (5.2)
Breast lump	6 (7.8)
Abscess vs cancer	11 (14.3)
Initial BI-RADS, no. (%)	
1	1 (1.3)
2	27 (35.1)
3	22 (28.6)
4	20 (26.0)
5	7 (9.1)
Median duration before diagnosis (range), month	1 (0–73)
Histology-proven GM, no. (%)	
Yes	72 (93.5)
No	5 (6.5)
Histology (n=76), no. (%)	
• Acute on chronic inflammation, no granulomas	4 (5.3)
• Acute on chronic inflammation with granulomatous component	15 (19.7)
• Granulation tissue with granulomas	5 (6.6)
• Granuloma	2 (2.6)
• Granulomatous inflammation	36 (47.4)
• Granulomatous mastitis	10 (13.2)
• Xanthogranulomatous inflammation	4 (5.3)
Microorganisms cultured (n=46), no. (%)	
No bacterial growth	30 (65.2)
Corynebacterium	7 (15.2)
Prevotella	1 (2.2)
Proteus	1 (2.2)
Bacillus	1 (2.2)
Staphylococcus	6 (13.0)
Median number of flares (range)	2 (1–12)
Initial treatment, no. (%)	
Antibiotics	43 (55.8)
Steroids	15 (19.5)
Observation	11 (14.3)
Surgery	7 (9.1)
Defaulted	1 (1.3)
Used steroids in treatment, no. (%)	
Yes	39 (50.6)
No	38 (49.4)
Median number of flares after initiating steroids (range)	1 (0–7)
Surgery as part of treatment, no. (%)	
Yes	34 (44.2)
No	43 (55.8)
Median number of flares after initial surgery (range)	1 (0–11)
Used antibiotics in treatment, no. (%)	
Yes	53 (68.8)
No	24 (31.2)
Median number of flares after initial antibiotics (range)	1 (0–11)
Treatment before remission (n=76), no. (%)	
Antibiotics	9 (11.8)
Steroids	28 (36.8)
Steroids with immunomodulators	5 (6.6)
Observation	12 (15.8)
Surgery	21 (27.6)
Surgery and steroids	1 (1.3)
Defaulted treatment	1 (1.3)

BMI: Body mass index, BI-RADS: breast imaging reporting and data system

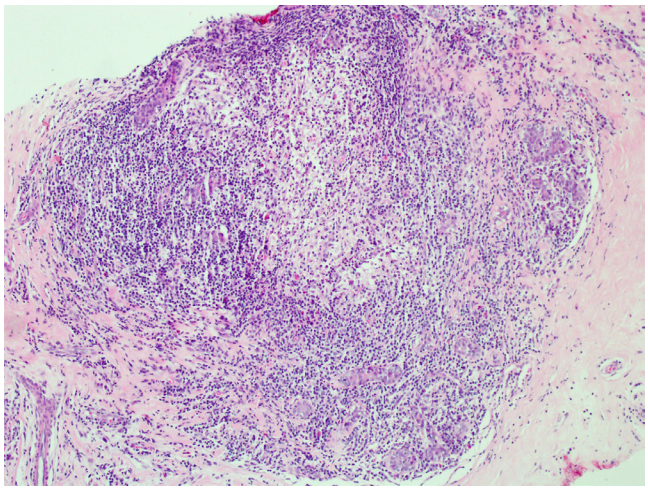

Fig. 1. Breast tissue showing a lobular-centric inflammatory infiltrate, with a granulomatous component. (Haematoxylin and eosin stain, magnification 100x)

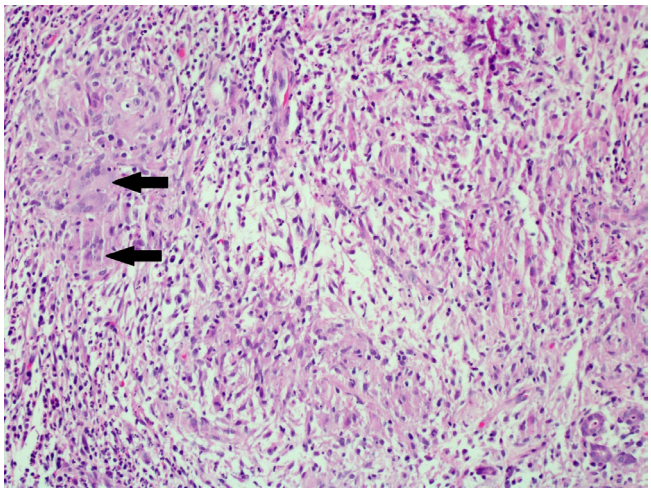

Fig. 2. High power view of the aggregates of epithelioid histiocytes forming granulomas. Multinucleated giant cells are present (arrows). (Haematoxylin and eosin stain, magnification 200x)

treatment was 1, no matter the treatment modality, and there was no statistical significance (P=0.411).

Forty-three of 77 patients (55.8%) were initially treated for a breast infection with oral antibiotics. Of these, 30.2% (13 of 43) resolved without further treatment after a median duration of 16.1 (11.6–37.9) weeks. However, 69.8% (30 of 43 patients) failed to resolve with antibiotics and an alternative treatment was initiated after a median interval of 6.3 (1–319.6) weeks. There was no significant difference in flares between patients who had positive cultures and those with sterile cultures, both of whom received antibiotics (P=0.099).

Fifteen (19.5%) patients were started on steroids as initial treatment. Of these, 12 (80.0%) resolved without further treatment after a median duration of 13.2 (6–47) weeks. Three of the 15 patients with initial treatment of steroids did not respond well, with 1 proceeding with surgery, and 2 requiring immunomodulators after a median duration of 36.6 weeks of steroid treatment. Of all the 77 patients, 24 (31.2%) eventually received steroids after failure of other initial treatment modalities (21 after initial antibiotics, 1 after observation and 2 after surgery). There was no significant difference in the relapse rates of IGM in relation to when steroids were started (whether early in the disease, or after 2 flares) (P=0.827).

The dosing schedule was varied, but with majority starting at 60mg prednisolone daily on tailing dose (ranging from 5mg to 90mg daily). Twenty-five of the 39 patients who received steroids in the course of IGM treatment successfully achieved remission on prednisolone, with 15 (38.5%) requiring only 1 cycle of tailing high dose prednisolone. The median duration of steroid treatment was 14.4 (4.0–62.0) weeks. Eight had a flare of IGM on tailing dose of steroids, with subsequent remission.

Seven (9.1%) patients with IGM had an initial treatment of surgery—5 incision and drainages for an initial diagnosis of breast abscess and 2 excision biopsies for removal of new breast lump. Two of these 7 patients (28.6%) had a remission with surgery alone. Majority of IGM patients with initial surgery required further treatment with steroids, antibiotics or further surgery. A total of 34 (44.2%) IGM patients eventually received surgery, with 13 achieving remission after 1 surgery. There were no characteristics in the surgery or steroid groups, which affected the occurrence of a relapse.

The initial BI-RADS score of the IGM patients who resolved spontaneously without any treatment was higher than those who required treatment (P=0.039). There were no other distinguishing characteristics such as patient demographics or initial working diagnosis.

Follow-up

The median follow-up period was 18 (1–131) months. Fifteen (19.5%) of the 77 patients defaulted follow-up. A significant proportion of these were domestic helpers who were in the country on work visas, and were sent back to their home countries. Others felt symptomatically better and declined return clinic reviews.

Of the 31 (40.8%) patients who received only a single modality of treatment, 17 had no further flares. Being in the high flare group (flare of ≥3 times) was 8-fold

higher when requiring multimodal treatment (*P*=0.003, odds ratio [OR] 7.710, 95% confidence interval [CI] 2.025–29.350).

Forty-five (59.2%) of 76 patients with IGM required a multimodal treatment approach to achieve remission. The main modality to achieve final remission was surgery in 44.4% of patients, followed by steroids in 37.8% of patients.

In 25 patients in the high flare group, the final modality to achieve complete remission was steroidal treatment in 10, steroids and immunomodulators in 5, antibiotics in 1, and surgery for 9 patients. The demographics of the high flare and low flare group were largely similar (Table 2). There is a 10-fold increased odds of smokers having a high number of IGM flares (*P*=0.031, OR 10.444, 95% CI 1.092–99.859). There was no

Table 2. Comparison of characteristics of patients with high flares and low flares

	High flare (n=25)	**Low flare (n=52)**	***P* value**
Median age (range), years	36 (25–53)	36 (24–84)	0.550
Mean age, years	37.3	38.9	
Menopausal status, no.			0.692
No	22	44	
Yes	3	8	
Race, no. (%)			0.362
Chinese	16 (64.0)	28 (53.8)	
Malay	6 (24.0)	17 (32.7)	
Indian	1 (4.0)	3 (5.8)	
Others	2 (8.0)	4 (7.7)	
Comorbidities, no.			0.450
None	13	32	
Diabetes	4	1	
Hypertension	2	3	
Asthma	2	0	
Hyperlipidaemia	1	2	
Psychiatric disorder	1	6	
Others	2	6	
Immunosuppressed, no.			0.098
Yes	3	1	
No	22	51	
Gave birth previously (n=70), no.			0.274
Yes	15	44	
No	5	6	
Oral contraceptive use (n=72), no.			0.163
Yes	3	2	
No	19	48	
Breastfeeding (n=66), no.			0.772
Yes	14	32	
No	5	15	
Obese (n=47), no.			0.344
BMI>25	15	18	
BMI<25	4	10	
Smoking (n=70), no. (%)			0.031
Yes	4 (18.2)	1 (2.1)	
No	18 (81.8)	47 (97.9)	
Initial BI-RADS, no.			0.192
1	1	0	
2	11	16	
3	7	15	
4	4	16	
5	2	5	

BMI: body mass index; BI-RADS: breast imaging reporting and data system

significant difference in the number of flares after steroids, steroids with immunomodulators, or surgery, were commenced (P=0.343).

Fig. 3 shows the Kaplan-Meier curve demonstrating no difference in IGM flare over time, no matter the initial treatment received (P=0.835), nor the specific type of treatment modality received throughout their IGM course (P=0.534) (Fig. 4).

Six patients were super-relapsers, outliers who had 6–12 IGM flares. All of them required multimodality treatment, involving a combination of antibiotics, steroids, surgery and immunomodulators. Three of the 6 patients received immunomodulators. The median number of flares after commencing immunomodulators was 3. One patient even requested for and underwent a bilateral mastectomy, as she was unable to tolerate the recurrent IGM flares.

It took a median of 77 (8–2,237) days to achieve the diagnosis of IGM for super-relapsers, compared to the group within the normal distribution taking 35 (0–544) days (P=0.0001). The super-relapser group was also found to have a lower rate of histology-proven IGM (66.7%), compared to 95.8% in the other group (P=0.006). This is despite all patients in the super-relapser group having had biopsies taken for histology.

DISCUSSION

IGM is a rare inflammatory condition affecting the breast. Only 77 cases were diagnosed in a single tertiary breast centre over 11 years. It largely affected women in their reproductive years, at a median age of 36, in keeping with the literature.[13]

When investigated for microorganisms, 65.2% of patients had a sterile culture, while 15.2% had *Corynebacterium* growth, similar to previous studies.[1,14] The diagnosis of IGM should be considered in recurrent breast abscesses if cultures are sterile, or show *Corynebacterium* growth.

A differential racial representation of IGM incidence has been described, with a higher incidence in Asians, Turkish, Hispanics and Far Eastern populations.[4,15-17] The population of Singapore is made up of 13.4% Malays and 74.3% Chinese.[18] In contrast, a higher proportion of Malay women (29.9%) and lower number of Chinese women (57.1%) were noted to have IGM. Malay women may trend towards an increased likelihood of IGM than Chinese women.

The high flare and low flare groups were largely similar (Table 2), apart from smoking as a risk factor. Our results revealed a 10-fold increased odds of smokers having a high number of IGM flares (P=0.031). This is in keeping with other studies,[4,19] which also reported smoking as a risk factor for IGM recurrence. One in 25 women (4.8%) in Singapore are daily smokers, with a trend towards the tobacco industry targeting women as potential customers.[20] Smoking has been linked with promoting autoimmune diseases such as rheumatoid arthritis by releasing intracellular proteins from reactive oxygen species activated or injured cells, altered presentation of antigens by cigarette smoke-impaired antigen-presenting cells, and altered regulatory B and T cell functions.[21-23] Smoking is also a known risk factor for recurrent breast abscesses and mammillary fistulae.[24] Smoking should be discouraged in women with IGM.

IGM patients in the low flare group tended to only require a single modality of treatment in comparison to the high flare group (P=0.003). It is possible that the clinical course of those with a low chance of recurrence is inherently milder and will likely get better spontaneously, in spite of the treatment administered. Unlike other studies, we did not find parity, breastfeeding or breast infection to be risk factors for IGM recurrences.[4]

Unfortunately, there is a high flare group of patients in whom there will be recurrent flares of IGM. In our patients, 63.6% had at least 2 flares of IGM, compared to 78% of patients in Néel et al.'s study;[2] 32.5% of our patients with IGM had 3 or more flares. Oftentimes, a single modality of treatment may not be sufficient and they will proceed to have a multimodal approach. IGM has a significant but deleterious impact on these patients' quality of life.[1] We noted 1 woman in our study who tried every modality of treatment—antibiotics, steroids, immunomodulators, incision and drainage—but still had 6 recurrences. She ultimately chose to undergo bilateral mastectomy.

The diagnosis of IGM was delayed significantly in the super-relapser group, possibly attributed to the lack of histology to prove IGM. While there was no significant difference in the treatment received, recognition of IGM may help to pace the expectation of the clinical course of IGM for both patients and physician. The subsequent follow-ups, investigations and treatment modalities may also be better tailored for patients with IGM.

The diagnosis of IGM is, ultimately, a clinical diagnosis. IGM should be considered when a young woman has 2 or more episodes of waxing and waning

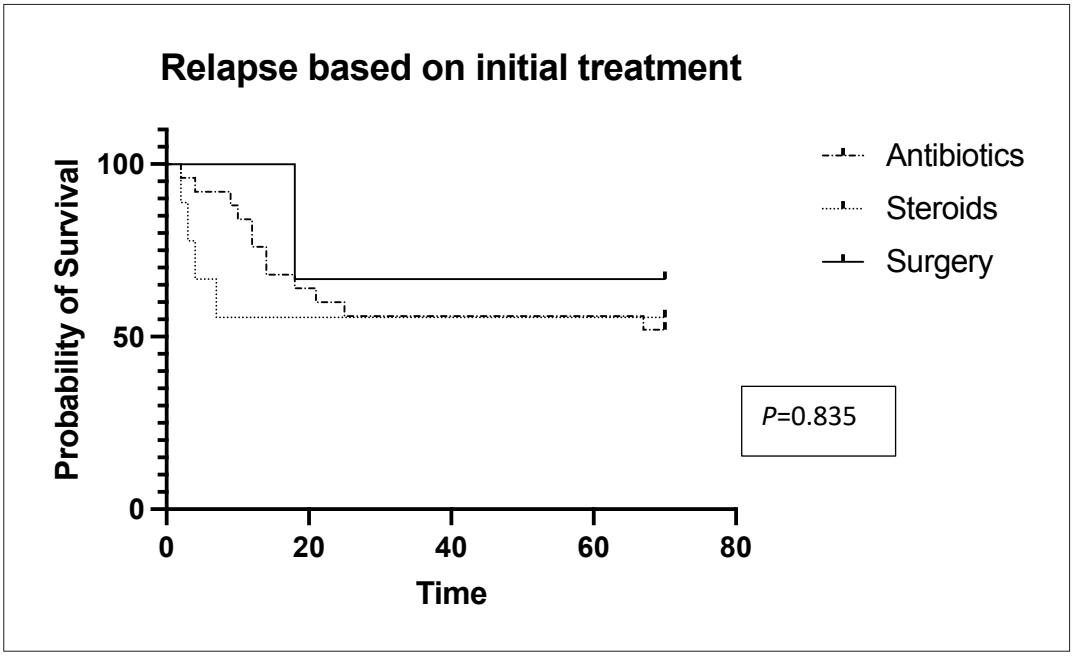

Fig. 3. Kaplan-Meier curve demonstrating relapse over time, based on the initial treatment received.

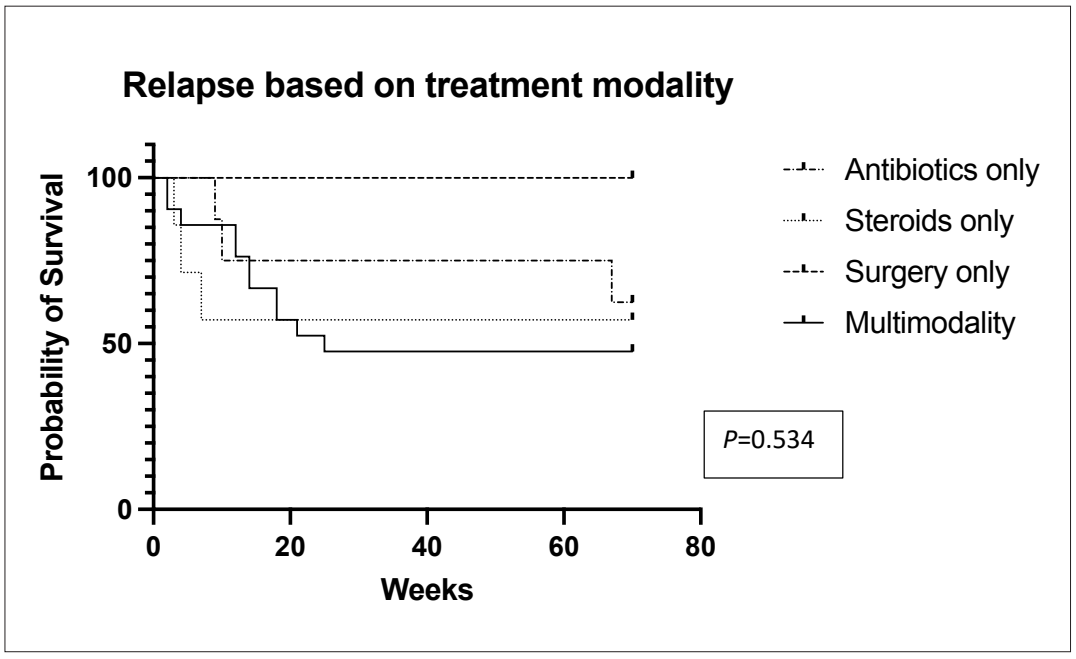

Fig. 4. Kaplan-Meier curve demonstrating relapse over time, based on the treatment received.

breast inflammation or breast lumps, in spite of treatment instituted. A negative histology for IGM does not rule out the diagnosis of IGM.

Literature has no clear consensus on a superior modality of treatment for IGM remission.[4,7] The results of our study support this, revealing no significant difference in the number of flares of IGM whatever the initial modality of treatment (P=0.411). Even in the group with a high number of IGM flares, the type of treatment modality did not affect recurrence or remission (P=0.343). Martinez et al., who published the largest study to date on IGM with 3,060 patients in a systematic review did not observe a correlation between treatment methods and IGM recurrence.[4]

Study limitations

Some patients were lost to follow-up, either because of clinical improvement, or because of return to home countries in the case of foreign workers. As this was a retrospective study, there was no standardised approach among the different surgeons treating IGM patients, which may result in selection bias. As IGM is a rare condition, the number of patients in the current study was small. A multicentre study may be required to further validate the findings of this study.

CONCLUSION

IGM is a clinical diagnosis and there is no superior treatment modality in preventing its recurrence. Smoking is associated with a higher risk of IGM recurrence.

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ORIGINAL ARTICLE

Ann Acad Med Singap 2021;50:606-12
https://doi.org/10.47102/annals-acadmedsg.202132

A comparison of antenatal prediction models for vaginal birth after caesarean section

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ABSTRACT

Introduction: An antenatal scoring system for vaginal birth after caesarean section (VBAC) categorises patients into a low or high probability of successful vaginal delivery. It enables counselling and preparation before labour starts. The current study aims to evaluate the role of Grobman nomogram and the Kalok scoring system in predicting VBAC success in Singapore.

Methods: This is a retrospective study on patients of gestational age 37 weeks 0 day to 41 weeks 0 day who underwent a trial of labour after 1 caesarean section between September 2016 and September 2017 was conducted. Two scoring systems were used to predict VBAC success, a nomogram by Grobman et al. in 2007 and an additive model by Kalok et al. in 2017.

Results: A total of 190 patients underwent a trial of labour after caesarean section, of which 103 (54.2%) were successful. The Kalok scoring system (area under curve [AUC] 0.740) was a better predictive model than Grobman nomogram (AUC 0.664). Patient's age (odds ratio [OR] 0.915, 95% CI [confidence interval] 0.844–0.992), body mass index at booking (OR 0.902, 95% CI 0.845–0.962), and history of successful VBAC (OR 4.755, 95% CI 1.248–18.120) were important factors in predicting VBAC.

Conclusion: Neither scoring system was perfect in predicting VBAC among local women. Further customisation of the scoring system to replace ethnicity with the 4 races of Singapore can be made to improve its sensitivity. The factors identified in this study serve as a foundation for developing a population-specific antenatal scoring system for Singapore women who wish to have a trial of VBAC.

Ann Acad Med Singap 2021;50:606-12

Keywords: Antenatal scoring system, caesarean section, obstetrics and gynaecology, trial of labour after caesarean section, vaginal birth after caesarean section

INTRODUCTION

Caesarean section is one of the most common surgeries in the world. In Singapore, caesarean section rates have risen from 17.8% in 1999 to 34.0% in 2009.[1] With a higher number of caesarean sections, counselling and managing birth after caesarean section have become important.

Compared with elective caesarean section, vaginal birth after caesarean section (VBAC) reduces maternal hospital stay and recovery time, and allows future attempts at vaginal birth. It also reduces the risks associated with multiple caesarean sections such as adhesion formation, visceral injury, wound complications and abnormal placentation in any subsequent pregnancy. Placenta accreta spectrum, which may occur after caesarean section, is associated with massive obstetric haemorrhage, leading to a higher risk of hysterectomy and death. A trial of VBAC also carries risks including scar dehiscence and uterine rupture (0.47%),[2] which are associated with significant maternal and neonatal morbidity and mortality.

A lower segment caesarean section (LSCS) is preferred to a classical caesarean section as transverse abdominal incision is associated with less postoperative pain and an improved cosmetic effect.[3] Women with complicated uterine scars including a previous inverted T or J incision, and classical caesarean sections are contraindications to a trial of VBAC,[4] due to insufficient

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CLINICAL IMPACT

What is New

- Kalok additive scoring system was a better predictive model for successful vaginal birth after caesarean (VBAC) compared to Grobman nomogram in the Singapore study population.
- Patient's age, body mass index and history of successful VBAC were important factors for predicting VBAC.

Clinical Implications

- Customisation of a scoring system to improve its sensitivity for use with Singapore women may be explored.
- A population-specific antenatal scoring system allows for individualised counselling at start of pregnancy and facilitates joint decision-making between clinicians and patients.

data on uterine scar integrity and risk of uterine rupture.[2] Women with a history of 2 or more previous caesarean sections are at greater risk of uterine rupture (1.36%), hysterectomy (56/10,000 versus 19/100,000) and blood transfusion (1.99% vs 1.21%).[5] Hence, despite a 6.2% overall risk of perinatal death in the event of uterine rupture,[2] many authorities[3,6] concur that planned VBAC is a clinically safe choice for selected women with a single previous LSCS.

The desire for VBAC differs among patients. Each patient's background, priorities and risk tolerance for rare complications such as uterine rupture is different. Apart from the higher risk of emergency LSCS compared to elective repeat LSCS, there is tremendous psychological distress associated with emergency LSCS.[7] Hence careful counselling prior to labour is important in the management of patients with a previous caesarean section. There are various tools available in the literature to guide decision-making. An antenatal VBAC scoring system functions as a predictive tool for categorising patients into low and high probability groups for achieving VBAC. It can be used as an aid in individualised counselling of patients on the mode of delivery at the start of an antenatal journey, giving patients a realistic expectation of the likelihood of a successful VBAC. This facilitates a joint decision-making model mandated by the Montgomery ruling for informed consent.

The nomogram developed by Grobman et al. 2007[8] has been cross-validated and externally validated in many populations.[9,10] It includes 6 factors that can be obtained during the first antenatal visit: age, body mass index (BMI), race, number of vaginal deliveries since last LSCS, number of vaginal deliveries and recurrent primary indication. As per Grobman et al., recurrent indications for previous caesarean section refer to reasons for a first caesarean section that may happen again in the index pregnancy, such as cephalopelvic disproportion (CPD) and obstructed labour. Non-recurrent indications refer to causes that may not happen again in the index pregnancy such as breech presentation, malposition, malpresentation, or non-reassuring fetal status. The data from each patient is tabulated into a regression model and the predicted success rate is calculated.

The additive scoring system created by Kalok et al. in 2017 includes 5 factors: (1) non-recurrent indication of primary caesarean section; (2) previous vaginal delivery; (3) maternal booking BMI; (4) age; and (5) estimated fetal weight at or above gestational age (GA) of 36 weeks.[11] Factors 1 and 2 are each allocated 2 points and factors 3 to 5 are given 1 point each. The total number of points for each woman is calculated over a total score of 7. Kalok et al. found that a score of 4 or more is predictive of a successful VBAC with a sensitivity of 81% and specificity of 52.3%.

The study aimed to evaluate Grobman nomogram and the Kalok scoring system in predicting a successful vaginal birth after 1 prior caesarean section among the Singapore population.

METHODS

This was a retrospective observational study of antenatal patients of GA 37 weeks 0 day to 41 weeks 0 day, who underwent a trial of labour after 1 previous LSCS in KK Women's and Children's Hospital, Singapore, between 1 September 2016 and 30 September 2017. Patients with intrauterine death, multiple pregnancy or any contraindication to vaginal birth, such as non-cephalic presentation, placenta praevia, previous uterine rupture and previous classical caesarean section were excluded from the study. Patients with unknown previous incision or caesarean section with extension of uterine incision deemed not suitable for vaginal birth were excluded from the study.

Data on maternal demographics, obstetric history, current pregnancy details and outcomes were collected. The variables analysed included indication for previous LSCS, number of vaginal deliveries before the index pregnancy (including successful VBAC), BMI at first antenatal visit, maternal age, gestational diabetes or pre-existing diabetes, fetal outcomes and presence of

uterine rupture or dehiscence. Uterine rupture refers to clinically significant disruption of all uterine layers leading to changes in maternal or fetal status, and is usually diagnosed clinically. Uterine dehiscence refers to clinically occult uterine disruption that may not have any significant clinical signs and symptoms. Both uterine rupture and dehiscence can be confirmed during surgery. The use of induction or augmentation agents was also noted. For comparison with Grobman nomogram, recurrent indications for previous caesarean section included CPD, failure to progress and failed induction. Patients with incomplete documentation were excluded.

The VBAC success rate was estimated using 2 scoring systems: (1) Grobman nomogram via an online publicly accessible calculator designed by Grobman (https://mfmunetwork.bsc.gwu.edu/PublicBSC /MFMU/VGBirthCalc/vagbirth.html); and (2) Kalok additive scoring system. The predicted mode of delivery was then compared with the eventual mode of delivery, and the area under the curve (AUC) of receiver operating characteristic (ROC) curves were analysed. Maternal characteristics were also compared between women who had successful vaginal birth(s) (including previous successful VBAC) and those who did not, using chi-square test for categorical variables and 2-sample t-test for continuous variables. A *P* value of <0.05 was taken as statistically significant. Factors that were found to be statistically significant and/or significant based on literature reviews were then further analysed using binary logistic regression analysis to calculate the odds ratio (OR). The data was analysed using SPSS Statistics software version 26 (IBM Corp, Armonk, US).

Ethical board approval for this study was obtained from the SingHealth Centralised Institutional Review Board (reference number 2018/2809).

RESULTS

During the study period, there were a total of 482 women who delivered after 1 previous LSCS. Of which, 292 women were excluded from the study (289 opted for elective LSCS, 1 had incomplete records and 2 had stillbirths). A total of 190 women underwent trial of labour after 1 prior LSCS and were included in the analysis. One hundred and three (54.2%) women had a successful VBAC and 87 (45.8%) women required emergency LSCS due to failed VBAC. Those who had a successful VBAC had higher parity, lower mean BMI, a history of prior vaginal delivery or VBAC (Table 1). Women who had a membrane sweep in the antenatal period showed an increasing trend towards a successful VBAC.

The factors that were found to be statistically significant or significant based on literature reviews were further analysed using binary logistic regression analysis (Fig. 1). Previous successful VBAC increased the chance of a subsequent successful VBAC delivery by 4.75 times (Fig. 1). Higher maternal age (OR 0.915, 95% CI [confidence interval] 0.844–0.992) and higher BMI at booking (OR 0.902, 95% CI 0.845–0.960) had lower odds for successful VBAC delivery. Other factors such as parity, recurrent indication for previous LSCS, previous vaginal delivery and membrane sweep were not statistically significant in predicting a successful VBAC.

Of the 103 live term birth from successful VBAC, only 1 (1.0%) neonate was admitted to the Neonatal Intensive Care Unit (NICU), and 3 (2.9%) required special care support. Compared to the 87 live term birth from unsuccessful VBAC, 2 (2.3%) neonates were admitted to NICU and 4 (4.6%) required special care support. The mean () birth weight of neonates delivered via VBAC was 3,092g (standard deviation [SD]=374.28), compared to 3,182g (SD=448.82) (*P*=0.132) for those who delivered via emergency LSCS.

There was 1 case of uterine rupture (0.5%) and 3 (1.6%) cases of uterine scar dehiscence. None of the 19 patients who were induced or augmented in labour had complications of uterine rupture or dehiscence. Emergency LSCS was performed and the rupture or dehiscence was confirmed intraoperatively for all 4 cases. The patient who had the uterine scar rupture was admitted for latent phase of labour, which was prolonged (1,140min). There was non-reassuring fetal status that alerted the team of a possible uterine rupture, and a crash caesarean section was carried out immediately. The patient subsequently underwent a caesarean hysterectomy due to massive postpartum haemorrhage post-closure of the uterus. There was persistent bleeding from the infundibulopelvic ligament into the mesosalpinx despite haemostatic suture (estimated blood loss of 1 litre). The cord gases were: arterial pH 6.7, base excess -17, lactate 4.6, venous pH 6.8, base excess -13.6 and lactate 5.14. The neonate's 1- and 5-minute Apgar scores were 4 and 6, respectively and was subsequently admitted to NICU. The baby was discharged well thereafter.

The mean predicted probability of VBAC among the study population calculated using Grobman nomogram was significantly higher for the group with successful

Table 1. Characteristics of patients who attempted term VBAC during the study period

Characteristics	Total	Unsuccessful VBAC	Successful VBAC	*P* value
Patients, no. (%)	190	87 (45.8)	103 (54.2)	–
Age, mean (SD), years	32.0 (4.47)	32.1 (4.06)	31.6 (4.79)	0.454
Parity, mean (SD)	1.59 (1.03)	1.38 (0.77)	1.78 (1.19)	0.008
Race				0.685
Chinese	53 (27.9)	22 (41.5)	31 (58.5)	
Malay	83 (43.7)	37 (44.6)	46 (55.4)	
Indian	33 (17.4)	18 (54.5)	15 (45.5)	
Others[a]	21 (11.1)	10 (47.5)	11 (52.4)	
BMI at booking visit, mean (SD), kg/m^2	25.2 (5.41)	26.7 (5.68)	23.9 (4.88)	0.001
Recurrent indication[b] for previous LSCS, no. (%)	60 (31.6)	33 (55.0)	27 (45.0)	0.083
Previous vaginal delivery, no. (%)	63 (33.2)	21 (33.3)	42 (66.7)	0.015
Previous VBAC, no. (%)	40 (21.1)	10 (25.0)	30 (75.0)	0.003
GDM/pre-existing DM, no. (%)	25 (13.2)	11 (44.0)	14 (56.0)	0.769
Membrane sweep, no. (%)	11 (5.8)	5 (23.8)	16 (76.2)	0.003
Last EFW measured, mean (SD), g	2675 (676.38)	2678 (734.06)	2673 (626.70)	0.962
Duration from last LSCS, mean (SD), year	4.9 (3.12)	4.9 (3.23)	4.9 (3.05)	0.941
Induction/augmentation agent used, no. (%)	19 (10.0)	8 (42.1)	11 (57.9)	0.734

BMI: body mass index; DM: diabetes mellitus; EFW: estimated fetal weight; GDM: gestational diabetes mellitus; LSCS: lower segment caesarean section; SD: standard deviation; VBAC: vaginal birth after caesarean section
[a] Other nationalities such as Filipino, Vietnamese, Thai, etc.
[b] Recurrent indication for previous LSCS includes cephalopelvic disproportion, failure to progress, failed induction

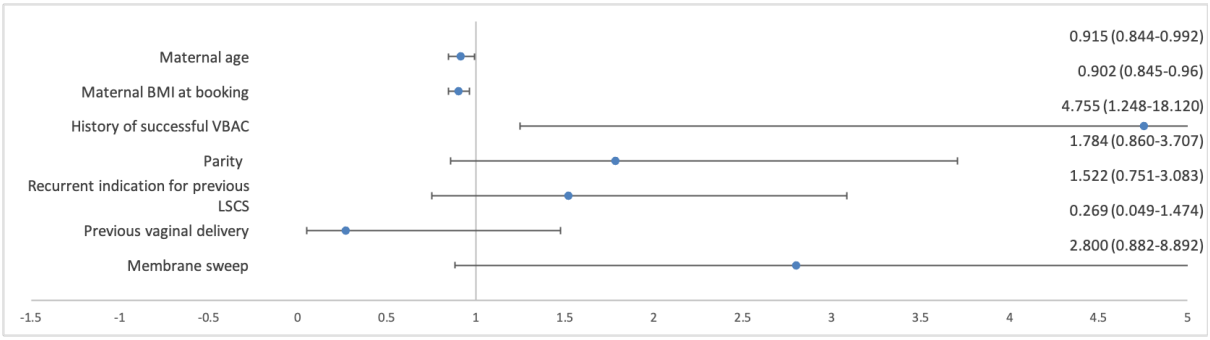

Fig. 1. Logistic regression analysis of the factors associated with successful vaginal birth after caesarean section in the study population.
BMI: body mass index; LSCS: lower segment caesarean section; VBAC: vaginal birth after caesarean section

VBAC (78.9%, SD 13.274) compared to that of the group with unsuccessful VBAC (71.0%, SD 12.934) (P<0.001, 95% CI -11.770 to -4.021). The model's prediction of VBAC success rate is represented by the ROC curve in Fig. 2. The AUC of this curve is 0.664 (95% CI 0.585–0.742).

Table 2 illustrates the sensitivity and specificity of the Kalok scoring system, with either a score of 4 or more (used by Kalok et al.) or a score of 3 or more indicating successful VBAC. When applied to our study population, the scoring system is as sensitive (76.7% vs 81%) but less specific (28.7% vs 52.3%)

Table 2. Effectiveness of the additive scoring system developed by Kalok et al.

	Score ≥3	Score ≥4	Kalok et al.
Sensitivity, %	85.4	76.7	81.0
Specificity, %	18.4	28.7	52.3
Positive predictive value, %	55.3	56.0	84.6
Negative predictive value, %	51.6	51.0	46.0
Negative likelihood ratio	0.792	0.811	NA
AUC of ROC (95% CI)	0.835 (0.774–0.897)	0.740 (0.667–0.813)	0.700

AUC: area under the curve; CI: confidence interval; ROC: receiver operating characteristic

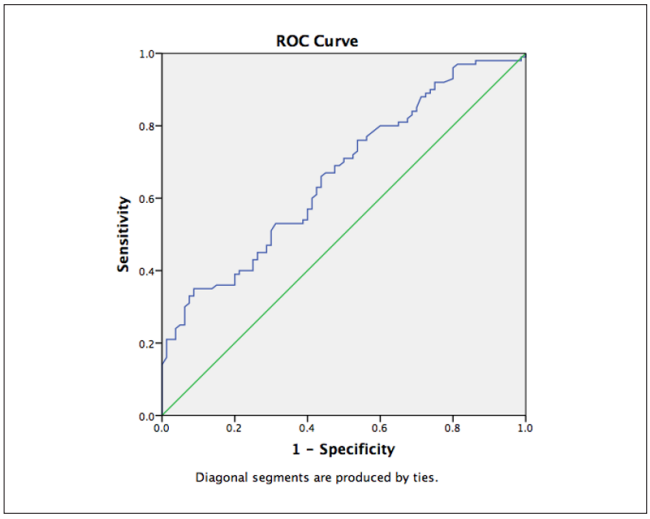

Fig. 2. Receiver operating characteristic (ROC) curve for the prediction of vaginal birth after caesarean section success using Grobman nomogram. The area under the curve is 0.664 (95% confidence interval 0.585–0.742).

when compared to actual published statistics in the development of the Kalok system. A score of 3 or more to indicate a successful VBAC appears to have a higher AUC of ROC (0.835) than when a score of 4 or more is used (AUC 0.740) (Fig. 3).

DISCUSSION

The VBAC success rate in our study population was 54.2%. This was lower compared to other institutions with rates of 60–80%.[12,13] The lower VBAC rate may be related to the institutional practice where prostaglandin induction or augmentation with oxytocin is not favoured in VBAC patients. Induction and augmentation improve VBAC success rates, but also increase the risk of uterine rupture. Many factors have been found to affect the success of VBAC. They are commonly included in VBAC scoring systems to identify patients who are good candidates for trial of labour after caesarean section. However, these models differ in

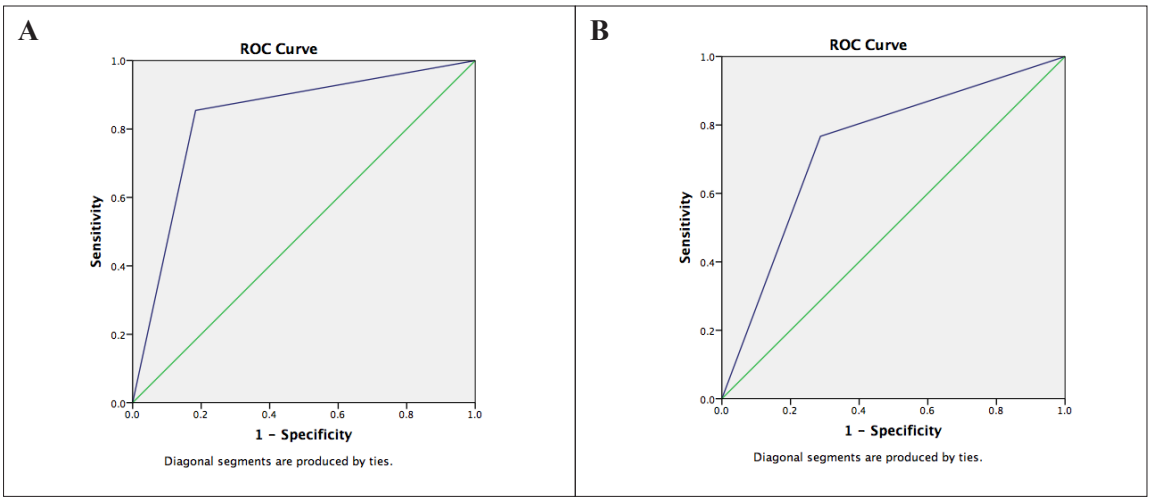

Fig. 3. Receiver operating characteristic (ROC) curves for the prediction of vaginal birth after caesarean section success using Kalok scoring system.
(A) Score of ≥3 predictive of successful VBAC, area under the curve 0.740 (95% confidence interval [CI] 0.667–0.813). (B) Score of ≥4 predictive of successful VBAC, area under the curve 0.835 (95% CI 0.774–0.897).

their performance to consistently predict the success of VBAC.

The scoring system by Kalok et al.[11] (AUC 0.740, 95% CI 0.667–0.813) was more accurate than the nomogram developed by Grobman et al.[8] (AUC 0.664, 95% CI 0.585–0.742) as an antenatal tool to predict the success of VBAC in our study population. One possible reason is that Kalok et al. developed the scoring system based on the population of Malaysia, which may have potential similarities with the Singaporean population and also similar clinical practices. One of the 6 antenatal factors included in the Grobman nomogram is race. Women of different geographical regions and hence different ethnicities have differently shaped birth canal,[14] and this can affect the success of VBAC. In Singapore, there are very few patients with a Hispanic or African American background and this may have affected the performance of the nomogram for the local population. The Kalok scoring system was found to have high sensitivity but low specificity. The negative likelihood ratio was as high as 81.1%, which indicated that its predictive value might not be reliable. If a lower score cut off (≥3) had been used for VBAC success prediction, sensitivity and AUC increased but the specificity was lower. Neither scoring system was designed to predict the risk of complications such as uterine scar rupture or a scar dehiscence.

The positive association concluded in this study between previous successful VBAC, lower maternal age and maternal BMI at booking with successful VBAC delivery was generally similar to Grobman's conclusions in his nomogram development. A high maternal BMI predisposes a woman to gestational diabetes and fetal macrosomia, which can result in an unsuccessful trial of VBAC. Similarly, advanced maternal age predisposes women to more obstetric complications such as gestational diabetes, gestational hypertension and pre-eclampsia. For such "high risk" pregnancies, the clinical threshold for obstetric interventions during trial of VBAC may be lowered. This would result in higher rates of emergency caesarean sections. Both high maternal BMI and advanced maternal age are risk factors for dysfunctional labour. The main differences were those of race (P=0.685) and non-recurrent indication for previous LSCS (P=0.244) that were found to be insignificant in our population. These may explain why Grobman nomogram was not sensitive in predicting VBAC success in our study population.

A Chinese study by Xu et al.[15] in 2019 looked at the effectiveness of the Grobman nomogram in their study population, and compared its performance with that of a modified nomogram with 5 new factors including maternal residence instead of maternal race. They found that the Grobman nomogram was suitable for Chinese pregnant mothers, and there were no marked differences between the 2 models of AUC (0.811, 95% CI 0.751–0.870 vs 0.834, 95% CI 0.891–0.886). This implied the presence of other possible reasons, apart from maternal residence, to explain why the Grobman nomogram was not as effective in predicting successful VBAC in the Singapore population. These could include factors such as lack of use of induction or augmentation per local practice and preference. In the study by Xu et al., around 19.5% of participants had induced labour and 19.3% had augmented labour with oxytocin. Only 10% of participants in the current study had induced or augmented labour.

Interestingly, the current study suggested that membrane sweep may be associated with successful VBAC (Table 1). Membrane sweep is a method of non-pharmacological induction of labour that has been found to reduce the need for formal induction of labour.[16] Previous studies[17,18] did not find any significant benefit of membrane sweep in increasing the rate of VBAC.[19] Membrane sweep was not found to be significantly associated with successful VBAC in logistic regression analysis (OR 2.8, 95% CI 0.882–8.892) (Fig. 1). This may be due to the small sample size of participants who had membrane sweep (n=11). Nevertheless, it may be of worth to consider membrane sweep when managing patients keen for VBAC.

This study was limited by its retrospective nature and small sample size. In addition, only the antenatal factors affecting the success of VBAC were analysed. No intrapartum factors were evaluated. The analyses were also limited to term pregnancies and patients with only 1 previous caesarean section. The scoring systems only looked at the success of vaginal birth and were not able to successfully predict outcomes of uterine rupture/dehiscence. Nonetheless, this study serves as a preliminary study for future prospective studies. Further customisation to the current antenatal scoring systems, such as replacing Hispanic or African American background with the 4 ethnic races of Singapore, may be done to develop an antenatal VBAC scoring system specific to the Singapore population to predict the success of VBAC. This study highlights to clinicians the favourable factors (younger age, lower booking BMI and history of successful VBAC) for successful VBAC which can be discussed with the couple in antenatal clinics, before reaching a joint decision regarding the mode of delivery.

CONCLUSION

The current study showed that the scoring system by Kalok et al. was more useful in predicting VBAC success in the Singapore population. However, neither the Grobman nomogram nor the Kalok scoring system had high sensitivity in predicting VBAC, suggesting the need to develop a scoring system tailored for Singapore women. There are limited data available regarding factors that improve VBAC success rate in Singapore. The factors identified in this study (younger maternal age, lower maternal BMI at booking visit and history of successful VBAC) serve as a foundation for the development of an additive prediction model for VBAC in the Singapore population.

Acknowledgements

We thank the Department of Maternal Fetal Medicine, KK Women's and Children's Hospital, Singapore for their assistance, Serene Ong for her administrative assistance and Jiawen Ong for assisting with data collection.

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ORIGINAL ARTICLE

Ann Acad Med Singap 2021;50:613-8
https://doi.org/10.47102/annals-acadmedsg.2020597

Singapore's COVID-19 "circuit breaker" interventions: A description of individual-level adoptions of precautionary behaviours

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ABSTRACT

Introduction: Effectiveness of COVID-19 control interventions relies significantly on behavioural modifications of its population. Differing adoption rates impacts subsequent COVID-19 control. Hence, positive and sustained behavioural modification is essential for disease control. We describe the adoption rates of behavioural modifications for Singapore's "circuit-breaker" (CB), the national public health response to the COVID-19 crisis, among the general population in the community.

Methods: We conducted an interrupted-time series study using retrospective secondary data. We compared the proportion of Singaporeans who reported adopting specific behaviour modifications before, during and after CB. Behaviours of interest were working from home, performing hand hygiene, using face mask in public, and avoiding crowded areas. We compared change in incidence rates for community COVID-19 cases among the general population across the same time periods.

Results: There was an increase in face mask usage (+46.9%, 95% confidence interval [CI] 34.9–58.8, $P<0.01$) and working from home (+20.4%, 95% CI 11.7–29.2, $P<0.01$) during CB than before CB in Singapore. Other self-reported behaviours showed no statistically significant difference. Change in daily incidence rates of community COVID-19 cases decreased from additional 0.73 daily case before CB to 0.55 fewer case per day during CB ($P<0.01$). There was no significant difference among all behaviour adoption rates after CB. Daily incidence of community cases continued to decrease by 0.11 case daily after CB.

Conclusion: Community incidence of COVID-19 in Singapore decreased during CB and remained low after CB. Use of face masks and social-distancing compliance through working from home increased during CB. However, it is unlikely to influence other sources of COVID-19 such as imported cases or within foreign worker dormitories.

Ann Acad Med Singap 2021;50:613-8

Keywords: Behaviours, COVID-19, public health

INTRODUCTION

In response to the COVID-19 pandemic, many countries have adopted similar public health measures such as enforced social distancing via lockdowns or universal face mask usage.[1-5] However, population compliance with these behavioural interventions varies, likely due to differences in intervention, implementation and country characteristics.[1-3,5] The differing compliance levels resulted in varying effectiveness of COVID-19 control despite similarity in interventions.[6] In South Korea, one of the key factors in the country's effective control of COVID-19 was good public acceptance and compliance with COVID-19 control measures.[5] In contrast, despite similar strategies employed in the UK, public unreceptivity and non-compliance in the community resulted in lack of effectiveness.[7] Therefore it is important to measure and encourage recipient support and compliance with the interventions to ensure effective disease control.

The first COVID-19 case in Singapore was reported in February 2020.[8] Daily reported incidence of local community cases increased from single-digit counts in early March to more than 30 in the first week of April. This was despite border control measures

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CLINICAL IMPACT

What is New

- Community COVID-19 incidence in Singapore decreased during circuit breaker and remained low after.
- Use of face masks and social-distancing compliance increased during circuit breaker.

Clinical Implications

- Positive and sustained behavioural modifications are essential for COVID-19 control.

and social-distancing advisories.[8] A nationwide containment intervention or "circuit breaker" (CB) was thus enacted from 7 April to 1 June 2020. As many countries experienced resurgences post-lockdown,[3,5] Singapore's lockdown was gradually relaxed in phases. Further details are available in the literature.[9-11]

Singapore's CB measures included various forms of mandatory behavioural modifications with legal penalties such as fines. However, individual compliance with these specified behaviours has varied even with legal mandates. A cross-sectional study in Ghana described only 18.9% adoption of face masks on public transport despite it being mandatory at the time of the study.[12] In contrast, a video-analysis study showed compliance with mandatory face mask usage as 85.5% in South Korea and 99.4% in China.[13] To our knowledge, there is a lack of descriptive literature on Singapore's behavioural modification adoption rates. This is worrying particularly as there have been anecdotal reports of non-compliance in the news media.

We describe the effectiveness of Singapore's public health response to the COVID-19 crisis, looking at adoption rates of behavioural modification and other public health measures.

METHODS

Design

We conducted an interrupted time-series study to retrospectively evaluate Singapore's national COVID-19 interventions. Our study population was the general population residing in the community, not including foreign workers or imported cases.

Outcomes

Behavioural modifications

As part of the CB measures, all non-essential workplaces and organisations were mandated to close or implement work-from-home arrangements. As directly measured data on the number of organisations implementing work-from-home arrangements were not available, we used a proxy downstream measure (proportion of workers that reported being able to work from home) although this was less than ideal.

Other behavioural modifications were self-reported compliance with face mask-wearing in public areas, personal hygiene via handwashing or hand sanitiser use, and avoidance of crowded areas. This was derived from secondary data on Singaporeans via an online survey conducted by Imperial College and YouGov Plc.[14]

Change in local community COVID-19 incidence

We collected daily reported local COVID-19 cases (daily incidence) as reported by the Ministry of Health Singapore (MOH) and compared the change in daily incidence (incidence growth or slope).

Maintenance of behavioural modifications

We compared the above-mentioned outcomes between the periods during and after CB. Singapore had a graded approach to release of CB restrictions, termed as Phase 1 (2–19 June 2020) and Phase 2 (20 June 2020–28 December 2020). For simplicity of assessment and due to the short duration of these phases, we combined both into a single time period of "after CB".

Data sources

For disease incidence, we used publicly available COVID-19 press release data from MOH. Disease counts were obtained from mandatory nationwide reporting by doctors and clinical laboratories to MOH.

We used publicly available aggregate anonymised survey data on Singaporeans' self-reported behaviours to measure adoption of behavioural modifications. Survey questions were developed by the Institute of Global Health Innovation at Imperial College London.[14] The weekly cross-sectional surveys were conducted online by YouGov Plc internationally. Survey samples were stated to be representative of the general public, based on age, gender and within-country regions. Approximately 1,000 Singaporeans were

invited to complete the surveys every week from 21 February 2020 to 1 May 2020, and on a biweekly basis thereafter. Financial incentives by YouGov Plc were provided via points accrual from survey completion (SGD25 for 5,000 points). Each completed survey awarded participants approximately 400 points. Response rates were 99% or higher for survey questions relevant to our study.

Survey respondents were asked their frequency of certain behaviours in response to COVID-19 over the past week. Behaviours were: avoiding crowded public areas, performing handwashing or using hand sanitiser, using face masks in public areas, and avoiding of workplaces (or working from home). Responses were categorised into binary outcomes of compliant ("frequently" or "always") or not-compliant ("sometimes", "rarely" or "not at all"). Data is publicly available from the Imperial College London YouGov Covid 19 Behaviour Tracker Data Hub data repository (https://github.com/YouGov-Data/covid-19-tracker).

Statistical analysis

Data were categorised according to 3 time periods: (1) before CB (1 January–6 April 2020), (2) during CB (7 April–1 June 2020), and (3) after CB (2 June–5 August 2020), with the exception of COVID-19 incidence. We anticipated the CB to affect secondary transmission. Hence, we applied a 14-day (twice the average incubation period) lag after the start and end of CB for comparisons of COVID-19 incidence between the time periods.

Data were summarised and presented as proportions, counts or means with standard deviations as appropriate.

Segmented regression was used for slope and level comparisons across time periods. We tested for autocorrelation and non-stationarity in the data,[15] and reported confidence intervals using Newey-West standard errors wherever correction for autocorrelation was required.[16] All statistical analyses were carried out in R Version 4.0.2.

Triangulation

As these outcomes were drawn from separate non-combinable datasets and there is a risk of bias if analysed together, we only visually compared trends between outcomes and qualitatively assessed whether they were coherent with our hypothesis. As this study used secondary publicly available data, no ethics or institutional review board approval was required.

RESULTS

Work-from-home arrangements

The average proportion of Singaporeans reporting work-from-home arrangements was 17% (11–31%) prior to the CB. There was a statistically significant increase during the CB (20.4%, 95% confidence interval [CI] 11.7–29.2, $P<0.01$), compared to before CB (Table 1). There was no statistically significant difference between periods during and after CB.

Face mask usage, handwashing, and avoiding crowded areas

Before CB, the proportion of individuals wearing face masks in public was on average 25% (standard deviation [SD] 5.4%). During the CB, it increased to 86% (SD 7.7%), as shown in Fig. 1A. The difference in average proportion before and during CB was statistically significant (46.9%, 95% CI 34.9–58.8, $P<0.01$). There were no significant changes in the other self-reported behaviours (Figs. 1B and 1C). Individuals reported a high tendency to avoid crowded public areas even prior to the CB (69%, SD 12%, $P=0.80$) compared to during CB (85%, SD 1.1%, $P=0.80$), and for performing handwashing or hand sanitiser use (83%, SD 3.2% vs 84%, SD 0.8%, $P=0.48$). These behaviours remained high with no significant difference after CB (Table 1).

Local community COVID-19 incidence

Before CB, the incidence growth rate was positive (0.73, SD 0.05), indicating an increasing incidence of 0.73 local case in the community day by day. During CB, the incidence growth rate became negative (-0.55, SD 0.07), reflecting a daily decrease in incidence. The difference in growth rate between the two periods was significant (-1.28, 95%CI -1.48 to -1.08, $P<0.01$). After CB, the change in daily incidence of cases remained negative but at a gentler gradient (-0.11, SD 0.06; change in slope: 0.44, 95% CI 0.26 to 0.62, $P<0.01$), as shown in Fig. 2.

DISCUSSION

Behavioural modifications (proportion of Singaporeans wearing face masks in public, and those reporting work-from-home arrangements) showed an increase between the periods before CB and during CB. The increase is likely due to these behavioural modifications being made mandatory. In Singapore, "social-distancing ambassadors" were deployed to

Table 1. Reported adherence to Singapore's "circuit breaker" measures

	Proportion self-reported behaviour			Change between periods, level change estimate (95% confidence interval)	
Time period relative to circuit breaker	Before	During	After	Before versus during	During versus after
Wearing face masks in public, % (SD)	25.4 (5.4)	86 (7.7)	90.2 (1.8)	**46.9 (34.9 to 58.8)**	12.7 (-8.8 to 34.3)[a]
Avoiding crowded public areas, % (SD)	68.7 (12.1)	84.6 (1.1)	80 (3.2)	-1.6% (-15.3 to 12.2)	3.4 (-8.0 to 14.8)
Performing handwashing or hand sanitiser use, % (SD)	82.6 (3.3)	83.8 (0.8)	80.4 (1.3)	-1.9 (-7.8 to 4.0)	-3.6 (-10.2 to 2.9)
Working from home, % (SD)	17.3 (7.5)	51.4 (3.2)	38.9 (7.7)	**20.4 (11.7 to 29.2)**	15.2 (-3.5 to 34.0)

[a] Confidence interval reported using Newey-West standard errors
Bold numbers are statistically significant

actively remind non-compliant members of the public to comply with face masks or social distancing. Punitive measures were also included in the legislation with strict enforcement.

We found a slope-change of the daily incidence of COVID-19 cases from positive (increasing daily incidence) to negative (decreasing daily incidence) during the CB. Our study estimated the lockdown effect at negative growth rate of -1.28 cases daily. This was in line with other studies, where lockdowns reduced case incidence growth rates.[6,17]

When the CB was lifted in a phased manner, there was a continued but lesser reduction in daily incidence growth rate compared to during the CB. This dose-response relationship lends further support to the causal-attribution relationship between the CB and the observed outcomes. All behavioural modifications remained stable and did not differ significantly between the periods during and after CB. This is likely due to the measured behaviours continued to be mandatory or public health recommendations.

Given these findings in adoption rates of behavioural modification and community COVID-19 incidence, we can assume that the CB was effective in controlling transmission in the general Singapore population in the community (outside the foreign worker dormitories). Some of the drivers for the CB's effectiveness were: enforced social distancing via mandatory work from home or suspension of services for all non-essential businesses, and universal face mask usage. These were outcomes that showed a significant increase in compliance and were also documented as effective containment measures in the literature.[1,4,6,17-21] However, our results only show an association between the intervention component and its effect; there was insufficient strength for causality given the cross-sectional nature of data and the difficulty in comparability between datasets.

Our study focused on the general population in the community. However, a large proportion of Singapore's COVID-19 cases occurred due to the outbreak in foreign worker dormitories early into and during the CB. This was due to multiple factors, including high population density and poor living conditions. Additional measures were required to control the outbreak.[22,23] Thus, while we found CB to be effective in controlling community cases among the general population, these may be unlikely to influence other sources of COVID-19 such as imported cases or within the foreign worker dormitories.

Our study has some limitations. In epidemics, one of the ideal outcome measures for interventions is the effect on secondary transmissions. These include estimations of reproduction number (Rt) based on the infectious profile of the disease and parameters such as serial interval distribution, duration and proportion of asymptomatic spread.[24,25] Given our limited data, coupled with the large proportion of asymptomatic infections for COVID-19, this would have required multiple assumptions and resulted in potentially unreliable estimates. Hence, while not ideal, we only analysed incidence pre and post CB to reflect the impact of these interventions on the spread of cases.

We had chosen to fit simple linear models across different time periods for simplicity of analysis and ease of interpretation of effects as averages for each period. Admittedly, this model is not fully representative of the complexities in reality. Other models such as those with quadratic or cubic effects, while providing results that are less straightforward in interpretation, would more fully characterise the trends being studied.

We used secondary cross-sectional data from multiple sources. These datasets were not combinable, making study of temporal associations on an individual level difficult. There may be bias in comparing trends due to differences in the sampled populations across time and between data sources. Hence, we were only able to

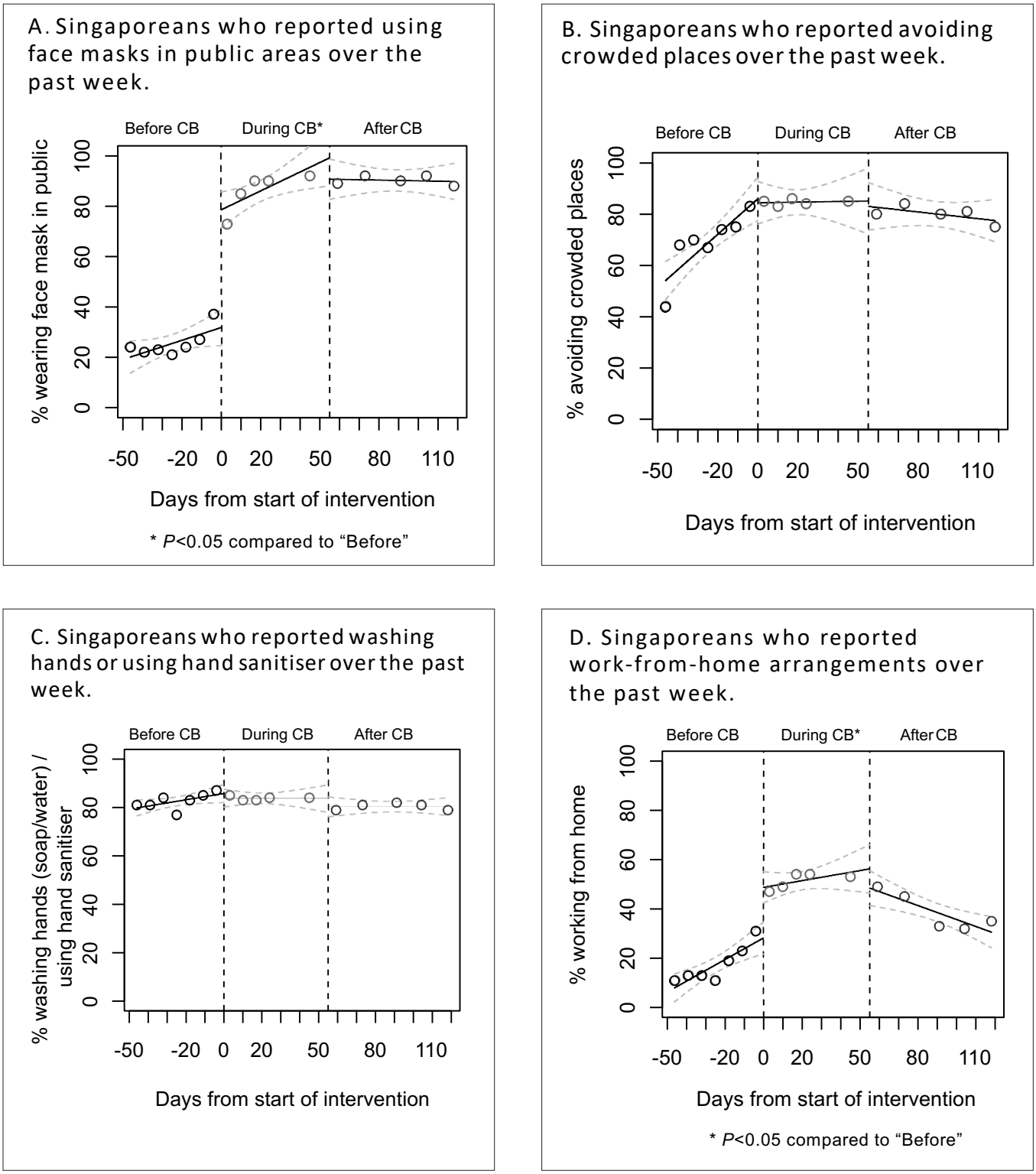

Fig. 1. Reported adherence to Singapore's "circuit breaker" measures.

perform qualitative inferences of association and at a population level. While we lacked a parallel counterfactual in our study design, the interrupted time series design allowed us to study the partial withdrawal of CB interventions and identify a dose-response relationship. Our findings, while showing similar results to that in the literature, further builds on it by providing longer temporal view across periods of varying degrees

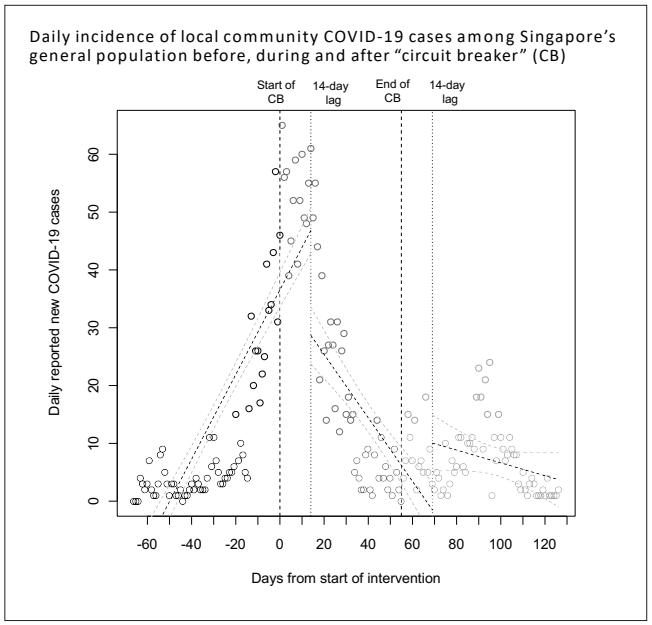

Fig. 2. Incidence of community COVID-19 in Singapore.

of interventions. We recommend further longitudinal cohort research at an individual level to determine the association between behavioural modification and observed COVID-19 control.

CONCLUSION

Community COVID-19 incidence in Singapore decreased during CB and remained low after CB. Usage of face masks and social-distancing compliance through working from home increased during CB. However, it is unlikely to influence other sources of COVID-19 such as imported cases or within foreign worker dormitories.

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REVIEW ARTICLE

Ann Acad Med Singap 2021;50:619-28
https://doi.org/10.47102/annals-acadmedsg.2021244

Living with COVID-19: The road ahead

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ABSTRACT

Introduction: The COVID-19 pandemic has affected the world for more than a year, with multiple waves of infections resulting in morbidity, mortality and disruption to the economy and society. Response measures employed to control it have generally been effective but are unlikely to be sustainable over the long term.

Methods: We examined the evidence for a vaccine-driven COVID-19 exit strategy including academic papers, governmental reports and epidemiological data, and discuss the shift from the current pandemic footing to an endemic approach similar to influenza and other respiratory infectious diseases.

Results: A desired endemic state is characterised by a baseline prevalence of infections with a generally mild disease profile that can be sustainably managed by the healthcare system, together with the resumption of near normalcy in human activities. Such an endemic state is attainable for COVID-19 given the promising data around vaccine efficacy, although uncertainty remains around vaccine immunity escape in emergent variants of concern. Maintenance of non-pharmaceutical interventions remains crucial until high vaccination coverage is attained to avoid runaway outbreaks. It may also be worthwhile to de-escalate measures in phases, before standing down most measures for an endemic state. If a variant that substantially evades immunity emerges, it will need to be managed akin to a new disease threat, with pandemic preparedness and response plans.

Conclusion: An endemic state for COVID-19, characterised by sustainable disease control measures, is likely attainable through vaccination.

Ann Acad Med Singap 2021;50:619-28

Keywords: COVID-19, endemic, non-pharmaceutical interventions, transition, vaccination

INTRODUCTION

The COVID-19 pandemic has made an unprecedented impact on global morbidity, mortality and healthcare measures to contain the infection.[1] Multiple waves of infections in 2020 and 2021 have resulted in significant disruptions to healthcare, economies and societies globally, with few countries able to avoid major epidemics. In the initial pandemic response, without the availability of effective therapies or vaccines, non-pharmaceutical interventions (NPIs) formed the main measures against the virus. These included border control measures, case-based and community-based NPIs—such as testing, isolating cases, contact tracing and quarantining of close contacts, mask wearing, physical distancing, and reducing of community activities.[2]

The availability of COVID-19 vaccines from late-2020 offers a potential tool to end the pandemic. Early data from Israel, which had vaccinated over 60% of its population,[3] suggest that a vaccine-driven strategy coupled with phased reduction of NPIs could be a way to transition towards an endemic end state.[4,5] Whether this level of vaccine coverage in the absence of NPIs is adequate to maintain low COVID-19 hospitalisations and deaths, especially in light of more transmissible variants, remains to be seen. In addition, there is uncertainty over the optimal approach to transition

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CLINICAL IMPACT

What is New

- COVID-19 strategies in many countries have been focused on stringent measures. However, these are unlikely to be sustainable over the long term.
- This review examines evidence for a vaccine-driven COVID-19 exit strategy and discusses how a transition can be made from a pandemic state to an endemic one.

Clinical Implications

- More countries are ramping up vaccination efforts with the hope of transitioning from a COVID-19 pandemic state towards endemicity and restoring normalcy in society and human activities.
- One calibrated approach to transition towards endemicity would be to lift non-pharmaceutical interventions in phases while ramping up vaccination coverage, with less restrictions imposed upon vaccinated individuals.
- This will avoid unnecessary spikes in COVID-19 infection rates, deaths and strain in healthcare capacity, which can derail progression towards endemicity.

to an endemic end state. As more countries ramp up vaccination efforts, it is timely to explore the steps needed to safely transition to COVID-19 endemicity.

A vaccine-driven COVID-19 exit strategy with cautious transition is the most likely path for countries that have stringently controlled COVID-19 within their borders, such as Singapore. In this review, we examine the current evidence around a vaccine-driven COVID-19 exit strategy and how countries may shift from the current pandemic to an endemic state.

ENDEMIC COVID-19

Exit strategies

Many approaches to the control of COVID-19 have been attempted. Some countries such as Sweden had initially attempted to attain herd immunity through natural infection, although not officially stated as part of the nation's strategy, which had resulted in surges in infections, overwhelmed healthcare systems and high rates of mortality.[6] No country has succeeded in achieving herd immunity for COVID-19 through natural infection alone despite continued transmission for over a year, with many pivoting away from this strategy in the face of escalating hospitalisation and mortality.[7] COVID-19 infection fatality rate has been estimated at up to 15% among older adults, and fatalities have also been seen in children, highlighting how such a strategy would be extremely costly from both the health and socio-economic standpoints, particularly in vulnerable populations.[8] In addition, emerging evidence on post-acute COVID-19 syndrome ("long COVID") indicates possible long-term sequelae beyond 4–12 weeks in around 30% of survivors from disease onset.[9] The World Health Organization (WHO) has described the attempt to reach herd immunity through natural infection without any control measures as "scientifically problematic and unethical", and cautioned against such an approach due to the "unnecessary infections, suffering and death".[10]

In contrast, countries like New Zealand, Australia and China have aimed for an elimination strategy through implementing extensive NPIs, including strict border closures, region-wide lockdowns, school closures and stringent physical distancing measures. However, these measures are resource-intensive and entail significant economic and societal costs that not many countries can bear, especially those without large domestic economic markets.[11] Prolonged and extensive NPIs could also lead to other adverse health and social consequences, such as worsening mental and physical health problems, and exacerbating inequity in access to education and health services.[12]

Global eradication of COVID-19 is implausible for the foreseeable future given the high transmissibility of SARS-CoV-2 virus, the propensity for the virus to mutate and escape immunity from prior infection or vaccination, and the lack of global coordination of disease elimination measures. A pure elimination strategy is impractical in most countries reliant on flows of trade and people, such as Singapore, as the risk of importing the disease remains high while transmission continues globally.[13] Rather, COVID-19 will inevitably be endemic, much like many other common respiratory diseases.[14] Therefore, an exit strategy that restores normalcy, or near-normalcy, while protecting lives and minimising adverse impact on the society is much sought after. Such a strategy entails arriving at the state of substantial immunity to reduce the health burden from natural infection, which effective COVID-19 vaccines and reasonable NPIs can facilitate. It will require attaining high levels of vaccine coverage in the population and avoiding large surges in infections in the meanwhile. Ultimately it may replace the need for ongoing large-scale disease control efforts.

COVID-19 vaccine-driven endemic state

This desired end state will entail endemicity not just in epidemiological terms, but also in societal terms with regards to the approach to COVID-19. The virus will still be circulating in the population, occasionally causing outbreaks or seasonal epidemics but with levels of disease burden that can be managed by the healthcare system without being overwhelmed. This is akin to other endemic diseases such as dengue fever and seasonal influenza which may cause severe disease, but generally do not threaten overall healthcare capacity or disrupt socio-economic activities. For countries that now place a tight lid on transmissions, such a state will allow them to shift their primary focus onto disease burden instead of a fixation on the force of infection.

Might such a state of near-normalcy be attainable for COVID-19, or would COVID-19 continue to require significant NPIs even after the vaccination roll-out is over? Current data around the COVID-19 vaccines offer insight and promise.

With a vaccine roll-out that saw over 80% of its adult population being vaccinated with the Pfizer-BioNTech BNT162b2 vaccine, in addition to some pre-existing natural immunity after earlier waves of infection, Israel saw a sharp decline in COVID-19 cases and lifted most NPIs on 1 June 2021. This included doing away with its Green Pass vaccine-certificate system, restrictions on gathering sizes and mandatory mask wearing, and also the partial opening of its borders to vaccinated travellers.[15] However, trends after the lifting of NPIs showed an uptick in infected cases, primarily due to the spread of the Delta variant in unvaccinated individuals. This has led to the resumption of some NPIs such as travel advisories, reinstatement of mandatory mask wearing in schools in outbreak regions, contact tracing and quarantine.[16] It is yet unknown whether the rates of severe disease and death will follow a similar upward trajectory in the longer term, or whether infections will stabilise at a low level with time.

While it is difficult to set a level of disease burden that would be acceptable to the community, comparison of COVID-19 to seasonal influenza could help to put things into perspective. Annual seasonal influenza in the US was estimated to result in up to 45 million infections, 810,000 hospitalisations and 61,000 deaths.[17] The burden of disease from influenza is similar across the world, with estimated 291,243 to 645,832 global deaths annually,[18] yet it is a disease we have grown to live with.

COVID-19 has been clearly a more severe disease in the absence of prior immunity (Table 1), resulting in mortality up to 40 times that of seasonal influenza in the US in 2017. Between 2010 and 2020, among adults aged above 18 years in the US, influenza vaccine coverage ranged between 37.1% and 48.4%, with vaccine effectiveness between 19% and 60%.[19,20] With COVID-19 vaccination, higher coverage with more effective vaccines may substantially reduce the overall infection incidence.

Table 1. Comparison of estimated epidemiological parameters of seasonal influenza and COVID-19

Parameters	Seasonal influenza	COVID-19, as of 6 May 2021	Relative rate ratio, crude
Basic reproduction number	Median 1.28 (IQR 1.19–1.37)[21] US: 1.8–3.1[22]	Mean 3.32 (95% CI 2.8–3.8)[23]	2.59
Incidence rate per 100,000 person days	Global: 1.95[24] (lower respiratory tract infections, 2017)	Global: 58.5 (6 May 2021)[25]	30
Hospitalisation rate per 100,000 person days	Global: 0.34 (2017)[24]	Global: 0.86 (6 May 2021)[25] US: 1.42[26] UK: 1.36[26] Israel: 1.02[26]	2.5
Mortality rate per 100,000 person days	Global: 0.005 (2017)[24]	Global: 0.20 (6 May 2021)[25]	40
Vaccine coverage, at least 1 dose (%)	US: 37.1–48.4[19] (2010–2020)	US: 53.3 UK: 64.3 Israel: 63.9 (25 June 2021)[27]	–
Vaccine effectiveness (%)	19–60[20]	51–94 (WHO EUL)[28]	–

Note: Global COVID-19 incidence rates of incidence, hospitalisation and mortality were derived from cumulative rates/numbers where needed by using a global population of 7.7 billion and with a time period from 1 February 2020 to 6 May 2021.
CI: confidence interval; IQR: interquartile range; WHO EUL: World Health Organization Emergency Use Listing
Superscript numbers: Refer to numbers in REFERENCES

Comparing COVID-19 hospitalisation and mortality rates among vaccinated persons in Israel against that of seasonal influenza in the US and England (Table 2), it is apparent that the rates of severe outcomes of COVID-19 hospitalisation and mortality are substantially reduced among vaccinated persons to a magnitude similar to that of seasonal influenza. While not a precise comparison, the magnitudes are comparable. Nevertheless, further monitoring will be required and should include examining how this data will stand up to other variants of concern, such as the Delta variant.

Earlier simulations have provided indications on the extent of vaccination coverage and vaccine effectiveness required to suppress the incidence of SARS-CoV-2 infections. One study suggested that with a basic reproduction number (R_0) of 2.5, a vaccine coverage of 70% with vaccine effectiveness of 75% would be required to prevent an epidemic or subsequent wave of infection, and the background incidence would be stably sustained at a low level.[32] The coverage required approached 100% if vaccine effectiveness fell towards 60%, reinforcing the equal importance of both R_0 and vaccine effectiveness. In another simulation, the projected mortality in the UK from 2022 to 2024 increased from 1,000 to 63,000 deaths when the vaccine efficacy was reduced from 85% to 60%, assuming the same level of vaccine coverage of 95%, 90% and 85% coverage in those aged 80 years and older, 50–79 years, and 18–49 years, respectively.[33] On the other hand, effective vaccines alone will be insufficient in averting a pandemic if coverage is low.[33]

The Pfizer-BioNTech BNT162b2 vaccine and Moderna mRNA-1273 vaccine are the most efficacious COVID-19 vaccines thus far, with efficacies of greater than 90% for symptomatic disease.[34-36] The extent of indirect vaccine protection to the population has also been studied, with an increase of 20 percentage points in population coverage with Pfizer-BioNTech BNT162b2 vaccine being associated with a reduction in the positive test fraction of unvaccinated population by twofold.[37] However, the Pfizer-BioNTech BNT162b2 vaccine has showed reduced effectiveness against the Delta variant, with a recent estimate at 79% for symptomatic disease.[38] This does not mean that the desired endemic state cannot be achieved, as it can still reduce disease burden to a level manageable for healthcare systems and mild infections would be of less significance. In general, vaccines' effectiveness against severe disease is very high and in this respect, Johnson & Johnson's Janssen Ad26.CoV2.S vaccine had reported effectiveness of greater than 80%, Sinovac-CoronaVac vaccine 100% in its WHO Emergency Use Listing Procedure (EUL) submission, and the Pfizer-BioNTech BNT162b2 vaccine had observed effectiveness over 90% against hospitalisation with the Delta variant.[38-40] As such, we can expect vaccines to markedly reduce the healthcare burden by a corresponding extent through its direct protection from hospitalisations and deaths. Nevertheless, direct protection from severe disease alone is less effective in minimising the disease burden than if the herd immunity threshold could be surpassed, perhaps together with immunity from natural infection. As disease burden is concentrated among vulnerable populations, it is particularly important to aim for high vaccination coverage among them and in persons around them.

Table 2. Comparison of disease profile of COVID-19 with and without vaccination (Israel) against that of influenza in persons aged 65 and older (US and England)

	Rates among persons aged >65 years, in 100,000 person days				
	COVID-19[3]		**Influenza, median (range)[a]**		
	Israel (Unvaccinated)	Israel (Vaccinated)	US[17] (2010–2020)	England[29]	Singapore[30,31]
Mortality	6.6	0.2	0.17 (0.06–0.27)	0.18 (0.08–0.53)[b]	0.46[d]
Hospitalisation	21.7	0.8	1.29 (0.58–2.91)	0.37 (0.23–0.51)[c]	0.85 (0.77–1.20)[e]

[a] Influenza rates are of cumulative incidence rates from respective country's influenza season divided by 365 days across entire calendar year and represent conservative estimates as influenza cases beyond the influenza season are few and not reported.
[b] Years 2015–2020
[c] Years 2018–2020
[d] Years 1996–2003
[e] Years 2010–2017
Superscript numbers: Refer to numbers in REFERENCES

However, more data on vaccine protection from the Delta variant are needed. Also, studies modelling COVID-19 disease burden have generally not considered the different protection levels for asymptomatic infection and severe disease together, and this is an important area to examine. Overall, with the current data on vaccine effectiveness and real-world evidence, a vaccine-driven end state is feasible and provides optimism that an end to the pandemic may be in sight. Maximising direct individual-level protection and achieving high population-level immunity from vaccination are both important to strive for, particularly as the former may be more robust against variants with higher transmissibility.

Achieving the endemic end state

With this endemic end state in mind, we considered how transition from a pandemic-response footing to an endemic state may take place. As countries continue with vaccination efforts, some level of NPIs should be maintained until an optimal level of vaccination coverage has been achieved to avoid outbreak recrudescence.

How high should the target vaccination coverage be?

The herd immunity threshold for COVID-19 was estimated to be around 65–75% assuming a basic reproduction number (R_0) of between 2.8 and 3.8, and may be as high as 90% depending on population characteristics, vaccine effectiveness and transmission dynamics.[4,23] In addition, the Delta variant was observed to have a 60% increase in the effective reproduction number compared to the Beta (B.1.351) variant.[41] This may imply an R_0 of around 4.5–6, which would raise the required herd immunity threshold to 78–83%, rendering this practically impossible to achieve with imperfect vaccine effectiveness.

While a useful reference point, achieving the herd immunity threshold in the overall population should not be the sole factor being considered. There remain reservoirs of susceptibility, including those contraindicated, resistant to vaccinations or at high-risk for spread, which could form conduits of transmission. Young children below the age of 12, for instance, who are at the moment not recommended to receive the vaccines, will form a nucleus of susceptible individuals in which clusters could form.[42] A high percentage of vaccine coverage could also mask the presence of susceptible and vulnerable fractions, which are predisposed to severe disease and outbreaks. It would be important for vaccination efforts to cover vulnerable populations such as the elderly and those with comorbid medical conditions as they would disproportionately suffer the burden of disease.

The target vaccination coverage should also consider how individual protection from severe disease would contribute to substantially reduce the COVID-19 disease burden. Vaccination targets should then be set to levels whereby the resulting infection and disease burden is manageable for a country's healthcare system in the setting of minimum NPIs. Towards this goal, a high vaccination coverage in vulnerable populations would also be crucial, beyond the overall population coverage.[43] To account for these, modelling studies would be needed to inform each country's strategy, taking into consideration its own context, local epidemiology, and its healthcare capacity.

Achieving high vaccination coverage may be challenging due to several factors. First, trials have only recently commenced among children, and they have thus been left out of vaccination programmes due to the lack of safety and efficacy data in this population. This limits the maximum vaccine coverage that could be attained in the population. Vaccine hesitancy is another barrier that many jurisdictions struggle with. With COVID-19, this may be in the form of conspiracy beliefs, misinformation, fear over side effects, understating the risk of the disease and lack of confidence over the vaccine's rapid approval process.[44] As of December 2019, encouraging proportions of the population strongly agreed that vaccines were important, with 60% of persons in Singapore indicated as such, with proportions in the US, UK and Israel reported at 75%, 59% and 46%, respectively.[45] Nevertheless, vaccine hesitancy can affect vaccine uptake, which in turn could lead to higher rates of infections and deaths, and necessitate longer maintenance of NPIs.[46] It is hence important for strong health promotion efforts to address this.

Approaches to encourage vaccine uptake can include mandating and incentivising vaccination. It is not possible to force vaccination on individuals who refuse to be vaccinated, and COVID-19 vaccines are currently provisionally authorised for pandemic use.[47] A more targeted and educational approach could be to incorporate COVID-19 vaccination into the standard of medical care for specific populations, to require vaccination or regular testing among employees of organisations with high risk of exposure to the infection, or to systematically provide COVID-19 vaccination through pre-existing national vaccination programmes. The latter has been effective in preventing childhood vaccine-preventable diseases.[48] The use of incentives is another approach

to increase vaccination uptake. Granting vaccinated concessions and exemptions from NPIs are justifiable on public health grounds due to the direct and indirect risk reductions conferred by the vaccination, and would need to be paired with health promotion efforts.[49]

When can non-pharmaceutical interventions be relaxed?

NPIs have played a key role in controlling infections. In the pandemic state, the focus has been on minimising, or even eliminating the impact of infections. This required aggressive measures. In the endemic state, most NPIs could be eased and lifted; but until high vaccination coverage is reached, there is a need to maintain them to suppress uncontrolled infection spread and minimise deaths.[33,50] With low population-level immunity rates, premature lifting of NPIs—including quarantine of contacts of cases, physical distancing and mask wearing—could lead to significantly higher number of COVID-19 infections, hospitalisations and deaths.[4] It would be prudent to consider the substantive removal of NPIs only after evidence-based pre-determined vaccination targets, or population-level immunity thresholds, are surpassed in the vulnerable and general populations.

How should non-pharmaceutical interventions be relaxed?

While it is clear that countries need to maintain some NPIs until a significant proportion of the population has been vaccinated, what is less certain is the optimal approach and timing to relax NPIs as vaccination coverage increases (i.e. transition towards endemicity).[51] A calibrated transition approach would be to maintain NPIs, with relaxed interventions for vaccinated individuals, until a pre-determined vaccination target has been achieved before gradual relaxation of most NPIs.

Relaxation of measures should be focused on vaccinated persons during the transition towards endemicity on 2 counts. Firstly, on public health grounds, vaccinated persons have substantial protection from infection and severe disease, which may be equal to or superior to the NPIs alone. Second, this provides an incentive for the uptake of vaccination, although the timing should preferably be when vaccines are accessible to all to avoid inequity in access.

The many unknowns, particularly with respect to variants of concern, warrant a period of close monitoring and calibrated relaxation even after countries achieve their vaccination targets. This ensures that the actual disease trends that unfold are as expected (through earlier modelling studies), and provides the reassurance for subsequent policy shifts. A gradual relaxation approach also avoids sudden surges in cases after lifting of NPIs, which could potentially result in high hospitalisation and death rates. Some countries such as the UK have opted for more substantial lifting of restrictions, resulting in surges in the number of cases; however, trends indicate that severe disease rates among the elderly remain suppressed by high vaccination coverage,[38] and such monitoring requires further study. The optimal time point and rate for lifting NPIs will therefore need to be based on observations from various real-world settings, coupled with modelling studies and population-level preferences.

While a vaccination target informed by data and modelling would be the prerequisite for the lifting of NPIs, the progressive relaxation would also need to be informed by data confirming the success of vaccine protection. Crucially, with the relaxation of NPIs, surveillance data on the resulting infections and disease would need to be monitored to ensure that they are in accordance with the expected or modelled trends and remain manageable for the local healthcare capacity. The transition would also need to be guided by other observational evidence and qualitative assessment of a country's situation. Real-world data on the threshold for optimal vaccination coverage and effectiveness in preventing severe disease would be closely watched, such as that reported from Israel,[3] but accrual of definitive evidence would unlikely be timely as countries concurrently transition. There would also need to be a shift in the narrative of how a population deals with COVID-19—from that of a dangerous pandemic to an endemic disease that everyone has to live with. A graduated transition would help the public gain confidence and acceptance as they are eased into a new approach, especially in countries that have adopted stringent measures for a protracted period.

Broadly, NPIs can be considered across 3 domains: border controls, case-based NPIs and community-based NPIs. These NPIs could then be calibrated across 3 states: the pandemic state, transition state and endemic state (Table 3).

NPIs in the transition state

In the transition state, measures should be focused on suppressing infection spread while ramping up vaccine coverage. Some border measures will still be required to minimise importing large number of new infections. Contact tracing and testing also remain important and may be enhanced to identify and isolate cases quickly, with modifications to facilitate effective and targeted operations with potentially increasing number of cases. Nevertheless, community-based NPIs could be gradually

Table 3. Overview of measures across different states for countries adopting an elimination or close-to-elimination strategy in the pandemic state

Domains	Pandemic state	Transition state	Endemic state
General approach	Eliminate infection with aggressive and comprehensive measures.	Continued suppression of infection rates and spread while achieving high vaccine coverage.	Maintain stable disease profile and rates afforded by high vaccine coverage.
Testing	Extensive coverage and comprehensive testing requirements.	Continue with testing but may ease for vaccinated persons.	Not generally required except for high-risk settings. Symptomatic testing will likely remain for surveillance.
Contact tracing	Aggressive tracing and testing of contacts, wide containment rings.	Focused tracing to ensure high yield and effectiveness.	Cease tracing around individual cases. Outbreak investigation and management reserved for high-risk settings.
Quarantine	Dedicated quarantine facilities.	Move towards home-based quarantine.	Generally no quarantine.
Isolation / Case management	Facility-based isolation, stringent discharge criteria.	Move towards a period of facility-based isolation followed by home-based isolation.	Self-isolation at home with medical leave.
Community measures	Stringent restrictions and requirements.	Slow easing, particularly granted to vaccinated persons.	Minimal key measures with focus on public education and messaging, and personal responsibility.
Travel	Border controls and quarantine of travellers.	Facilitate travel initially for vaccinated persons, while retaining measures aimed at surveillance and detection of infection.	Minimal restrictions although less intrusive requirements may still be required.
Vaccination	Focus on priority groups, achieving broad coverage.	Maximise coverage by targeting difficult-to-reach segments.	Maintain vaccine protection, consider booster vaccinations where relevant.

tapered down as vaccine coverage increases, especially for vaccinated individuals in low-risk settings.

NPIs in the endemic state

Herd immunity is a desirable goal before a shift to the endemic state but may not be possible as mentioned before. As long as vulnerable populations can be highly protected from severe disease with the vaccine, the resulting infections can be mitigated with a manageable healthcare burden. Countries that transition to the endemic state when a target vaccination coverage is achieved should do so cautiously, given the uncertainty of direct vaccine protection and herd immunity levels with the new variants of concern. Upon achieving endemicity, most NPIs could be lifted. Nevertheless, a differentiated approach may be required for higher-risk settings with vulnerable populations and for groups that cannot be vaccinated. This may include retaining some level of testing and key NPIs, such as mask wearing.

Booster vaccines

Vaccine-conferred immunity is pivotal for the strategy and maintenance of the endemic state. However, there is uncertainty whether immunity will prevail over time and if booster vaccinations are required. Boosters may be required if there are emergent variants that evade immunity, or if immunity wanes substantially over time. Despite reduced vaccine effectiveness, data thus far suggest that there is still substantial protection from vaccination against the current variants of concern, particularly protection from severe disease.[3,39,52] More recently, the concern has been around the Delta variant, for which a decrease in neutralising activity by vaccine-induced antibodies has been reported.[53] Nevertheless, the UK has reported reassuring data that the Pfizer-BioNTech BNT162b2 vaccine continues to have vaccine effectiveness around 80% against symptomatic disease.[38,39] Further monitoring and study would still be needed to confirm the findings.

On waning immunity, neutralising antibody titres have been observed to decline with time after vaccination, although there has been no indication that this declines to a level that abrogates protection.[54] Other components of the immune system, such as T-cells, also contribute to long-term immunity.[55] Thus far, the Pfizer-BioNTech BNT162b2 vaccine has been reported to have preserved efficacy for at least 6 months post-vaccination,[56] although longer-term data would still be needed.

The critical role that vaccination protection plays in maintaining an endemic state necessitates early design

and implementation of possible booster vaccination strategies, including what boosters to use and to acquire them early. The operational complexity for delivering booster vaccines could be comparable with the original vaccination campaign. Countries may consider preserving sufficient vaccination capacity, capability and infrastructure in case a booster vaccine would need to be rapidly deployed.

Pharmaceutical interventions

While the focus has been on vaccination due to its effectiveness in preventing infection and disease, other effective pharmaceutical interventions could also help reduce the disease burden of COVID-19. Numerous promising trials are ongoing to develop new pharmaceutical agents or repurpose existing drugs to prevent or treat COVID-19. Currently, available pharmaceutical interventions are partially effective and mostly centred around the treatment of severe disease, including agents such as dexamethasone, antivirals and monoclonal antibodies. Many are parenteral and would still require hospital admissions.[57] Nevertheless, there may be oral agents in the future for treatment in the ambulatory setting that prevents severe disease and may also serve as prophylactic agents;[58] this may further reduce both disease and healthcare burden. In all, effective pharmaceutical agents are important to complement NPIs and vaccination, and they will play a bigger role as more effective and accessible treatments become available.

How should new variants that substantially evade vaccine-induced protection be addressed?

Even after attaining the endemic state, the final equilibrium can still be thwarted by a new variant that can evade vaccine-induced or natural immunity substantially, and may be exacerbated if it is more virulent or transmissible. Variants need to be monitored for these parameters, and international surveillance for the emergence of such variants would be crucial. In such a scenario, endemicity may no longer hold and adopting a pandemic approach again may be required. In a way, this is akin to the approach taken for influenza, which has the usual seasonal circulation, and rare but consistent pandemic events.

CONCLUSION

There is evidence that an endemic state is attainable for COVID-19 given the promising data around vaccine efficacy, although uncertainty remains around emergent variants of concern. In the endemic state, most measures can be stepped down with societal activities at close to pre-COVID-19 levels. SARS-CoV-2 infections would be prevalent, but the health burden would be greatly moderated and manageable for the health system. Meanwhile, maintenance of NPIs remains crucial until a high level of vaccination coverage is attained, to avoid runaway outbreaks and high health and socio-economic impact.

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REVIEW ARTICLE

Ann Acad Med Singap 2021;50:629-37
https://doi.org/10.47102/annals-acadmedsg.2020623

Guidance on performance and reporting of high-resolution oesophageal manometry and ambulatory pH monitoring in Singapore

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ABSTRACT

Introduction: We aimed to provide a practical and evidence-based guide on the indications, performance and reporting of high-resolution oesophageal manometry (HRM) and ambulatory pH monitoring (PHM) in adult patients in Singapore.

Methods: The guideline committee comprised local gastroenterologists from public and private sectors with particular expertise in aspects of HRM and PHM, and it was tasked to produce evidence-based statements on the indications, performance and reporting of these tests. Each committee member performed literature searches to retrieve relevant articles within the context of domains to which they were assigned.

Results: Twelve recommendation statements were created and summarised.

Conclusion: Standardising key aspects of HRM and PHM is imperative to ensure the delivery of high-quality care. We reported the development of recommendations for the performance and interpretation of HRM and ambulatory reflux monitoring in Singapore.

Ann Acad Med Singap 2021;50:629-37

Keywords: Gastro-oesophageal reflux disease, GERD, high-resolution oesophageal manometry, oesophagus, pH testing

INTRODUCTION

High-resolution oesophageal manometry (HRM) and ambulatory pH monitoring (PHM) are essential for evaluating oesophageal symptoms. Guidelines in this article were created to provide practical and evidence-based guidance on the indications, performance and reporting of oesophageal physiological tests in adult patients in Singapore. This document is therefore aimed at healthcare professionals treating patients with these symptoms. Guidance on these tests is available in Western countries.[1,2] However, at the time of writing, there was a notable lack of Singapore guidance despite these physiological tests being used widely. Therefore, there was a need to establish local guidance to limit variations in practice. The coronavirus disease 2019 (COVID-19) situation also allowed us to reflect on our institutional practices and resulted in changes in practice that we have reflected in these guidelines.

METHODS

The creation of these guidelines was commissioned by the Chapter of Gastroenterologists of the College of Physicians, Singapore, under the auspices of the Academy of Medicine, Singapore. The guideline committee comprised local gastroenterologists from public and private sectors with particular expertise in aspects of HRM and PHM, and it was tasked to

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CLINICAL IMPACT

What is New

- These are the first Singapore guidelines for the performance and interpretation of high-resolution oesophageal manometry and ambulatory reflux monitoring.

Clinical Implications

- Performance of these physiological tests varies widely.
- Guidelines in this study were created to provide practical and evidence-based guidance on the indications, performance and reporting of oesophageal physiological tests in adult patients in Singapore.
- This guidance is aimed at healthcare professionals treating patients with these symptoms.

produce evidence-based statements on the indications, performance and reporting of these tests. These statements were formulated using the population, intervention, comparator and outcome format to guide the search for evidence. Each committee member performed literature searches to retrieve relevant articles within the context of specific questions and domains to which they were assigned. The written segments from each member were then consolidated by the main author and circulated to the entire committee for further review. This document was externally reviewed and endorsed by the Specialty Board of the Chapter of Gastroenterologists, Council of the College of Physicians and Council of the Academy of Medicine, Singapore.

Each recommendation statement has an associated assessment of the quality of evidence and strength of recommendation based on the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system, which specifically separates the strength of the evidence from the strength of a recommendation.[3] All members of the committee were asked to rate each statement using a 5-tier system: A+: strong agreement; A: agree with reservation; U: undecided; D: disagree with reservation; and D+: strongly disagree. The wording of recommendations that did not reach at least 80% substantial agreement (A+, A) was modified, and further online voting was undertaken until substantial agreement was attained. The guidelines were crafted using the Reporting Items for Practice Guidelines in Healthcare to ensure quality and completeness.[4]

RESULTS

Statement 1: Patients undergoing high-resolution oesophageal manometry or ambulatory pH monitoring should have a prior oesophagogastroduodenoscopy, with oesophageal biopsies if indicated (e.g. eosinophilic oesophagitis), to exclude structural and mucosal causes.

GRADE evidence: High

Strength of recommendation: Strong

Level of agreement: 100% strongly agree

Statement 2: Patients with obstructive oesophageal symptoms without mechanical causes should undergo high-resolution oesophageal manometry.

GRADE evidence: Very low

Strength of recommendation: Strong

Level of agreement: 83% strongly agree, 17% agree with reservation

Patients should have an oesophagogastroduodenoscopy performed prior to HRM or PHM, especially if the indication is dysphagia, as endoscopy allows evaluation o f oesophageal structural abnormalities that may potentially increase complication risk during catheter insertion. Additionally, oesophageal biopsies should be obtained, particularly if eosinophilic oesophagitis is a differential diagnosis.[1] Likewise, endoscopy also can evaluate reflux symptoms to objectively diagnose pathological gastro-oesophageal reflux disease (GORD) in the presence of high-grade erosive oesophagitis, Barrett's oesophagus or peptic strictures. However, despite its high specificity, oesophagogastroduodenoscopy has a low sensitivity for the diagnosis of GORD[5] and therefore cannot conclusively exclude GORD.

Barium imaging can be considered if endoscopy is not possible. A static contrast study can diagnose majority of lesions within the oesophagus, while a timed barium oesophagram is useful in the evaluation of oesophageal motility disorders.[1] However, barium imaging is a suboptimal screening modality for dysphagia with 69% sensitivity and 50% specificity in detecting oesophageal motility disorders.[6] Patients with obstructive symptoms without a mechanical cause may harbour an oesophageal motility disorder; therefore we recommend that an HRM be performed since it is useful in diagnosing oesophageal motility disorders such as achalasia and ineffective oesophageal motility.[7]

Statement 3: Patients with symptomatic gastro-oesophageal reflux disease not responding to proton pump inhibitor therapy (compliant with 20mg omeprazole equivalent for 8–12 weeks) should undergo ambulatory pH monitoring.

GRADE evidence: Very low

Strength of recommendation: Strong

Level of agreement: 67% strongly agree, 33% agree with reservation

Patients with symptoms from suspected GORD should first undergo a therapeutic trial of a proton pump inhibitor (PPI) since this is cheaper, less invasive and more widely available than PHM. The equivalent of 20mg of omeprazole taken appropriately for 8–12 weeks would be deemed a therapeutic trial of PPI.[1] However, symptoms, PPI response and low-grade erosive oesophagitis (Los Angeles Classification grades A and B) on endoscopy are not conclusive evidence for GORD and also do not always correlate with abnormal reflux burden on PHM performed off PPI therapy.[8] Hence, these constitute unproven GORD and require PHM before escalation of management.[8]

Patients being planned for laparoscopic anti-reflux surgery should undergo preoperative PHM to confirm pathological acid exposure time (AET), an association between symptoms and reflux episodes, or both, as preoperative pathological AET and positive symptom scores[9] lead to better long-term patient satisfaction and less symptoms post surgery. Many extraoesophageal symptoms have been associated with GORD.[10] PHM allows demonstration of association between symptoms and reflux episodes, and therefore enables the diagnosis or exclusion of pathological GORD. Patients who demonstrate increased acid exposure and associated symptoms are more likely to respond to acid suppression therapy, and thus PHM can be used to optimise pharmacological treatment of these patients.[11] Indications for HRM and PHM are summarised in Table 1.

Statement 4: Patients should be fasted adequately prior to high-resolution oesophageal manometry, or ambulatory pH monitoring, or both. Adequate instructions regarding medications to be stopped should be provided. Written informed consent should be obtained and documented clearly.

GRADE evidence: High

Strength of recommendation: Strong

Level of agreement: 100% strongly agree

Patients undergoing oesophageal physiological tests should fast for at least 6 hours prior to the test to reduce the risk of vomiting during catheter insertion or during endoscopic-guided insertion of the wireless capsule. However, if achalasia is highly suspected, a longer fasting period of 12 hours may be considered.[12] During the monitoring period, patients are encouraged to continue with regular activities and food during regular times, and avoid carbonated beverages. A diary of mealtimes, symptoms and recumbence periods has been advocated to improve diagnostic accuracy and analysis of symptoms occurrence.[13]

Medications that alter oesophageal motility function such as nitrates, calcium channel blockers, opiates, prokinetics and anticholinergic drugs should be stopped for 48 hours pre-procedure as tolerated.[12] If PHM is to be done off acid suppression medications, PPIs should be stopped for 7 days and histamine-2 receptor antagonists stopped 3 days before the study.[1] Patients on antiplatelet and anticoagulant drugs should be informed about a small increased risk of bleeding, particularly from the nose during catheter insertion. Based on published literature and existing guidelines, there is insufficient evidence to support withholding of antiplatelet and anticoagulant drugs routinely.[1] However, the bleeding risk should be tailored to the individual; and for patients on warfarin, it is prudent to ensure that the international normalised ratio is not above therapeutic range.

Table 1. Indications for high-resolution oesophageal manometry and pH monitoring

High-resolution oesophageal manometry	Ambulatory pH monitoring
Obstructive oesophageal symptoms (dysphagia, chest pain)	Evaluation of gastro-oesophageal reflux disease (heartburn, regurgitation, extra-oesophageal symptoms)
Evaluation of gastro-oesophageal reflux disease, especially prior to catheter placement for pH monitoring	Belching disorders
Anti-reflux surgery pre-evaluation	Anti-reflux surgery pre-evaluation
Symptoms post anti-reflux surgery	Symptoms post anti-reflux surgery
Rumination syndrome	Evaluation of lung transplantation candidates

HRM and PHM are generally regarded as low-risk procedures and can be conducted in a standalone medical clinic. Major complications are rare, but there exists in the literature a case report of oesophageal perforation[14] and finding of decrease in oxygen saturation with increased heart rate.[15] Although wireless PHM is generally well tolerated, some subjects may experience throat discomfort, dysphagia, chest discomfort and foreign body sensation.[16] Standard risks of upper endoscopy apply if wireless PHM is applied.[17] In addition, risks specific to wireless PHM include premature detachment, poor data transmission, failure to detach, failure to attach, capsule aspiration, capsule retention, mucosal tears, bleeding and perforation.[16] Patients should also be informed about magnetic resonance imaging (MRI) compatibility of the attached device, and specific precautions should be taken based on the manufacturer's recommendations. A screening X-ray should be undertaken to ensure that the capsule has passed if an urgent MRI examination is required.[1]

The procedure, along with risks mentioned above, should be explained to the patient appropriately and written informed consent obtained and documented clearly.

Statement 5: Symptomatic patients with suspected GORD should undergo ambulatory pH monitoring off acid suppression if there is no previous objective evidence of GORD.

GRADE evidence: Moderate

Strength of recommendation: Strong

Level of agreement: 83% strongly agree, 17% agree with reservation

In patients with no previous evidence of GORD, PHM should be performed off acid suppression therapy to quantify reflux and maximise chances of diagnosing significant symptom reflux association.[18] Those with high GORD probability should undergo the study on twice daily PPI, as few patients have persistent abnormal acid exposure on twice daily PPI.[18] This allows better phenotyping of refractory non-erosive reflux disease and functional heartburn.[19]

Statement 6: High-resolution oesophageal manometry should be performed using 10 swallows of 5mL with 20–30 seconds between each swallow, in the supine position. A minimum of 7 evaluable swallows is recommended for meaningful interpretation. The use of adjunctive testing provides additional information and improves the sensitivity of detecting clinically relevant oesophageal dysmotility, and consideration for use should be individualised.

GRADE evidence: Moderate

Strength of recommendation: Strong

Level of agreement: 83% strongly agree, 17% agree with reservation

The HRM procedure should be performed according to published Association of Gastrointestinal Physiologists guidelines.[20] This is performed using 10 water swallows of 5mL with a rest period of 20–30 seconds between each swallow and conventionally performed while supine. Although current classification algorithms are based on 10 water swallows in the supine position, studies have shown that interpretation is possible if at least 7 swallows are adequate.[21]

As these standardised manoeuvres are not representative of normal physiology, adjunctive swallows using provocative measures in the upright-seated position may be used. Adjunctive tests include multiple rapid swallows (5 water swallows of 2mL, 1–2 second apart),[22] rapid drink challenge (free drinking of 200mL of water with a straw),[23] the use of viscous solutions,[24] a solid bread bolus[25] and a solid test meal.[26] Although certainly useful for clinical investigation, provocative measures are refined specific measures whose universal adoption may be impractical, and the application of these manoeuvres should be individualised.

Statement 7: We recommend manual review of high-resolution oesophageal manometry tracings and reporting according to the Chicago Classification. The report should include (1) reasons for referral; (2) diagnosis based on Chicago Classification; and (3) summary of results including the mean and median integrated relaxation pressure, mean distal contractile integral, and distal latency values.

GRADE evidence: High

Strength of recommendation: Strong

Level of agreement: 50% strongly agree, 33% agree with reservation, 17% undecided

Reporting of HRM

General information

The following items should be in the procedure report: reason for referral, clinical diagnosis, summary of results, tabulated results and communication to referring provider.[27] Mandated documentation of recommendations for follow-up evaluation and treatment was considered inappropriate since HRM is a diagnostic aid to be used in concert with other clinical information. Any symptoms reported during the HRM study and their correlation with the HRM findings should be included.

Interpretation

Published manufacturer-specific normal values should be used, as data have suggested that catheter-specific "normal" data are required for correct diagnosis according to the Chicago Classification.[28] If utilised, the form of adjunctive testing undertaken should be included with appropriate normal values. There should be a manual review of the entire HRM tracing, with the aim of providing a clinically interpretable summary. All HRM studies must be interpreted according to a formally validated scheme, and the scheme used should be documented. We have agreed that analysis and reporting of manometry should be performed according to the Chicago Classification, which is the version 3.0 classification at the time of writing.[7] Key information required in the report includes the median reading of 10 integrated relaxation pressure values, the mean value of the distal latency, and the mean distal contractile integral values for 10 single water swallows of 5mL. An HRM diagnosis according to the Chicago Classification should be given whenever possible, although it is emphasised that the final diagnosis for an individual patient should be based on a careful consideration of clinical features, and radiological or endoscopic findings, or both, in addition to the HRM findings.

Statement 8: A minimum period of 16 hours is recommended for catheter-based monitoring and at least 48 hours of extended monitoring is recommended for wireless capsule monitoring.

GRADE evidence: High

Strength of recommendation: Strong

Level of agreement: 83% strongly agree, 17% agree with reservation

An international consensus has recommended a minimum of 16 hours of monitoring (excluding meal times) to obtain clinically meaningful data.[29] As there can be considerable day-to-day variability in oesophageal acid exposure and symptom reporting, a prolonged period of 48 hours of wireless PHM can potentially produce a higher sensitivity for reflux detection and associated symptom events.[30]

Statement 9: Details in the ambulatory pH monitoring report should include (1) reasons for referral; (2) diagnosis; and (3) summary of results including acid exposure time, number of reflux episodes and symptom association profiles. Additional impedance parameters (mean nocturnal baseline impedance, post-reflux swallow-induced peristaltic wave index) are useful adjunctive tests and the reporting of these parameters can be individualised.

GRADE evidence: Low

Strength of recommendation: Strong

Level of agreement: 50% strongly agree, 33% agree with reservation, 17% undecided

Statement 10: Automatic analysis of pH monitoring is adequate, provided that the recordings are checked for accurate mealtimes, posture changes and symptom reporting. A manual review of the 2-minute time window prior to a reflux event and symptom event is suggested to obtain accurate reflux quantification and symptom association analysis.

GRADE evidence: Moderate

Strength of recommendation: Conditional

Level of agreement: 50% strongly agree, 33% agree with reservation, 17% disagree

Reporting of PHM

General information

The report should include patient identification details, date of the test, indications for procedure and a list of current medications, particularly whether acid-suppressing drugs were stopped or continued during the study.

Interpretation

Data are analysed using proprietary software and interpreted by the reporting physician. The following parameters should be included for acid exposure: percentage of total time at pH<4, percentage of upright time at pH<4, percentage of supine time at pH<4, and number of episodes at pH<4 for >5 minutes. The symptom index and symptom association probability of the patient's symptoms during the study should be included.

The pH recordings in healthy volunteers and patients were manually edited to remove episodes of spurious acid reflux caused by ingestion of food or drinks by excluding mealtimes from the automated pH analysis. Comparison of the results showed a close agreement in all pH parameters for distal oesophageal pH recordings.[31] Thus, it is important to manually check patients' recordings for artefacts, meal periods and symptom events to allow a reliable assessment of the AET using the automated analysis. However, automated analysis overestimates non-acidic reflux events and provides inaccurate symptom association analysis in up to 20% of patients.[32] On the other hand, manual analysis of the entire 24-hour monitoring period for

reflux events and reflux symptom association is time-consuming, and individual physicians have to decide on the balance between automated and manual analysis.

Oesophageal PHM variables

Oesophageal AET is defined as the percentage of total recording time at pH<4 in the distal oesophagus 5cm above the lower oesophageal sphincter. AET is extracted from both pH and pH-impedance data and is the most reproducible metric and most useful single discriminator to define oesophageal acid burden.[33] Based on current consensus,[8,29] total AET<4% is consistently physiological and AET>6% is consistently pathological. AET readings of 4–6% require additional diagnostic tests.

The wireless PHM device is associated with marginally increased 95th percentile AET values compared with those of healthy controls (4.4–5.3%)[34], but similar thresholds can be applied for both the catheter- and wireless-based PHM devices. The number of reflux episodes measured on PHM can be used as an adjunct in predicting treatment outcomes.[35]

Symptom association analysis

The symptom index and symptom association probability are the most commonly used parameters to establish the reflux symptom association profile. However, only episodic symptoms with a finite onset and offset, such as heartburn, acid regurgitation, cough and chest pain, can be subject to evaluation of the symptom reflux association. It is crucial for patients to accurately record symptom events by pressing the symptom button in the symptom diary at the immediate onset of symptoms as any delay may render the symptom index, symptom association probability, or both, negative. Careful instruction to patients is essential for accurate recording.

Adjunct metrics

Oesophageal baseline impedance correlates inversely with mucosal integrity and oesophageal acid burden. It has been shown that GORD patients with pathological AET had lower average baseline impedance readings than did patients with functional heartburn and healthy controls.[36] A simplified method to measure baseline impedance using the mean nocturnal baseline impedance has been proposed.[37] This is obtained from measuring baseline impedance over 3 periods of 10 minutes at 3cm and 5cm above the lower oesophageal sphincter during the nocturnal sleep period in the absence of swallowing or reflux episodes.[38,39] A mean nocturnal baseline impedance threshold of <2,292Ω identified patients with erosive reflux disease with 91% sensitivity and 86% specificity; among pH-positive GORD patients, the sensitivity and specificity was 86%.[38] Further prospective studies are required to better define the role of baseline impedance and mean nocturnal baseline impedance in GORD evaluation.

Following a reflux episode, a post-reflux swallow-induced peristaltic wave (PSPW) demonstrated on pH-impedance monitoring is observed in healthy volunteers and represents chemical clearance of the oesophagus.[38] A PSPW is defined as a 50% drop in impedance relative to the pre-swallow baseline originating from the proximal to distal impedance sites, followed by >50% return to baseline in the distal impedance sites. The PSPW index is calculated manually by counting the number of reflux episodes that are followed by a PSPW within 30 seconds, and dividing by the total number of reflux episodes. The PSPW index is significantly lower in patients with reflux oesophagitis or with non-erosive reflux disease than in patients with functional heartburn and healthy controls,[38] and may potentially be more accurate than AET and mean nocturnal baseline impedance in predicting PPI responsiveness.[39] More studies are required before these novel pH-impedance parameters can be applied for routine GORD evaluation.

Statement 11: High-resolution oesophageal manometry and pH monitoring should be performed and interpreted by individuals who have achieved competency and have been given privileging rights by their institution's clinical privileging system.

GRADE evidence: Low

Strength of recommendation: Strong

Level of agreement: 50% strongly agree, 50% agree with reservation

The quality of the individual performing and interpreting the study was considered to be integral to HRM, and the technician and interpreting physician should show competency in HRM.[27] The performance of catheter-based PHM is similar to that of HRM catheter insertion and is often done in the same sitting by the same individual. Therefore, we would take both into account. The recommendations regarding minimum procedural volume required for competency[27] are included in Table 2.

Case volume by itself, however, should not be the sole determinant of competency in interpreting these studies. We suggest that once competency is established, it is up to their local clinical privileging

Table 2. Minimum case volume required for establishing competency

Performance of high-resolution oesophageal manometry, catheter-based ambulatory reflux monitoring, or both	Perform 20 to establish competency
Interpret high-resolution oesophageal manometry	Interpret 50 to establish competency
Interpret ambulatory reflux monitoring	Interpret 25 to establish competency

systems to determine the rights for continued interpretation of these procedures.

Statement 12: During the COVID-19 pandemic, all gastrointestinal motility laboratory staff should undergo training for standard infection control and proper usage of personal protective equipment.

GRADE evidence: Moderate

Strength of recommendation: Strong

Level of agreement: 50% strongly agree, 50% agree with reservation

For detailed guidance on the practice of these oesophageal tests during the COVID-19 pandemic, we refer readers to the Asian Neurogastroenterology and Motility Association statements.[40] Several key points that are worthy of inclusion have been incorporated in our guidelines.

DISCUSSION

Risks of procedures and actions taken to mitigate risks

All elective and non-urgent HRM and PHM are considered high-risk procedures and deferment should be considered if there is a high risk of COVID-19 transmission within the community,

All staff involved in performance of these procedures have to abide by the institution infection policy: standard, droplet and airborne precautions with full personal protective equipment are highly recommended, and the procedure should be performed in negative-pressure rooms whenever possible. All staff involved should undergo training for standard infection control and the proper usage of personal protective equipment.

Triage of patients prior to procedure

All patients should be triaged and screened for fever and respiratory symptoms (shortness of breath, runny nose, cough, sore throat and anosmia), history of close contact with confirmed or suspected COVID-19 cases, and travel history to high COVID-19 prevalence area within the last 14 days. There should also be a recalling system in place to proactively prioritise rebooking of patients for procedures when deemed safe to resume normal activities.

Follow-up of patients for contact tracing

Patients who have undergone these procedures should be given advice to contact the motility laboratory staff if they develop COVID-19 within 14 days. Staff should contact the patient by phone on day 7 and day 14 to ask about the development of COVID-19 symptoms or presence of any recent diagnosis of COVID-19. Any patient suspected of having COVID-19 should be guided to seek medical opinion immediately. Contact tracing should be performed for possible patients and staff exposed to suspected or confirmed cases.

Areas for future research

The guideline development process has highlighted areas for future research. An HRM study may be compromised in the hands of an incompetent technician or an interpreting physician, regardless of technology quality. It appears that there are marked variations in practice quality in Singapore. Also, studies have shown that trainees who achieved competency did so at differing case volumes. Moreover, the majority of trainees failed to demonstrate competency in HRM even after interpreting 50 HRM cases. These results suggest that using a minimal case volume to assess oesophageal HRM competency is inaccurate; furthermore, most trainees need to interpret more than 50 cases to achieve competency. Therefore, some of the key areas to pursue include a formal determination of what constitutes competency in performing HRM or PHM; and a more structured training programme for trainees to establish competency in HRM and PHM interpretation.

Limitations

Our guidelines were written by a few individuals who were all gastroenterologists, and we therefore had minimal input from other disciplines. There may be potential bias in such a small steering group, and the cost or resources, along with preferences of the endusers, may not have been sufficiently considered.

CONCLUSION

Standardising key aspects of HRM and PHM is imperative to ensure the delivery of high-quality care. We reported the development of recommendations for

the performance and interpretation of HRM and PHM in Singapore. Despite substantial agreement on these recommendations, variations in practice existed even among our panel of 6 experts, highlighting the role of future research on training and competency evaluation.

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COMMENTARY

Ann Acad Med Singap 2021;50:638-42
https://doi.org/10.47102/annals-acadmedsg.2021136

Learning during the pandemic: Perspectives of medical students in Singapore

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ABSTRACT

The COVID-19 pandemic has significantly disrupted medical education, particularly affecting clinical-year students. Educational institutions often had to halt, shorten or impose significant restrictions on their hospital rotations due to strict infection control and social-distancing guidelines implemented in tertiary healthcare institutions, as well as manpower and logistical constraints amid the pandemic. Thus, distance-based learning platforms such as online lectures and case-based teaching were increasingly adopted in place of bedside and face-to-face tutorials. While interactive virtual case-based discussions are generally useful in imparting clinical reasoning skills to medical students, they are unfortunately not able to fully replicate the experience of clerking, examining and managing real patients in the wards, which is a quintessential process towards building clinical acumen and attaining core clinical competencies. Therefore, for final year medical students who are preparing for their Bachelor of Medicine and Bachelor of Surgery (MBBS) examinations, many are naturally concerned by how learning in this "new normal" may affect their ability to make the transition to become competent junior doctors. As such, we seek to share our learning experiences as the first batch of medical students to have completed our entire final year of clinical education amid the COVID-19 pandemic, and offer 4 practical suggestions to future batches of students on how to adapt and optimise clinical learning under these circumstances: actively engaging in virtual learning, making the most of every clinical encounter, learning how to construct peer teaching/practice sessions, and maintaining physical and psychological well-being.

Ann Acad Med Singap 2021;50:638-42

The COVID-19 pandemic has been a major disruption to medical education worldwide and will continue to pose challenges to medical students and educators alike for some time to come until we transition into a post-vaccinated world. In early to mid-2020, clinical clerkships were initially halted in many countries[1,2] before being gradually re-introduced, as medical educators recognised their importance for medical students. Nonetheless, clinical postings were often shortened and replaced with home-based online learning due to manpower, logistical and social-distancing constraints. Depending on local institutional guidelines, students on clinical clerkships also faced significant restrictions—such as being barred from entering high-risk areas like isolation wards for patients with acute respiratory symptoms, intensive care units, operating theatres and the emergency department,[3,4] as well as "crossing" over to other wards or teams to clerk patients admitted under another subspecialty.[4] For final year medical students preparing for their Bachelor of Medicine and Bachelor of Surgery (MBBS) examinations, there are concerns on how these changes may affect their clinical competency as junior doctors[5]—as Sir William Osler declared, "Medicine is learned by the bedside and not in the classroom." Hence, in this commentary, we aim to share our experiences as the first batch of medical students to have completed our entire final year of clinical education amid the COVID-19 pandemic, and

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offer practical suggestions on learning strategies in this "new normal", which may be beneficial to future batches of medical students.

Tip 1: Active engagement in virtual learning. In our medical school, physical classes exceeding 50 students and approximately half of clinical attachments were shifted to home-based virtual learning[6] where online platforms such as Zoom and Microsoft Teams facilitated case-based tutorials. Clinical tutors typically interact with 20–30 students, guiding them through history-taking, physical examination, differential diagnoses and investigation/management plans either verbally or through online polling platforms such as PollEv. While online classes may not fully replicate the clinical training provided in hospital rotations,[7] they do provide us with several benefits if we maximise them.

Firstly, home-based learning allows more time for pre-preparation and post-session consolidation of learnt content. In particular, consistent note-making is important to assimilate and process the vast amounts of clinical content we acquire on a daily basis. Notes can be classified into approaches to clinical manifestations and specific conditions. For example, an "approach to dyspnea" should cover key points in history-taking, physical examination and investigations for an undifferentiated patient with first presentation of breathlessness. Conversely, notes on "asthma" ought to cover all aspects of the condition—including the definition, epidemiology, risk factors/aetiology/precipitating factors, pathophysiology, clinical manifestations, diagnostic criteria, investigations, management and complications of disease and treatment. The practice of such concept mapping is powerful in helping students integrate their knowledge, engage in critical thinking[8] and form "illness scripts" to link theory to practice.[9] To ensure the accuracy of our notes, we cross-referenced to multiple reliable and up-to-date sources including textbooks, official guidelines, review articles in academic journals, UpToDate, StatPearls and Medscape. In particular, articles on the *Singapore Medical Journal*'s Continuing Medical Education and the Singapore Family Physician journal provide insights into local clinical practices.

Secondly, we find that coming up with questions before each home-based tutorial significantly helps with our learning as this process creates self-awareness of current knowledge and gaps, promotes productive thinking, and inculcates a scientific habit of mind.[10] Furthermore, students can take the opportunity of online tutorials to clarify on how Singapore's clinical practices may differ from international guidelines, when contextualised to our local patient cohort. Hence, in contrast to hospital-based clinical tutorials that may be more ad hoc, structured online tutorials afford greater predictability that we can capitalise on to maximise learning.

Tip 2: Making the most of every clinical opportunity. A major challenge to medical education in the COVID-19 pandemic is the reduction in patient contact. Locally, clerkships were shortened, or modified such that students do not "cross teams or wards" to clerk patients under other sub-disciplines,[4] for infection control purposes. This presents new difficulties for final year medical students, who tend to be preoccupied with clerking many patients across different sub-disciplines with good clinical signs to examine in order to prepare for the final MBBS examinations. However, the new cohorting restrictions in local hospitals meant that we had to adapt our clinical learning to maximise every clinical interaction. To do so, we find that it is important to take full ownership of several patients admitted under our assigned medical teams—that includes comprehensive clerking, examining, reading up on past clinical notes, drafting new clinical entries and presenting updates on our patients during ward rounds. In particular, the process of drafting up our own management plans before discussing with the medical team is important for developing clinical acumen. When we spend more time on each patient in our assigned teams, we can better appreciate and participate in the provision of holistic healthcare that goes beyond addressing the presenting complaint, to managing psychosocial issues, discharge planning and step-down care. In a way, the reduced breadth of clinical exposure has led to greater depth of learning and a more holistic clinical clerkship experience.

Finally, we are able to find ample learning opportunities by being thorough in clerking our patients within the confines of a single ward team. For instance, a patient with interstitial lung disease may have an underlying connective tissue disease for which we can perform a rheumatological examination. In fact, we may occasionally discover incidental clinical findings that we can learn from and value-add to patient care. For example, aortic stenosis or mitral regurgitation murmurs can be quite prevalent in the elderly population.[11]

Tip 3: The value of peer teaching and practice sessions. In the lead-up to our final MBBS examinations, practising case scenarios with each other became ever more important in honing our history-taking and physical examination skills, given the reduced patient contact during the COVID-19 pandemic. To maximise the efficacy of each session, we found it useful to prepare a

set of case scenarios with PowerPoint slides, including a task vignette, examination findings and discussion questions (Fig. 1). To simulate real-life clinical scenarios, we inserted cardiovascular and respiratory sound files, video clips of gait patterns, and images of rheumatological findings. The clinical findings were released sequentially to the candidate, when the correct examination step was performed.

The benefits of peer teaching are well documented.[12,13] Firstly, it is known to be effective because of cognitive and social congruence,[14] where peer teachers can better pitch the study session at an appropriate level, empathise with gaps in clinical knowledge, and help learners feel more comfortable clarifying their doubts.[15] Secondly, the peer teacher also learns from the session as a good understanding of theoretical concepts is required to quiz and educate the learner.[16] In addition, the peer teacher enhances his/her knowledge through self-reflection when preparing the teaching material[16] and wrestling with new and opposing information that emerges from active discussion with the learner.[17] In a way, peer teaching in medical education becomes a direct application of the constructivist learning theory.[18]

Beyond clinical content, peer-assisted learning also helps to build collegiality among medical students who will be fellow colleagues in future. It has recently been reported that communication and interpersonal skills among medical students can be improved through this educational modality.[16]

In the broader context, integration of peer teaching into the medical curriculum may even potentially relieve the immense pressure on clinical educators who not only

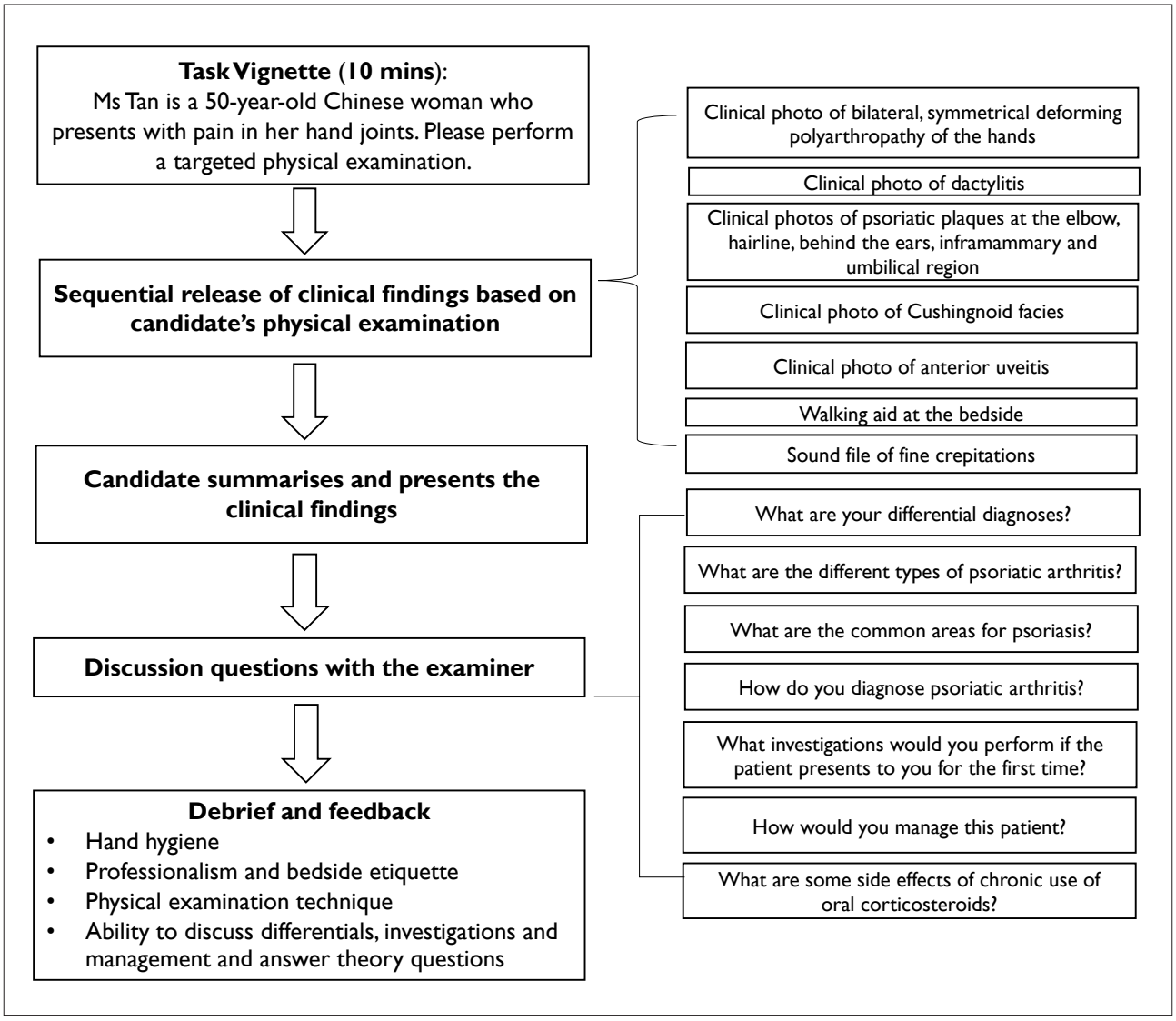

Fig. 1. Illustration of a practice case scenario.

have to manage a surge in clinical duties, but also deal with challenges in re-organising both clinical patient care and educational curriculum for medical students.[19]

Tip 4: Maintaining physical and psychological well-being. A priority when resuming clinical training for medical students amid the COVID-19 pandemic is to safeguard the physical health of both the students and patients. In a recent study, medical students viewed the provision of adequate personal protective equipment (PPE) as most important for safety when restarting clinical rotations.[20] Locally, beyond the provision of PPE training for students, tertiary healthcare institutions and medical schools have instituted infection control guidelines that include mandatory twice-daily temperature recording, installation of Singapore's contact tracing phone application "TraceTogether", and documentation of every clinical encounter in an online portal for contact tracing purposes.

Finally, the COVID-19 pandemic has unfortunately taken a toll on the mental health of medical students, with reportedly higher rates of depression, stress and anxiety.[20,21] As preparations for the final MBBS examinations under COVID-19 circumstances can be quite stressful, peer support is potentially useful to strengthen resilience and reduce levels of distress.[22,23] For us, peer support came from batchmates with whom we did our clerkship rotations, and existing student communities such as our "House" System and undergraduate medical society. In addition, we found reassuring the ready availability of psychosocial support from the school in the form of periodic virtual town hall sessions with faculty members, professional counselling services and mindfulness workshops, which help with psychological strengthening and stress relief.[24]

Limitations. We acknowledge several limitations to the aforementioned learning strategies. Firstly, our approach to optimising home-based learning requires great commitment and self-discipline, which are known disadvantages of e-learning[25]. Secondly, the utility of our peer teaching pedagogy depends on various factors such as learning styles and the presence of a like-minded peer. Thirdly, there is a potential risk of inaccuracy in the content taught during peer-teaching sessions—hence it is important for students to cross-reference to reliable academic sources as mentioned earlier and clarify any unfamiliar content with their seniors or clinical tutors. Lastly, the generalisability of our learning strategies may be limited to medical students in countries adopting a similar approach in handling medical education amid the pandemic. For example, several countries such as the US,[26] UK[27] and Italy[28] had fast-tracked the graduation of their medical students last year to support their healthcare workforce to deal with the surging pandemic.

Clinical clerkship is a cornerstone of medical education that helps medical students transition from classroom learning to becoming competent junior doctors in the wards. With many countries facing multiple waves of COVID-19 infections, medical students have to be flexible in adapting learning methods whenever there are inadvertent disruptions to clinical clerkships. In this article, we share our experiences as the first batch of medical students to have completed our final year of clinical training amid the COVID-19 pandemic. We propose strategies for effective learning in this new environment that may be helpful to future batches of medical students.

Acknowledgements

The authors would like to extend heartfelt gratitude to our clinical tutors and the graduating class of 2021 in the Yong Loo Lin School of Medicine, National University of Singapore, with whom we have journeyed together and learnt much from in our final year preparations for the MBBS examinations.

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Ann Acad Med Singap 2021;50:643-5
https://doi.org/10.47102/annals-acadmedsg.202195

Leclercia adecarboxylata bacteraemia: Clinical features and antibiotic susceptibilities in 2 hospitals in Singapore

Dear Editor,

Leclercia adecarboxylata was first described by Leclerc in 1962.[1] Formerly designated as enteric group 41 and previously known as *Escherichia adecarboxylata*, it is a motile, gram-negative bacillus in the family *Enterobacteriaceae*.[2] It can be found in various environmental sources, as well as the gastrointestinal tract of humans and animals.[2,3] Following improved diagnostic techniques, *L. adecarboxylata* is increasingly recognised as a pathogen of clinical significance. It has been isolated from wounds, abdominal fluid and blood.[4] It is usually encountered as a monomicrobial infection in immunocompromised individuals or as part of a polymicrobial infection in immunocompetent hosts.[5] While previously reported isolates were susceptible to most antibiotics,[5,6] drug-resistant strains including extended-spectrum beta-lactamase (ESBL)-producing[7] and carbapenemase-producing strains[8-10] are increasingly reported.

Our review of microbiology laboratory records from 1 January 2005 to 31 May 2021 identified 8 cases of *L. adecarboxylata* bacteraemia in Singapore General Hospital and Changi General Hospital, Singapore. We present the antibiotic susceptibility profiles of all 8 isolates that were collected as part of laboratory surveillance. We also present the clinical features of 6 patients with *L. adecarboxylata* bacteraemia. Patient consent for review of 6 patients' medical records was waived by the SingHealth Centralised Institutional Review Board (Ref: 2020/2861). The medical records of the other 2 patients who presented after 1 November 2017 were not accessed, in compliance with the Human Biomedical Research Regulations 2017.

Over a period of 13 years from January 2005 to October 2017, a total of 6 patients were diagnosed with *L. adecarboxylata* bacteraemia. The mean age of the patients was 66 years old (range 49–79). All were Chinese males. Diabetes mellitus (100%) and hypertension (83.3%) were the most common comorbidities. Five out of 6 patients (83.3%) presented with primary bacteraemia where the source of infection was unknown. A skin and soft tissue infection was thought to be the source of infection in the other 1 patient. *L. adecarboxylata* was part of a polymicrobial bacteraemia in 3 patients. The most common co-infecting organism was *Klebsiella pneumoniae* (2 out of 3 patients). *Enterobacter cloacae* complex, *Acinetobacter lwoffii, Pantoea* spp., methicillin-susceptible *Staphylococcus aureus* and *Bacillus* spp. were the other co-infecting organisms. Bacteraemia, including the co-infecting organisms, cleared quickly once appropriate antibiotic therapy was initiated—there was no persistent bacteraemia in all 5 patients who had blood cultures repeated.

During the evaluation for the source of bacteraemia, advanced malignancies, namely metastatic lung malignancy and advanced hepatocellular carcinoma (HCC) with tumour thrombus in the portal vein, were incidentally diagnosed in 2 patients. The malignancies may have led to disruption in the mucosal barrier, leading to translocation of intraluminal bacterial flora across the damaged mucosa into the blood stream. This may explain why co-infecting organisms are commonly *Enterobacteriaceae* in polymicrobial bacteraemia involving *L. adecarboxylata*. In patients with *L. adecarboxylata* bacteraemia without an evident source, we recommend that patients undergo evaluation to identify the source of bacteraemia. An occult malignancy should be considered, especially if clinical clues such as weight loss or unexplained anaemia are present.

The isolates of *L. adecarboxylata* were susceptible to most of the tested antibiotics (Table 1). Detected in vitro antibiotic resistances were infrequent, and limited to first-generation cephalosporin (cephalothin and cefazolin) and trimethoprim/sulfamethoxazole. An intravenous beta-lactam or ciprofloxacin was the most commonly used empirical antibiotic. After antibiotic susceptibility was known, most patients were switched to oral ciprofloxacin. Two patients passed away within 30 days from the date of diagnosis for *L. adecarboxylata* bacteraemia. The first patient presented with sepsis, and was found to have advanced HCC. Death occurred 11 days after the diagnosis of bacteraemia. The other patient clinically recovered during the hospital stay, and was discharged to complete a 2-week course of ciprofloxacin. He passed away 3 weeks after discharge in a different institution.

While previously described isolates showed susceptibility to most antibiotics,[5,6] multidrug-resistant strains have been increasingly reported.[7,8,10] Among the

Table 1. Antibiotic susceptibility test results for the 8 *L. adecarboxylata* isolates

Antibiotics tested	Susceptible isolates (%)
Penicillins	
Ampicillin	8/8 (100)
Ampicillin/sulbactam	5/5 (100)
Amoxicillin/clavulanic acid	8/8 (100)
Piperacillin/tazobactam	8/8 (100)
Cephalosporins	
Cephalothin	0/1 (0)
Cefazolin	2/7 (28.5)
Ceftriaxone	8/8 (100)
Cefotaxime	4/4 (100)
Ceftazidime	5/5 (100)
Cefepime	8/8 (100)
Monobactams	
Aztreonam	8/8 (100)
Carbapenems	
Imipenem	8/8 (100)
Meropenem	6/6 (100)
Ertapenem	8/8 (100)
Aminoglycosides	
Amikacin	8/8 (100)
Gentamicin	8/8 (100)
Tobramycin	1/1 (100)
Fluoroquinolones	
Ciprofloxacin	8/8 (100)
Levofloxacin	6/6 (100)
Folate synthesis inhibitors	
Trimethoprim/sulfamethoxazole	5/6 (83.3)
Tetracyclines	
Minocycline	1/1 (100)
Nitrofurans	
Nitrofurantoin	5/5 (100)

Not all isolates were tested for all drugs listed. Minimum inhibitory concentration values are not available as disk diffusion testing was employed for susceptibility testing.

8 isolates that we have identified in the 2 hospitals in Singapore from 2005 to 2021, multidrug resistance was not an issue. When treating a patient with community-acquired *L. adecarboxylata* bacteraemia in which antibiotic susceptibility is still unavailable, we suggest an empirical regime consisting of an intravenous third-generation cephalosporin (e.g. ceftriaxone) until a polymicrobial source of infection, such as perforated viscus, is excluded. Alternatively, if there is no undrained collection that may raise concern for treatment-emergent resistance, ciprofloxacin may be considered. Intravenous ampicillin may also be used if there is no suspicion of co-infection by other bacteria. However, when there is poor clinical response to an empirical first-line antibiotic, antibiotic treatment should be broadened because of the possibility of a polymicrobial bacteraemia, and the increasing prevalence of multidrug-resistant *L. adecarboxylata* isolates.[7-9] Among our patients, it is noteworthy that co-infecting organisms include *E. cloacae* complex and *A. lwoffii*—organisms that have intrinsic or developed resistance to third-generation cephalosporins.

A limitation of our study is the absence of more recent isolates—while the review of laboratory records extended to 31 May 2021, the last isolate identified was in August 2018. Ongoing surveillance is necessary to identify the emergence of multidrug-resistant *L. adecarboxylata* in Singapore.

When treating patients with *L. adecarboxylata* bacteraemia, clinicians should be aware of the possibility of a polymicrobial bacteraemia, and the emergence of multidrug-resistant strains worldwide. Our study shows that drug resistance is not yet a common issue in Singapore. Further studies, involving other Singapore and overseas hospitals, are needed to better elucidate the antibiotic susceptibilities of this organism. In cases where the source of infection is not evident, an occult malignancy should be considered, especially if clinical clues are present.

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Ann Acad Med Singap 2021;50:646-8
https://doi.org/10.47102/annals-acadmedsg.202118

Novel in situ weighing device for immobile patients

Dear Editor,

Accurate, regular weighing of patients is an important aspect of good clinical practice for both diagnostic and therapeutic purposes.[1] However, nurses face major physical challenges when taking regular weight measurements for immobile patients.[2,3] As our society ages rapidly, the proportion of disabled inpatients will only increase.[4] Despite the availability of several commercial weighing devices, immobile patients are infrequently weighed, as these devices are either expensive, highly customised or impractical to use on a daily basis.

Hence, there exists a need for an accurate, low-cost weighing equipment that can be installed conveniently onto existing hospital beds to minimise patient transfer. This paper reports our project's development of a novel weighing device with these features, and its comparative performance against 3 commercial weighing devices in terms of accuracy, ease of use and cost. This project was a joint effort in Singapore, involving Tan Tock Seng Hospital's Department of Geriatric Medicine and the National University of Singapore's Department of Electrical and Computer Engineering.

Design and evaluation. Our novel in situ under-mattress weighing device consists of modular wireless scales that are retrofittable and scalable for hospital beds with different frame designs or number of bed panels (Fig. 1). Each module is fastened onto the bed frame with Velcro straps prior to the patient's admission, and no further installation is required after the first installation. While the patient is lying on the bed, the total weight of the patient (tabulated from each module) is read off a wireless central display device. The wireless modules allow for easy installation, transportation and disinfection. The device comes with a wall plug charger that recharges the 4 modules at once. The study was approved by the National Healthcare Group Domain Specific Review Board.

After its development, a study was conducted where the novel device's accuracy and ease of use were compared against 3 competitors' devices: scale-integrated bed (CareAssist ES155, Hillrom, Chicago, US), under-bed scale (Charder MS6000, Charder Medical, Taichung City, Taiwan) and sitting scale (SECA 952, Seca GmbH & Co. KG, Hamburg, Germany).

Two accuracy measures comprising absolute accuracy and incremental accuracy, were used to evaluate the accuracy of the devices. These measures are as specified by international standards for weighing devices.[5] Each experiment with known weights was repeated 5 times on each device, and overall mean and 2 standard deviations were computed. Finally, the device's degree of similarity in absolute accuracy was assessed using the intraclass correlation coefficient (ICC) as per Koo and Li.[6]

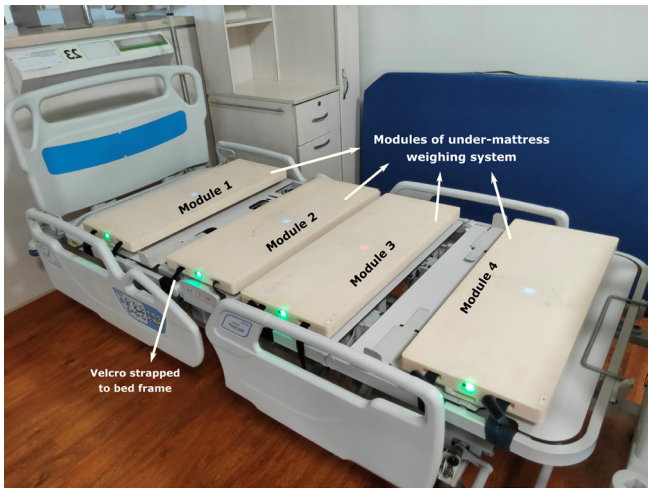

Fig. 1. Top view of the in situ under-mattress weighing device, with mattress removed. The modular devices (modules 1–4) are placed on top of 4 panels of the hospital bed frame. Velcro straps fasten the devices to the side of the bed frame. For a 4-panel hospital bed, 4 modules make up the weighing device.

As nurses are the end-users of the weighing devices, volunteer nurses' ratings were used to measure the devices' ease of use. Based on a significance level of 0.05 and 90% power to detect a mean difference of 1 in the rating, 150 participants were recruited.

The nurses were instructed on the installation and usage of the devices. Pairs of participants took turns to record each other's weight on each device. After their weighing experience with each device, they were asked to assess the 4 devices' ease of use based on a hypothetical scenario where they had to weigh an immobile patient daily for a week. The ease of use ratings were presented as a 5-point Likert scale, from "(1) Very easy" to "(5) Very difficult". The median score of the ease of use ratings was used for comparison of the devices.

Outcome of evaluation. All devices had an absolute accuracy and incremental accuracy that met the

requirements of the UK Weighing Federation for medical devices[7] (Table 1). The repeatability of measurements was also acceptable per requirements. There was also excellent agreement in the absolute accuracy of all devices by the ICC measure.

The nurses ranked all the 4 devices' ease of use, from the easiest to most difficult to use, with median scores of 1, 2, 3 and 4, respectively (Table 1).

Discussion. The novel device prototype developed in this study fared well against 3 competitors' devices in both technical and practical aspects. Given their similarity in accuracy, the devices were further compared for their ease of use and cost (Table 1).

Factors affecting the devices' ease of use include time taken to install the device, weight of the device and physical strain induced during weighing. Thus, sitting scales, which require immobile patients to be transferred to them, were ranked as difficult in our study. Hoists, including those with weighing functionalities, require effortful strapping of immobile patients. While direct patient transfer is avoided with the under-bed scale, it is physically straining for nurses to bend down to position heavy scales and roll the bed with a patient onto them. Ease of use has important implications in determining whether the device is ultimately used in the wards for regular weight measurements of immobile patients.

While scale-integrated beds offer the greatest convenience for nurses, not all hospitals may find them cost-effective. We acknowledge that the cost data in Table 1 is not directly comparable, since the cost for the novel device reflects its assembly cost price, while the cost of other devices consisted cost to purchase them for our study.

Though the novel device was ranked second for ease of use, its price would be much lower than that of the scale-integrated bed even at its reduced bulk purchase price. Should the novel device become a commercial product and its market price exceed the cost price reported, we are confident that it will present as a good economical and practical alternative to the other devices in our study, given its scalable modular design.[8]

Apart from the device's ease of use and cost, other practical considerations include size, storage space requirements and design issues. Scale-integrated beds do not require storage as they are used in the wards. Sitting and under-bed scales take up minimal space while weighing hoists require larger storage space. Our device can be attached to an existing ward bed, or disassembled and stored as a portable device, thus taking up a similar storage space as sitting and under-bed scales.

In the face of economic constraints where only a proportion of ward beds may include a weighing function, the novel device's design converts any ordinary ward bed to a weighing bed for the duration of a clinical need. This reduces additional disinfection work when patients require weighing, given that only disinfection of the novel device is required. In contrast, the use of scale-integrated beds, which involves transferring patients from an ordinary bed to the scale-integrated bed, would require disinfection of 2 beds.

There is scope to improve our study prototype by adding features such as fall detection and vitals monitoring in a cost-efficient manner.

Having a device in the wards to assist nurses with weighing immobile patients will not only improve the productivity of nurses but also increase the quality of patient care, especially in the geriatric wards and nursing homes. This study validated the novel device as a good cost-effective alternative to commercial devices in terms of accuracy and ease of use.

Acknowledgements

The study was jointly funded by the Ng Teng Fong Healthcare Innovation Programme (NTF_JUL2017_I_C1_D_04) and NUS Research Scholarship. The authors would like to acknowledge Ms Kalene Pek

Table 1. Comparison of the 4 devices' accuracy, rating for ease of use and actual cost

Device	Absolute error (kg)[a,b]	Incremental error (kg)[a,b]	Ease of use[c]	Cost (SGD)
Under-mattress scale (novel device)	0.2±0.0	0.0±0.0	2 (Easy)	1,500[d]
Scale-integrated bed	0.2±0.1	0.1±0.0	1 (Very easy)	9,800
Under-bed scale	0.1±0.1	0.0±0.0	3 (Average)	3,600
Sitting scale	0.2±0.1	0.0±0.0	4 (Difficult)	1,600

[a] Data represented as mean root mean square error ± 2 standard deviations
[b] Acceptable absolute and incremental errors are to be <0.2kg[7]
[c] Data represented as the median score of the ease of use ratings
[d] Cost for the novel device reflects its assembly cost price

Siling and Ms Audrey Yeo Jing Ping from the Institute of Geriatrics and Active Ageing, Tan Tock Seng Hospital for their effective administrative support throughout the project.

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Ann Acad Med Singap 2021;50:649-51
https://doi.org/10.47102/annals-acad medsg.202114

Managing the COVID-19 pandemic in non-purpose-built dormitories

Dear Editor,

The rate of coronavirus disease 2019 (COVID-19) infection in the foreign worker (FW) population in Singapore escalated in March 2020. A multiministry task force was set up in April 2020 to address the outbreak in FW residences.[1-3] FW residences are highly heterogenous, consisting of purpose-built dormitories and non-purpose-built dormitories (nPBDs). As the medical operations command (MOC) team that planned and executed the medical support plan (MSP) to contain the outbreak and deliver medical care to FWs in nPBDs, we discuss the key elements that served to stem the outbreak.

Unlike purpose-built dormitories that are typically large permanent structures specifically designed to meet FW living needs, nPBDs encompass a wide mix of smaller residences including temporary facilities such as construction temporary quarters and repurposed factory premises (factory-converted dormitories), with occupancies ranging between 10 and several thousand FWs.[4] The task group for nPBDs managed approximately 300,000 FWs living in approximately 1,300 nPBDs.

The diverse nPBDs and their localities dispersed across Singapore posed a challenge to delivering timely and appropriate care. As the deployment of on-site medical facilities was not feasible, a tiered plan was therefore adopted to efficiently allocate medical resources to nPBDs.

Our MOC team comprised 12 officers from diverse backgrounds—physicians, pharmacists, data analysts and administrators. The MSP comprised 4 key elements: (1) sectoral medical support; (2) mobile medical and nursing teams; (3) telemedicine and vital signs monitoring; and (4) electronic data capture, linkage and analysis. The operations were enabled by provisions in the Infectious Diseases Act and the emergency exceptions of the Personal Data Protection Act.[5,6]

Individual medical teams were deployed at 8 strategically located medical posts to provide sectoral coverage of nPBDs in industrial locations. Medical posts were equiped to deliver primary care and perform COVID-19 swab tests. Mobile medical and nursing teams were deployed to specific dormitories daily, based on a risk stratification algorithm developed by the MOC to identify high risk/needs dormitories. With "circuit breaker" measures—Singapore's version of lockdown—in place,[7] many FWs with chronic diseases were unable to attend follow-up appointments and obtain prescription refills. As such, nursing teams were deployed to specifically review all FWs above the age of 45 and those with existing chronic diseases, to arrange for their medication.

Telemedicine was made available under a regulatory sandbox by the Ministry of Health Singapore as a 24-hour service to all FWs. The simultaneous deployment of a vital signs monitoring application (FWMOM Care mobile app) for all dormitory-dwelling FWs, together with the distribution of pulse oximeters to all nPBDs, allowed twice daily vital signs monitoring (pulse rate and oxygen saturation) and detection of acute respiratory infection symptoms. When preset thresholds were exceeded (e.g. pulse rate above 120 beats per minute or oxygen saturation below 94%), the application would trigger a teleconsultation.

At the end of each day, data relating to all virtual and in-person consultations—captured via the MW (migrant worker) Health mobile app used by primary care providers to record vital aspects of the patient's condition for infectious disease surveillance—were channelled to the MOC centre. Data analysts processed "report sick" data of FWs, meshing it with telemedicine consultations and data collected by the Forward Assurance and Support Teams (FAST),[8] along with other secondary datasets on occupancy and age distribution of FWs in nPBDs. FAST comprise officers from the Ministry of Manpower, Singapore Armed Forces and the Singapore Police Force who perform onsite assessments of dormitory facilities. The availability of multifaceted data captured and analysed in near real time allowed for holistic risk assessments of all nPBDs daily, which in turn informed mobile team deployment decisions for the subsequent days. Fig. 1 shows a schematic diagram of the operations undertaken by the MOC team.

At a time when FW movements were restricted, telemedicine had been a useful modality of care delivery to the nPBDs, providing a broad basal level of coverage.[9,10] Medications were dispatched to stable patients with minor ailments for symptomatic relief. Follow-up telemedicine consultations 3 days after the

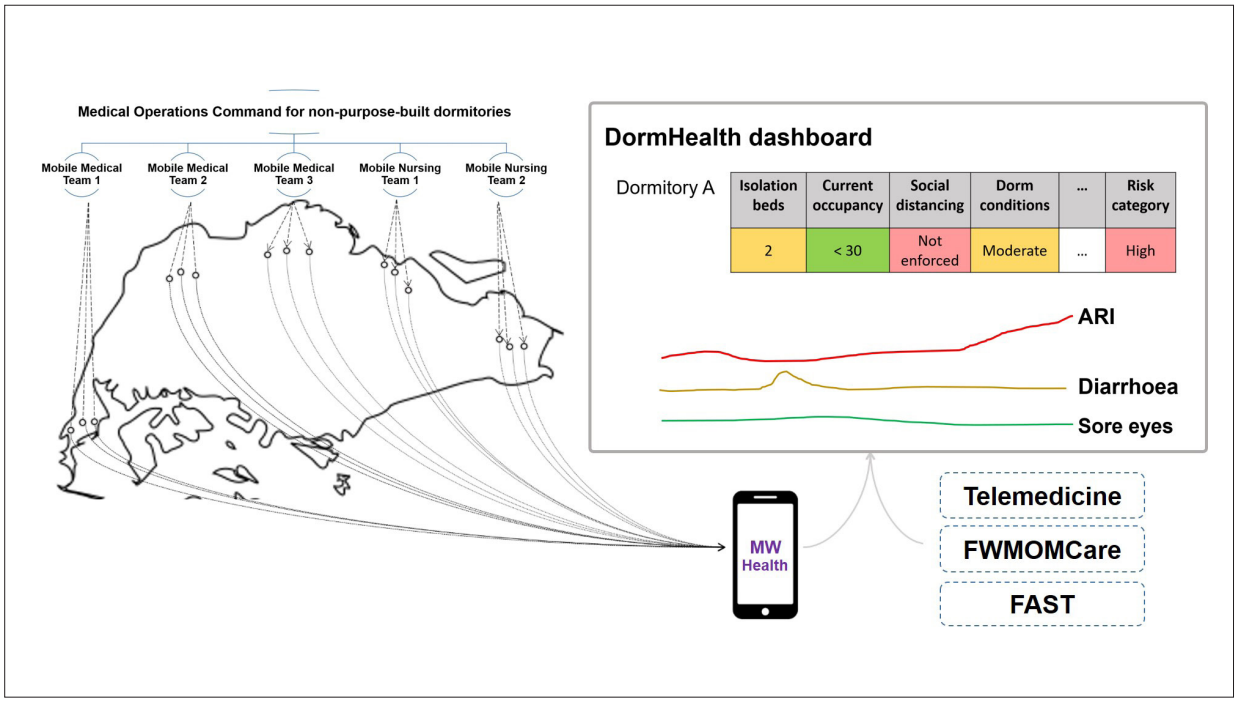

Fig. 1. Overview of operations by medical operations command for non-purpose-built dormitories as well as data capture, transfer and analysis for facilitating dormitory surveillance and decision making. Flow of data from 8 other sectoral medical posts that similarly use the MW Health mobile app to record migrant worker consultations is not shown.
ARI: acute respiratory infection; FAST: Forward Assurance and Support Teams; FWMOMCare: Ministry of Manpower Migrant Worker Care mobile app; MW Health: Migrant Worker Health mobile app.

initial consultation allowed patients to be discharged if symptoms were resolved.

While telemedicine played a key role, a limited physical examination meant that FWs who needed more thorough assessments had to be sent to the sectoral medical posts in a timely manner.[11] These posts (with some having in situ isolation facilities) provided the next layer of care, particularly for patients with acute respiratory infection symptoms. However, because of movement controls, dormitory operators were only allowed to send FWs to medical posts via a dedicated transport service. Timely communication of the medical needs of a worker following a telemedicine consult therefore became an important function of the MOC, to ensure efforts were coordinated and FWs received timely care. Providers could also activate ambulance services for FWs who were deemed to require urgent tertiary care.

The MOC mobile team deployments were primarily aimed at high-risk/needs dormitories. Nursing teams were deployed in dormitories where needs were less acute, while medical teams were deployed in dormitories with high numbers of COVID-19 cases. In scenarios where FWs were unable to leave their dormitories (e.g. varicella-zoster virus infection), a mobile medical team was deployed instead to review the FW on-site. Although the majority of FWs living in dormitories were relatively young and were of a certain level of physical fitness, the combination of the tiered, care delivery plan along with testing, conveyance and isolation strategy likely contributed to the very low numbers of COVID-19-infected FWs needing tertiary care.

The adopted MSP has been able to address the needs of FWs housed in 1,300 geographically dispersed nPBDs. Telemedicine and electronic data collection and analysis have been pivotal technology enablers in meting out the MSP. Coordination and communication between the MOC and Ministry of Manpower's operations team have also played a key role in addressing the needs of FWs in nPBDs. Having identified the requirements for servicing nPBDs; the data flow from both Ministry of Health and Ministry of Manpower; and the linkages for surveillance, we are now better placed to define resource requirements to address the current pandemic and prevent future COVID-19 outbreaks.

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Ann Acad Med Singap 2021;50:652-4
https://doi.org/10.47102/annals-acadmedsg.202151

Low-intensity shockwave therapy in the management of erectile dysfunction in Singapore

Dear Editor,

Erectile dysfunction (ED) is a distressing condition that affects up to half of men aged 30 and above in Singapore.[1] The prevalence is higher among men with cardiovascular risk factors, and it was reported that up to 63% of uraemic patients had severe ED in Singapore.[2] Low-intensity shockwave therapy (LiST) is a relatively new technology that is indicated for the treatment of ED.[3] The mechanisms involved in LiST include stimulation of mechano-sensors, activation of the neo-angiogenesis processes, recruitment and activation of progenitor cells, improvement in microcirculation, nerve regeneration, remodelling of erectile tissue, and reduction of inflammatory and cellular stress responses.[4] In this study, we prospectively evaluated the outcomes of our patients who received LiST as an adjunct to existing medical therapy for the management of ED.

Recruitment and assessment. The study was approved by the National Healthcare Group Domain Specific Review Board (Reference 2016/01010). Patients who presented to our Urology specialist outpatient clinic for ED were screened. All men above 21 years of age, who selected LiST as one of the modalities for treatment of ED and had a stable relationship with their sexual partner for more than 3 months, were recruited and gave written informed consent. Exclusion criteria included prior treatment with LiST, steroid therapy up to 6 weeks before first treatment, coagulation disorder and testosterone deficiency (total testosterone <8nmol/L). The patients were recruited from April 2017 to December 2017, and followed up from April 2017 to October 2018.

Eligible patients underwent 6 or 12 sessions of LiST. Patients who selected 6 sessions underwent 1 session a week, while patients who selected 12 sessions underwent 2 sessions a week. Shockwaves were delivered using the Duolith SD1 ultra machine (Storz Medical AG, Tägerwilen, Switzerland) in a similar protocol described by Chung and Cartmill.[5] During the treatment period, the patients continued to receive other medical therapies for ED, including phosphodiesterase type 5 inhibitors (PDE5is) and testosterone replacement therapy (TRT) when indicated. The patients' baseline demographics, data on cardiovascular risk factors, testosterone levels, baseline erectile function as determined by the International Index of Erectile Function 5 items (IIEF-5) scores and Erection Hardness Scores (EHS), and Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) scores were recorded. The patients' EDITS was assessed at 1-month follow-up, and IIEF-5 and EHS were assessed at 1-, 3- and 6-month follow-ups. SPSS Statistics software version 22 (IBM Corp, Armonk, US) was used for data analysis. The paired t-test was used to compare the differences in mean values of IIEF-5, EHS and EDITS before treatment and at follow-up visits. The level of statistical significance for all analyses was $P<0.05$.

Results. A total of 19 patients were recruited in the study. The mean age was 57.4 years (range 38–70), and all the patients had a duration of ED of at least 12 months (mean 46.3 months, range 12–120). Fifteen patients (79%) had at least 1 cardiovascular risk factor, which suggested a vasculogenic cause of ED. Six patients (32%) had diabetes mellitus, which suggested a combined vasculogenic and neurogenic cause of ED. All of the patients had been taking PDE5i for at least 3 months; 11 (58%) of whom were taking daily tadalafil, and the other 8 (42%) were taking on-demand PDE5i. Eight patients (42%) were on TRT, and the mean total testosterone of all patients was 13.7±4.0nmol/L at recruitment. Nine patients (47%) had moderate-to-severe ED based on IIEF-5 and EHS ≤2 at baseline, 9 patients (47%) had mild-to-moderate ED, and 1 patient (5%) had a complete response to on-demand sildenafil (IIEF-5=24, no ED).

Fourteen patients (74%) underwent 12 sessions of LiST, while 5 patients (26%) underwent 6 sessions. Sixteen patients (84%) returned for follow-up at 1 month, 17 patients (89%) returned at 3 months, and 11 patients (58%) returned at 6 months. At 1-month follow-up, the mean IIEF-5 for the 16 patients increased from a baseline of 13.1±5.7 to 15.9±6.1 (P=0.002), and the mean EHS increased from 2.44±1.03 to 2.88±0.81 (P=0.014). Three of the 16 patients (19%) had a ≥ 5-point increase in IIEF-5. Of these 16 patients, 15 completed the EDITS score. There was also an improvement in treatment satisfaction, as the EDITS score increased from a mean of 50.1±21.1 to

Table 1. Results outlining mean scores at baseline and follow-ups

	Variable	Mean scores at baseline	Mean scores at follow-up	*P* value
1-month follow-up (n=16)	IIEF-5	13.1±5.7	15.9±6.1	**0.002**[b]
	EHS	2.44±1.03	2.88±0.81	**0.014**[b]
	EDITS[a]	50.1±21.1	67.2±22.3	**0.005**[b]
3-month follow-up (n=17)	IIEF-5	12.7±5.7	17.2±6.5	**0.001**[b]
	EHS	2.41±1.00	2.82±0.95	0.069
6-month follow-up (n=11)	IIEF-5	11.6±6.0	16.9±6.8	**0.001**[b]
	EHS	2.18±1.08	3.00±1.10	**0.02**[b]

EDITS: Erectile Dysfunction Inventory of Treatment Satisfaction; EHS: Erection Hardness Scores;
IIEF-5: International Index of Erectil Function 5 items
[a] 15 of 16 patients completed EDITS
[b] $P<0.05$, significant values in bold

67.2±22.3 (P=0.005). At 3-month follow-up, the mean IIEF-5 for the 17 patients increased from a baseline of 12.7±5.7 to 17.2±6.5 (P=0.001), and the mean EHS increased from 2.41±1.00 to 2.82±0.95 (P=0.069). Eight of the 17 patients (47%) had ≥ 5-point increase in the IIEF-5. These improvements persisted at 6-month follow-up. The mean IIEF-5 for the 11 patients increased by 5.3 points (confidence interval [CI] 95% 2.8–7.9) from 11.6±6.0 to 16.9±6.8 (P=0.001), and mean EHS increased from 2.18±1.08 to 3.00±1.10 (P=0.02), shown in Table 1. Seven of the 11 patients (64%) had a ≥ 5-point increase in IIEF-5 at 6-months. There was no reported adverse event during the study period.

Discussion. In randomised control trials, LiST has been shown to improve IIEF and EHS in treatment groups compared to placebo groups.[6] A meta-analysis which included 14 studies and 833 patients from 2005 to 2015, showed that LiST could significantly improve IIEF (mean difference 2; 95% CI 0.99–3, P<0.001) and EHS (risk difference 0.16; 95% CI 0.04–0.29; P=0.01) with a therapeutic efficacy of at least 3 months.[7] Moreover, LiST had also been shown to convert a PDE5i non-responder to a PDE5i responder.[8]

In our study, we were able to replicate the findings in the early, open label, single-arm, cohort studies[5] with demonstration of statistically significant improvement in mean IIEF-5 at 1, 3 and 6 months, and statistically significant improvement of mean EHS at 1 and 6 months. Furthermore, out of 9 patients who were initially considered non-responders to medical therapy (EHS ≤2), 4 patients responded with EHS ≥3 and a ≥5 -point increase in IIEF-5 at 3-month follow-up. Also, 4 of the 10 patients who were responders to medical therapy had a ≥ 5-point increase in IIEF-5 at 3-month follow-up.

We acknowledge the limitations of our study, such as the lack of a control arm, small number of participants, patient dropout at 6-month follow-up, and the variability in the treatment protocol. In addition, 10 patients (53%) who were considered responders to PDE5i were included in the study.

Nevertheless, our study demonstrated significant improvement in mean IIEF-5 and mean EHS up to 6 months following addition of LiST to conventional medical therapy, regardless of prior response to PDE5i. LiST should be considered a useful adjunct to PDE5i in the management of ED.

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Ann Acad Med Singap 2021;50:655-6
https://doi.org/10.47102/annals-acadmedsg.202143

Rare *Klebsiella pneumoniae* anterior mediastinal abscess masquerading as cardiac tamponade

Dear Editor,

Mediastinal abscess, an uncommon medical condition caused by remote source of infection, rarely occurs in the absence of trauma or instrumentation. Acute pericarditis with cardiac tamponade, associated with a mediastinal abscess, is a rare clinical presentation; if left untreated, it is potentially fatal. We present a case that encompassed the rare association of a primary gram-negative mediastinal infection, with a reactive pericardial effusion, presenting as pericardial tamponade. The approach to extra-cardiac structure evaluation and the importance of initial wide-sector width image acquisition are detailed in this report.

A 29-year-old man, with medical history of obesity and type 2 diabetes mellitus (glycated haemoglobin/Hba1C 10.5%), presented to the emergency department with a 2-week history of substernal pleuritic chest pain and dyspnea. He was febrile on presentation (temperature 38.4°C), tachycardic (heart rate 112 beats/minute) and hypotensive (blood pressure 89/67mmHg) though saturating normally on room air. Clinical examination revealed muffled heart sounds with jugular venous distension.

Significant laboratory findings included leukocytosis (white cell count 15.17x10^9/L) with neutrophilia, elevated C-reactive protein of 188mg/L and hyperlactatemia of 3.2mmol/L. Blood culture showed no bacteria growth, and retroviral screen was negative. Electrocardiogram demonstrated widespread ST elevations and PR depression, suggestive of pericarditis. Initial chest radiograph revealed a wide mediastinum (Fig. 1).

Echocardiographic substernal view showed a large pericardial effusion measuring 2.9cm adjacent to the right heart, with right ventricular diastolic collapse. The suspected echogenic structure is seen anterior to the right ventricle. It was initially described as epicardial fat (Fig. 2A).

The clinical diagnosis was acute pericarditis complicated by cardiac tamponade. Urgent pericardiocentesis was done and 410mL of haemoserous fluid was aspirated. Analysis of the pericardial fluid revealed neutrophilic predominance, elevated lactate dehydrogenase, protein, and adeno-deaminase (ADA). It was negative for bacteriology, acid-fast bacilli staining and malignant cells. He was started on high-dose ibuprofen and colchicine.

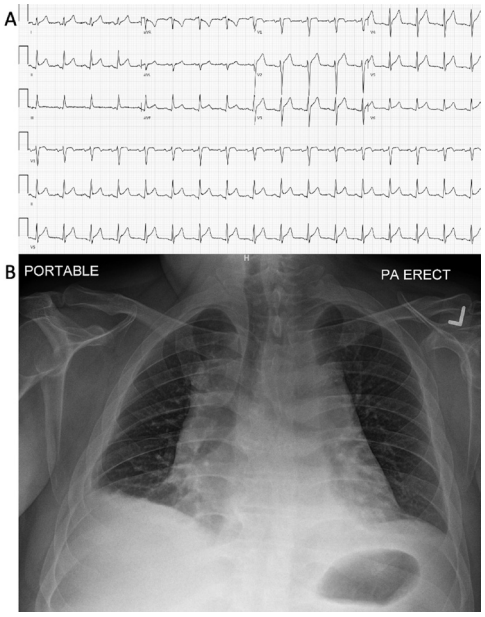

Fig. 1. (A) 12-lead electrocardiogram showing widespread ST elevations and PR depression, suggestive of pericarditis. (B) Initial chest radiograph revealing a wide mediastinum.

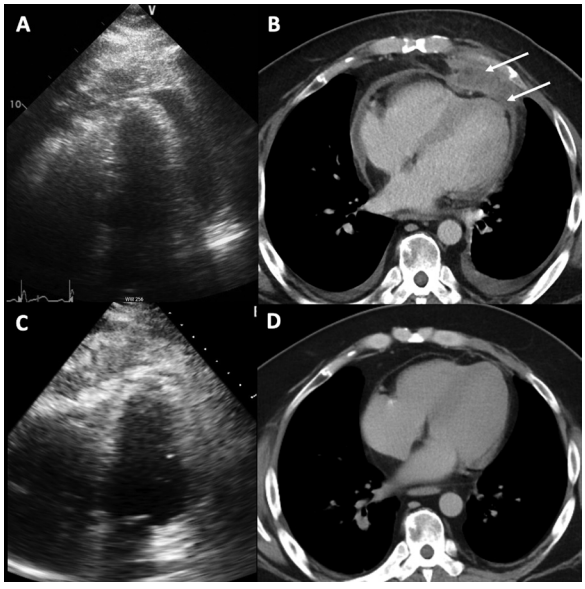

Fig. 2. (A) Echocardiogram before pericardiocentesis demonstrating large pericardial effusion with mixed echogenic density structure surrounding the cardiac apex. (B) Computed tomography (CT) of the thorax showing complex structure (upper arrow) with thick rim enhancement and internal mixed density fluid component centred at the cardiac apex involving the pericardium (lower arrow), measuring 2.9x8.4x6.4cm. This favours an abscess. (C) Repeat echocardiogram after pericardiocentesis. (D) Repeat CT of the thorax 6 months post-drainage showing resolution of pericardial abscess.

Computed tomography (CT) of the thorax revealed a large complex extra-pericardial structure adjacent to the cardiac apex with thick lobulated rim enhancement and internal fluid component (Fig. 2B). CT abdomen and pelvis did not reveal hepatic abscesses or other sources of sepsis that might result in secondary seeding. A follow-up echocardiogram showed a small residual pericardial effusion with a mixed echogenic density structure around the cardiac apex with pericardial margin seen separating the structure (Fig. 2C).

The patient underwent fluoroscopic-guided drainage of the mediastinal abscess. The alternative plan by the cardiothoracic surgeons was pericardiectomy with local drainage and washout if source control was unsuccessful despite fluoroscopic-guided drainage. Fluid culture of the abscess grew pan-sensitive *Klebsiella pneumoniae*. The ADA was 146 U/L. He was commenced on intravenous ceftriaxone for 2 weeks and transitioned to oral ciprofloxacin. CT of the thorax was repeated 6 months later which demonstrated resolution of the mediastinal abscess (Fig. 2D).

This case describes a rare occurrence of mediastinal abscess, a medical condition usually caused by remote source of infection, which has occurred in the absence of trauma or instrumentation.[1] Few case reports have described bacterial pericarditis and pericardial effusion resulting in tamponade,[2-4] with most treated with percutaneous[4] or surgical drainage[2,3] and concomitant intravenous antibiotics. The present case highlights the importance of performing targeted investigations to elucidate uncommon sources of acute pericarditis and tamponade in a young patient. The elevated ADA levels in pericardial fluid necessitate the exclusion of infective and mitotic causes, prompting further CT imaging. ADA is usually elevated in neutrophil-predominant effusions and is a more useful diagnostic tool in lymphocyte-predominant effusions, which are high in tuberculous pericarditis and neoplastic effusion.[5] In the present case, other common aetiologies of tuberculosis and malignancy were excluded with negative cytology and acid-fast bacilli staining.

Echocardiogram is useful in delineating normal structural findings around pericardium from other pathology. This case highlights the importance of obtaining an initial wide-sector width during acquisition of echocardiographic images to evaluate for extra-cardiac structures, even in an acute setting. These extra-cardiac structures can be easily missed if the initial sector width is too narrow. Moreover, it is important to distinguish epicardial fat from other pathological extra-cardiac structures. Epicardial fat is commonly anterior to the heart, in the atrioventricular and interventricular grooves. It is fairly immobile and has a granular reflection or texture within.[6] As illustrated in present case, the mixed echogenic density around the cardiac apex had pericardial margin separating the ventricle from the structure, suggestive of extra-pericardial collection. If the diagnosis of the extra-pericardial structure is still uncertain, chest CT remains an adjunctive tool in clarifying normal from pathologic variants of cardiac and extra-cardiac structures given its high spatial resolution and tissue characterisation of fat.[7]

The seemingly uncomplicated case of acute pericarditis and tamponade led to a unique discovery of a primary gram-negative extra-pericardial abscess that precipitated this inflammatory response. Clinicians need to keep a high index of suspicion of extra-pericardial collections in a young patient presenting with an acute pericarditis and tamponade. More attention is needed to actively look for extra-pericardial collections on the index echocardiogram, particularly with a wide-sector width image acquisition. Urgent interventions are required to drain both the cardiac tamponade and extra-pericardial abscess.

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Ann Acad Med Singap 2021;50:657-9
https://doi.org/10.47102/annals-acadmedsg.2020621

Returning to sports after an anterior cruciate ligament reconstruction: When is a good time?

Dear Editor,

Anterior cruciate ligament (ACL) reconstruction is the mainstay of treatment for active individuals with ACL injuries. The ability to return to pre-injury activity is important for patients after ACL reconstruction (ACLR).[1,2] Despite that, the ideal timeline for patients to return to sport after ACL reconstruction is widely debated.

Nine to 12 months after surgery have been recommended as an ideal timeline for ACLR patients to return to sports.[3] However, recent studies have shown a higher risk of reinjury up to 2 years after surgery and great variability in patient outcomes remains.[4] Therefore, we sought to evaluate functional improvement of our cohort of ACL reconstructed patients over a period of 2 years to determine if return to sports should be delayed.

Fifty-six consecutive patients (42 men and 14 women), who underwent a transportal 4-strand hamstring graft ACLR between 2016 and 2017, were recruited after institution review board approval. The mean age of these patients was 27.1 years (range 17–42) and all patients had been playing recreational sports at least twice a week before injury.

Our cohort underwent isolated ACLR, ACLR with meniscal debridement (MD), or ACLR with meniscal repair (MR). Patients with concomitant cartilage or multiligament surgeries were excluded. The mean duration of surgery for all cases was 62 minutes (range 48–80). The International Knee Documentation Committee (IKDC) subjective scores, Lysholm scores and Tegner scores were collected pre-surgery, 1 and 2 years after ACLR.

Postoperatively, all patients underwent a standard ACL physiotherapy protocol. Full weight-bearing was permitted for patients that underwent isolated ACLR or ACLR with MD. Protected weight-bearing (touch-down weight-bearing of 5kg for the first 3 weeks, then partial weight-bearing of 50% body weight for the next 3 weeks) was enforced for patients with ACLR with MRs for 6 weeks. Postoperatively, all patients were allowed range of motion 0–90° in a knee brace with progression to full range of motion after 6 weeks.

The patients were commenced on stationary cycling at 6 weeks, jogging at 4 months (if operated limb strength reached 80% of the contralateral limb), agility drills at 6 months and sports specific drills at 7 months. The physiotherapy sessions were scheduled weekly up to 6 weeks, fortnightly up to 3 months, and monthly after 3 months until 12 months.

The mean IKDC subjective scores, Tegner scores and Lysholm scores were compared using paired t-test. Post hoc analysis with Bonferroni correction was used to assess for difference between groups. Statistical significance was defined at a P value of <0.05 and analyses were carried out with SPSS Statistics software version 23 (IBM Corp, Armonk, US).

In our cohort, 15 patients had isolated ACLR, 13 patients had ACLR with MD, and 28 patients had ACLR with MR.

The IKDC subjective scores improved significantly between 1 year (81.1±12.7) and 2 years (86.9±10.1) post-surgery (P=0.016). There were also significant improvements (P<0.05) in IKDC subjective scores between 1 year and 2 years post-surgery in all groups (ACLR, ACLR+MD and ACLR+MR) (Fig. 1A).

The Tegner scores improved significantly between 1 year (5.6±1.6) and 2 years (6.4±1.9) post-surgery (P=0.001). There were significant improvements in Tegner scores in ACLR+MD (P=0.021) and ACLR+MR (P=0.043) groups between 1 and 2 years post-surgery. No difference in Tegner scores was seen in the isolated ACLR patient cohort between 1 and 2 years post-surgery (P=0.424) (Fig. 1B).

There was no difference in Lysholm scores between 1 year (91.4±7.6) and 2 years (88.7±14.6) post-surgery (P=0.27). This finding was consistent across all groups: isolated ACLR (P=0.324), ACLR+MD (P=0.151) and ACLR+MR (P=0.42) (Fig. 1C).

Twenty-four percent and 51% of our patients returned to sports at their pre-injury levels at 1 and 2 years, respectively. Among the 3 surgical intervention groups, no significant difference (P>0.05) was observed in improvement of IKDC subjective scores, Tegner scores and Lysholm scores at 1 year and 2 years postoperatively.

Our study reports a return to sports rate of 24% at 1 year and 51% at 2 years. Our findings are similar to those in the landmark prospective study of 122 patients by Ardern et al., who reported that 31% of patients returned to pre-injury levels at 1 year and 60% returned to their pre-injury levels at 2 years.[5] Welling et al.

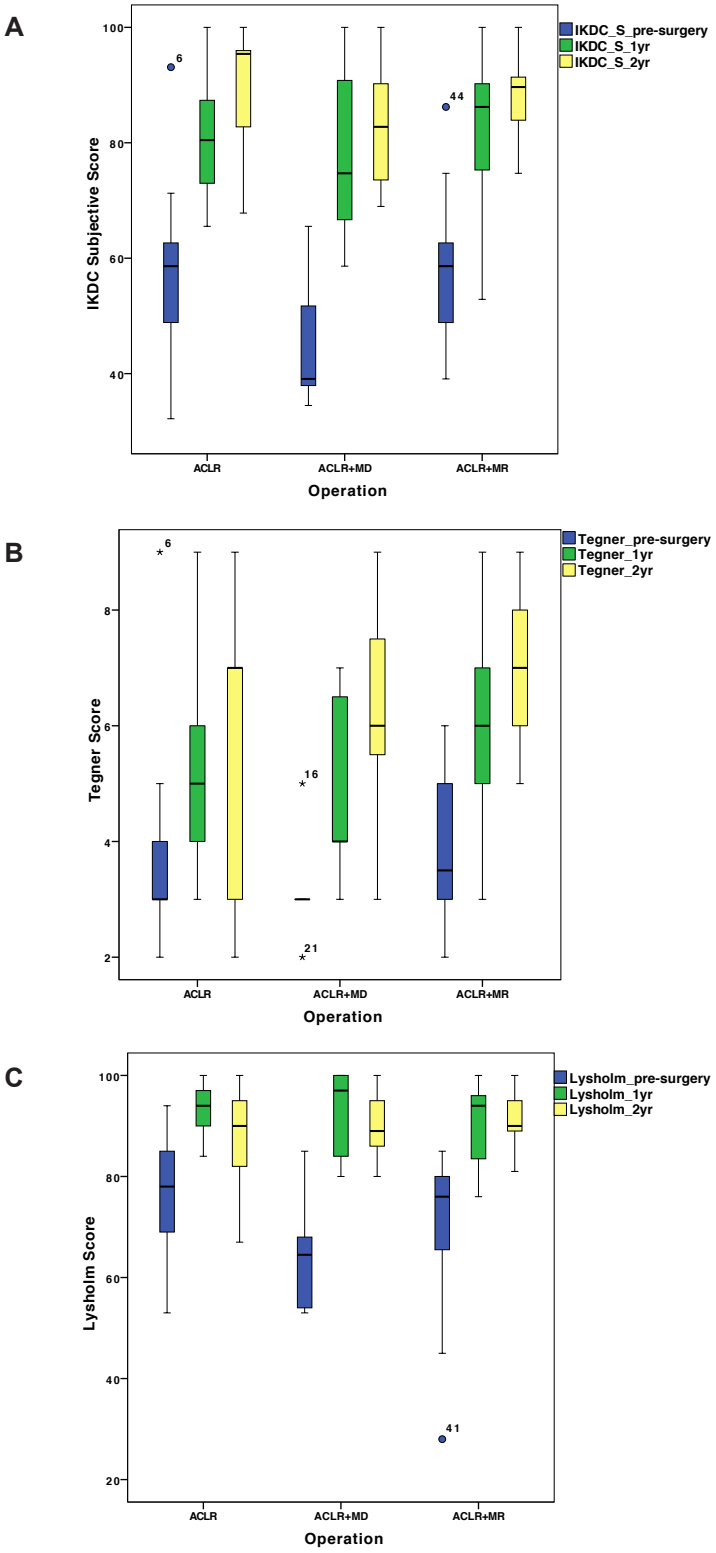

Fig. 1. Boxplots of isolated ACLR, ACLR + MD, and ACLR + MR. (A) Blue boxplot (pre-surgery IKDC subjective scores), green boxplot (IKDC subjective scores at 1 year post-surgery) and yellow boxplot (IKDC subjective scores at 2 years post-surgery). (B) Blue boxplot (pre-surgery Tegner scores), green boxplot (Tegner scores at 1 year post-surgery) and yellow boxplot (Tegner scores at 2 years post-surgery). (C) Blue boxplot (pre-surgery Lysholm scores), green boxplot (Lysholm scores at 1 year post-surgery) and yellow boxplot (Lysholm scores at 2 years post-surgery).

ACLR: anterior cruciate ligament reconstruction; IKDC: International Knee Documentation Committee; MD: meniscal debridement; MR: meniscal repair

reported that only 11.3% of patients met the return to sports criteria at 12 months, again emphasising the need to delay return to sports.[6] These findings reaffirm our recommendation to extend return to sports to a minimum of 12 months after surgery.

Our patients continue to improve in functional scores after 1 year of ACLR. This is supported by the improvement in IKDC subjective scores and Tegner scores between 1 and 2 years. Ithurburn et al. also showed that most of their study participants only achieved higher functional recovery based on knee outcomes scores at 2 years.[7] This supports our hypothesis that patients experience functional improvement up to 2 years post-ACLR.

In a 5-year follow-up study, Lee et al. reported that 62% of their post-ACLR cohort returned to sports at 5 years.[8] We report a return to sports rate of 51% at 2 years, suggesting a gradual temporal improvement post-ACLR.

Phillips et al. highlighted differences in outcomes for isolated ACLR and ACLR with concomitant meniscal surgery.[9] In our cohort, we found no difference in knee outcomes scores between patients who had isolated ACLR or ACLR with meniscus surgery at 1 and 2 years postoperatively.

The limitations of this study are the small sample size, lack of data on objective muscle strength during rehabilitation, and patient's motivation levels; these are known factors in predicting successful return to sports.[10]

Amalgamating our study findings with current literature, we suggest that 12 months is the earliest time for return to sports after ACLR. However, the consideration should not purely be time-based. Other factors such as limb strength, running gait, sports specific drills and patient motivation are important to attain the best possible conditions for a successful return to sports.

In conclusion, ACL reconstructed patients continue to exhibit functional improvement at 1 year after surgery, with more patients ready to return to sports at 2 years.

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Ann Acad Med Singap 2021;50:660-1
https://doi.org/10.47102/annals-acadmedsg.2021101

A linear density on imaging: Non-contrast CT as a useful localisation method

A 37-year-old man presented to the emergency department after breaking a hypodermic needle while injecting his right groin. Significant past medical history included intravenous drug use and epilepsy.

A radiograph of his right groin was performed (Fig. 1), demonstrating a metallic linear density projected over the right ischium suggesting a needle fragment foreign body, which was not visible or apparent on clinical examination. The fragment was not removed due to patient factors, and the patient was discharged with prophylactic antibiotics.

Seven years later, the patient presented again to the emergency department following a seizure due to non-compliance with anti-epileptic medication. A chest radiograph (Fig. 2) was performed.

Upon reviewing the chest radiograph, a non-contrast computed tomography (CT) scan of the thorax (Fig. 3) was requested to investigate further.

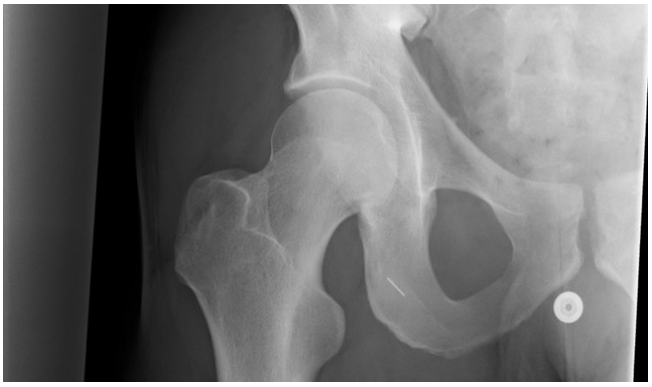

Fig. 1. Right frontal hip radiograph at first presentation.

What do Figs. 1, 2 and 3 demonstrate?

A. Acute pulmonary embolism
B. Imaging artefact
C. Needle embolisation to the heart
D. Needle embolisation to the lung
E. Presence of a charm needle

The chest radiograph (Fig. 2) shows a subtle linear density projecting over the right cardiac shadow. A repeat hip radiograph confirmed that the previously sited needle was no longer visible at the right groin. The non-contrast CT (Fig. 3) demonstrates a metallic linear foreign body density within a subsegmental branch of

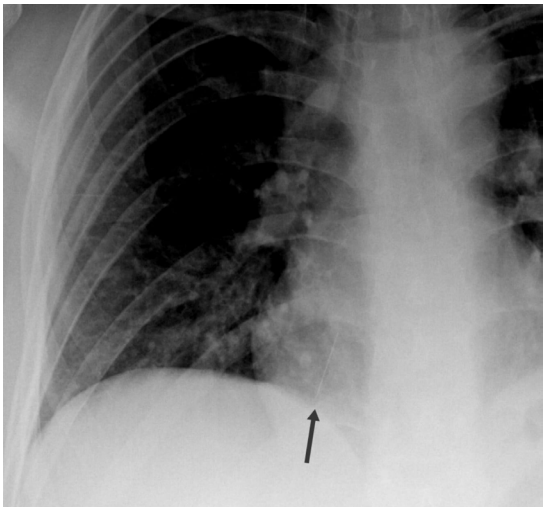

Fig. 2. Frontal chest radiograph. Arrow indicates a thin linear density over the right cardiac shadow.

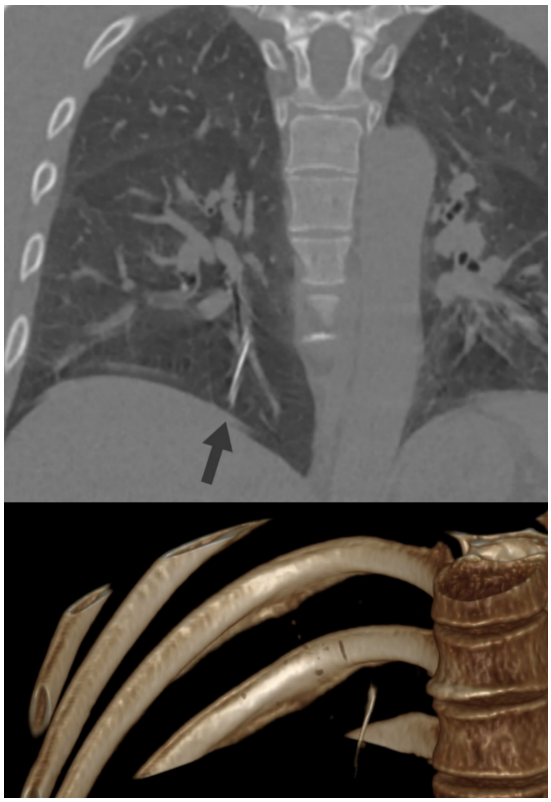

Fig. 3. Top panel: non-contrast computed tomography (CT) scan of the thorax in the coronal plane. Arrow indicates a linear density. Bottom panel: 3-dimensional volume rendered image from the CT of the thorax showing the linear density. (Colour figure available online.)

Answer: D

the right lower lobe pulmonary artery. This likely represents the migration and embolisation of the needle fragment from the right groin to the lung. There is blooming susceptibility artefact on the CT, a phenomenon caused by metallic density, resulting in the needle appearing larger than its actual size. The oblique position of the needle on the initial hip radiograph had caused it to appear shorter than its length on the CT scan.

Cardiothoracic surgeons' opinion was that removal of the foreign body would require surgery such as wedge resection or a right lower lobectomy. The patient did not opt for treatment and was discharged without planned follow-up.

Other causes of linear densities on X-ray radiographs and CT include artefact, iatrogenic or other foreign body material, and charm needles. Artefact, in this case, is highly unlikely given the persistent presence of the linear opacity on different modalities (radiographs and CT scan). The diagnosis of acute pulmonary embolism requires a CT pulmonary angiogram, i.e. a contrast-enhanced study to look for filling defects in the opacified pulmonary arteries. A non-contrast CT is a suitable protocol for troubleshooting the location of foreign bodies in the thorax. Contrast medium would have likely obscured the needle fragment within the pulmonary arterial branch from view, therefore attention must be paid to avoid performing the wrong imaging protocol. A chronic calcified pulmonary embolus may be concurrent and difficult to differentiate from an embolised needle tip or other foreign body in the pulmonary arteries. Increasing the window width on the CT, known in practice as "windowing", typically enables metallic density to be differentiated from high attenuation entities such as calcification.

Charm needles, or "susuk", are not commonly seen on imaging outside of Southeast Asia. These are talisman subcutaneously placed in the face or other body parts, and may form part of the differential for a linear density on imaging in the appropriate context. They are believed to enhance beauty and youth[1] and may be used as traditional medicine by some communities in Southeast Asia.

The radiograph appearances could have been attributed to a subcutaneous charm needle in a Southeast Asian context. Direct charm needle migration has been reported, though it occurred through the skull and into the brain.[2] Indeed, such cases are extremely rare, with their presence on imaging generally considered a benign entity. Eliciting a good clinical history from the patient, with consideration of cultural practices and background could exclude the presence of a charm needle.

Needle breakage by intravenous drug users is not an uncommon occurrence. However, needle embolisation to the lung or heart is rare and infrequent in literature.[3] Once migration to the thorax has occurred, the course of events somewhat depends upon the final location of the needle.

Reported complications include inflammatory mass formation requiring lung wedge resection, pneumothorax following migration from the heart via the mediastinum,[4] infective endocarditis, cardiac perforation and tamponade.[1]

Therefore, it is important to localise with CT whether the needle fragment lies within the heart or the lung, as chest radiograph appearances may be misleading.

Clinical management will depend on patient factors and willingness for intervention. However, most cases of needle embolisation to the lung are expected to follow a benign course,[3] and follow-up will depend on local practices.

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Acknowledgement

The Editorial Board of the *Annals*, Academy of Medicine, Singapore gratefully acknowledges the generous support of

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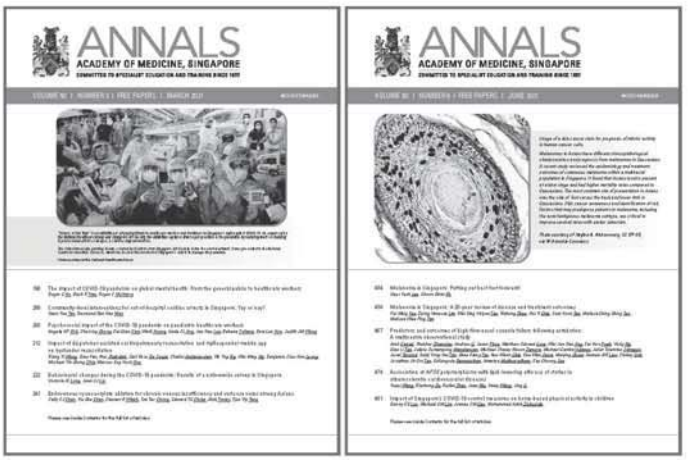

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