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*"There's biology in everything,
even when you're feeling spiritual."*

Helen Fisher, (1945 –)
Canadian-American anthropologist

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The Interface Between Medicine and Psychiatry: Neuropsychiatric Aspects of Systemic Lupus Erythematosus (SLE)

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Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease characterised epidemiologically by the preponderance of women, and pathologically by the loss of immunological tolerance to self-nuclear antigens and aberrant B- and T-cell responses.^{1,2} Similar to that of other regions around Southeast Asia, the prevalence of SLE in Singapore is 40/100,000.³ Amongst various organ involvement, neuropsychiatric SLE (NPSLE) is one of the most devastating presentations of the condition.⁴ NPSLE is likely the result of the interplay amongst the immunopathological actions of autoantibodies, intrathecal inflammatory mediators and cerebral microvasculopathy.⁵ The American College of Rheumatology (ACR) Ad Hoc Committee devised case definitions for 19 neuropsychiatric syndromes in SLE which comprise central and peripheral neurological, and psychiatric syndromes such as anxiety, depression and cognitive dysfunction.⁶ Irreversible organ damage, which potentially occurs when lupus-induced damage persists for more than 6 months, does not spare the neuropsychiatric system. Indeed, damage to the neuropsychiatric system has been dragging down the 5-year and 10-year survival rates of lupus patients over the past 50 years,⁷ in addition to the substantial socioeconomic burden it entails for those who survive.⁸

Historical Understanding of the Psychiatric Aspects of SLE

In the 1950s, reports of acute anxiety, depression, delusions and hallucinations in lupus patients started to emerge in the literature.^{9,10} Owing to the increased awareness and liaison with psychiatrists, the reported frequency of psychiatric symptoms amongst lupus patients increased from less than 20% before 1960 to 40% thereafter.¹¹ Forty-one percent of the lupus patients suffered from non-organic, non-psychotic psychopathology as compared to psychotic pathology such

as paranoid delusion and visual hallucinations.¹² Depression (39%) and anxiety (24%) are the commonest psychiatric comorbidities of SLE.¹³ Patients with SLE are susceptible to depression as a result of psychological reaction to the disease, the direct impact of inflammatory mediators on the brain, and the side effects of high-dose glucocorticoids.^{14,15} As compared to patients with other common rheumatic conditions, lupus patients are more likely to suffer from anxiety which is predicted by damage accrual, higher cumulative glucocorticoid dose and the presence of depression.¹⁶ Cognitive impairment, one of the commonest neuropsychiatric lupus manifestations, was found in 14% to 75% of lupus patients¹⁷ and associated with significant functional impairment. The ACR developed a set of standard neuropsychological tests to assess cognitive function which chiefly includes attention, executive function, memory and visuoconstructional abilities. Patients with SLE have been demonstrated inferior performance in all of these domains as compared to healthy individuals.¹⁸

In general, Asian lupus patients have more serious organ manifestations including NPSLE than their Caucasian counterparts.¹⁹ Locally, neuropsychiatric symptoms were found in 21% of Chinese lupus patients, with a female predominance and tendency to manifest early in the course of SLE.^{20,21} In this study, disturbances of orientation, perception and memory were the commonest lupus-related psychiatric comorbidities.

Some Recent Advances in the Understanding of Neuropsychiatric Aspects of Lupus

Cerebral atrophy, which can be caused by the reduction of the white and/or grey matter volume, is commonly described in lupus patients.²² Intriguingly, inflammation and atrophy of the white matter have been found to be more pronounced than those of the grey matter in lupus

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patients, especially in those with short disease duration.^{23,24} The involvement of white matter atrophy was generally correlated with anxiety, cognitive impairment, the duration of SLE and cumulative glucocorticoid dose.²⁴⁻²⁶ It is currently believed that the inciting impact of inflammation on the white matter precedes grey matter damage in lupus patients.^{24,26} Nevertheless, the differential clinical implications of white and grey matter damage remain to be elucidated in lupus patients.

A number of recent functional magnetic resonance imaging (fMRI) studies in lupus patients has generally revealed deactivations of various cortical areas responsible for working memory and executive function, accompanied by compensatory activations in other cortical areas for preserving cognitive functioning. For example, patients with childhood-onset SLE showed compensatory activations in the visual association area and the dorsolateral prefrontal cortex (attention area) but deactivations in the cingulate gyrus during the N-back working memory task.²⁷ Our recent fMRI study using the Wisconsin Card Sort Test (WCST) which probes cognitive set-shifting found that the cortico-basal ganglia-thalamic-cortical circuit, which is involved in response inhibition, was dysfunctional in adult lupus patients.²⁸ With the compensatory activations in the contralateral cerebellar and frontal areas, the performance of the WCST amongst the patients remained equivalent to that of healthy subjects despite the dysfunctional neural circuit.²⁸

The pathogenetic role of some autoantibodies in NPSLE remain controversial. For instance, high anti-ribosomal P titres were found to be associated with depression and psychosis,^{29,30} and anticardiolipin IgG was found to be related to cognitive impairment.³¹ While depression and memory impairment were noted in lupus patients with elevated serum titres of anti-NR2,³² most of the other similar studies refuted such relationships except those which studied the antibodies in the cerebrospinal fluid.^{33,34} Currently, the breach of the blood-brain barrier (BBB) is believed to be essential for the entry of pathogenic autoantibodies into the central nervous system which trigger neuropsychiatric symptoms.³⁵

Current Knowledge Gaps and Future Research Directions

The pathogenesis of neuropsychiatric symptoms in patients with SLE is still not fully elucidated. The major challenges in diagnosing and monitoring NPSLE stem from its diversity and protean clinical feature, and the lack of reliable lupus-specific neuropsychological assessment tools as well as valid diagnostic and prognostic biomarkers.³³ Targeted exploration of pathogenic autoantibodies and

inflammatory mediators leading to NPSLE coupled with longitudinal structural and functional imaging in tandem with prospective neuropsychological assessment of lupus patients are obviously paramount. Additionally, non-invasive assessment of the integrity of the BBB and its associations with neuropsychiatric symptoms and serum autoantibodies will shed more light on the pathophysiology of NPSLE.

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Causes and Features of Erythroderma

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Abstract

Introduction: Erythroderma is a generalised inflammatory reaction of the skin secondary to a variety of causes. This retrospective study aims to characterise the features of erythroderma and identify the associated causes of this condition in our population. **Materials and Methods:** We reviewed the clinical, laboratory, histological and other disease-specific investigations of 225 inpatients and outpatients with erythroderma over a 7.5-year period between January 2005 and June 2012. **Results:** The most common causative factors were underlying dermatoses (68.9%), idiopathic causes (14.2%), drug reactions (10.7%), and malignancies (4.0%). When drugs and underlying dermatoses were excluded, malignancy-associated cases constituted 19.6% of the cases. Fifty-five percent of malignancies were solid-organ malignancies, which is much higher than those previously reported (0.0% to 25%). Endogenous eczema was the most common dermatoses (69.0%), while traditional medications (20.8%) and anti-tuberculous medications (16.7%) were commonly implicated drugs. In patients with cutaneous T-cell lymphoma (CTCL), skin biopsy was suggestive or diagnostic in all cases. A total of 52.4% of patients with drug-related erythroderma had eosinophilia on skin biopsy. Electrolyte abnormalities and renal impairment were seen in 26.2% and 16.9% of patients respectively. Relapse rate at 1-year was 17.8%, with no associated mortality. **Conclusion:** Our study highlights the significant proportion of malignancy-related erythroderma in those whom common underlying causes such as dermatoses and drugs have been excluded. In cases of drug-related erythroderma, traditional medications and antituberculous medications are common causes in our population. Renal impairment and electrolyte abnormalities are commonly seen and should be monitored in patients with erythroderma.

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Key words: Cancer, Exfoliative, Malignancy

Introduction

Erythroderma is a dermatological reaction characterised by extensive erythema and scaling of the skin secondary to a variety of causes. An improved understanding of the characteristics and aetiologies of this condition will guide management. In this retrospective study, we aim to describe the characteristics and explore the associated causes of the condition in our population.

Materials and Methods

The profile of all inpatients and outpatients with erythroderma who visited the National Skin Centre (NSC),

during a 7.5-year period from 1 January 2005 through 30 June 2012 was retrospectively analysed. Erythroderma was defined clinically as erythema and scaling involving more than 90% of the body surface. The data collected included patient demographics, drug history, past medical and dermatological history, clinical findings (skin erythema, scaling, mucosal or nail involvement, lymphadenopathy, organomegaly, pedal oedema, pruritus, fever or chills), laboratory investigations (haematologic parameters, serum electrolytes, liver and renal function, albumin and inflammatory markers), skin biopsies, cultures and other disease-specific investigations (such as imaging and bone marrow examination). The disease course was analysed, with a follow-up period of 0 to 7.5 years.

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Results

There were 225 patients diagnosed with erythroderma during the study period. The mean age of the patients was 66.0 years (range, 1 month to 95 years), median 70 years, with a male-to-female ratio of 3:1. Majority were Chinese (78.0%), followed by Malays (15.0%), Indians (3.5%) and other ethnic groups (3.5%).

The most common clinical presentations were generalised erythema (100.0%), scaling (92.4%) and pruritus (92.0%). Lymphadenopathy (32.9%), chills (24.0%) and pedal oedema (19.6%) were common, while fever (4%), nail (3.5%), mucosal involvement (2.0%) and organomegaly (1.0%) were uncommon (Table 1).

Eosinophilia (58.2%), hypoalbuminemia (45.3%), electrolyte abnormalities (26.2%) and renal impairment (16.9%) were common laboratory findings. Skin or wound cultures were done in 24.4% of the patients, in whom 92.7% (51/55) had positive cultures results, with methicillin-sensitive *Staphylococcus aureus* (MRSA) being the most frequent organism isolated (64.7%, 33/51). In patients with positive skin or wound cultures, 17.6% (9/51) had associated raised inflammatory markers (total white cell count and C-reactive protein (CRP)), 35.3% (18/51) had thermoregulation (fever or chills) and 5.9% (3/51) had bacteraemia. Bacteraemia occurred in 15.9% (7/44) of those tested.

Serum tumour markers were measured as part of the malignancy workup in 60.0% (135/225) of the patients. These included alpha-fetoprotein (AFP), carcinoembryonic antigen (CA), prostate-specific antigen (PSA) (in males), CA 19-9 and CA 125 (in females). At least 1 of these markers were abnormal in 35.6% of these patients (48/135). However, there was no associated malignancy when further investigated in these cases, except for 1 patient with raised AFP and underlying hepatocellular carcinoma (HCC).

Skin biopsy was performed in 76.0% of the patients. The most common histological findings were subacute or chronic dermatitis (35.1%), followed by psoriasiform dermatitis (29.3%). In the biopsy specimens of patients with drug-related erythroderma, 52.4% had findings of eosinophilia, 4.8% showed interface dermatitis, and 4.8% had both of these features. In all the 4 patients with cutaneous malignancies, histological analysis was suggestive or diagnostic of cutaneous T-cell lymphoma (CTCL).

The aetiology of erythroderma can be classified into 4 main categories (Table 2). The most common causative factors were pre-existing dermatoses (68.9%, 155/225), idiopathic causes (14.2%, 32/225), drug reactions (10.7%, 24/225), and malignancies (4.0%, 9/225). Among the pre-existing dermatoses, endogenous eczema was most common (69%, 107/155), followed by psoriasis (20.6%, 32/155). The most commonly implicated drugs were traditional medications (20.8%, 5/24) and antituberculous medications (16.7%, 4/24). Other implicated agents include penicillin, omeprazole, Keppra®, thiazides, calcium channel blockers and Irressa®.

Forty-five percent (4/9) of the malignancies were primary cutaneous malignancies, consisting of mycosis fungoides (3/4) and Sezary syndrome (1/4), while 55.0% (5/9) were solid-organ malignancies, with 2 cases of hepatocellular carcinoma, 1 case each of nasopharyngeal, colorectal and non-small cell lung carcinoma. Four out of 5 cases of solid-organ malignancies were diagnosed after the onset of erythroderma as part of the malignancy evaluation, while 1 patient had pre-existing HCC. The initial findings of colorectal, lung and HCC were seen on computed tomographic scans, while nasopharyngeal carcinoma (NPC) was seen on nasoendoscopy.

In the treatment of erythroderma, 48.9% of the patients received antibiotics, 42.2% received systemic steroids and

Table 1. Clinical Features of Erythroderma

Clinical Feature	Wong KS et al, 1988 ⁶ (%)	Pal and Haroon, 1998 ¹ (%)	Akhyani et al, 2005 ⁵ (%)	Li J et al, 2012 ⁹ (%)	Present Study (% Out of 225 Patients)
Erythema	100.0	100.0	100.0	100.0	100.0
Scaling	100.0	84.4	100.0	100.0	92.4
Pruritus	NA	86.0	97.5	87.7	92.0
Lymphadenopathy	22.0	55.5	21.3	19.2	32.9
Chills	NA	64.4	NA	31.1	24.0
Pedal oedema	44.0	44.4	14.4	37.7	19.6
Fever	12.0	40.0	33.6	40.0	4.0
Nail involvement	NA	80.0	NA	29.6	3.5
Mucosal involvement	NA	36.6	1.0	NA	2.0
Organomegaly	9.0	25.5	4.0	NA	1.0

NA: Not available

8.4% required other types of systemic agents, including dapsone, ciclosporin, methotrexate (MTX), azathioprine, acitretin and interferon-alpha (used in Sezary syndrome). The outcomes of the patients were fairly good with no deaths directly related to the condition. Relapse rate at 1-year was 17.8%, most commonly in patients with underlying endogenous eczema.

Discussion

In our study, patients presented at an older age, with mean age of onset at 66.0 years. This is older than figures quoted in other studies, which ranged from 41.6 to 61.0 years.¹⁻⁴ There were 3 times more males in our study, in concordance with other studies.^{1,2,5-7}

The prevalence of most clinical features, including erythema, scaling, pruritus, lymphadenopathy, oedema, chills, organomegaly and mucosal and nail involvement, were similar to other studies.^{1,5} However, the prevalence of fever (4.0%) among our patients was much lower compared to other studies (33.0% to 37.8%).^{3,5,8}

Laboratory investigations showed renal impairment in 16.9% of our patients, likely secondary to dehydration from fluid losses and poor oral intake during severe acute illness. In contrast, although King et al⁸ and Yuan et al³ reported multiple other laboratory abnormalities, renal impairment was not reported. Skin or wound cultures were positive in 92.7% of the patients tested; however, only 17.6% of these patients had associated raised inflammatory markers and 5.9% associated bacteremia. Hence, the routine use of systemic antibiotics in patients with positive skin or wound cultures is not recommended, as these may represent skin commensals.

In patients with pre-existing dermatoses that is poorly controlled, erythroderma may occur during a flare of the skin disease.^{1,3,5,9} In such cases, the diagnosis is usually obvious. Otherwise, erythroderma remains a diagnostic challenge which often entails a thorough drug history and malignancy screening. In the latter, there is no consensus of when to initiate and what investigations to conduct. In a significant number of cases, despite extensive investigations, no cause was found and these were designated to have an idiopathic aetiology.

The various categorical causes of erythroderma in our study appear similar in frequency compared to previous studies (Table 3). Although malignancies were the cause of erythroderma in only 4.0% of our patients, from a practical point of view, they constituted 19.6% of the cases when drugs and underlying dermatoses were excluded. As such, an active search for an associated malignancy should be carried out in such cases. The frequency of malignancies in our study population was comparable to other studies (1.0% to 11.3%),^{3,5,9,10} comprising of both solid-organ and cutaneous malignancies. The higher incidence of HCC associated with erythroderma might be accounted for by the prevalence of this cancer in Asia, largely due to the ubiquity of hepatitis B infection in this part of the world.¹¹

In patients diagnosed with malignancy in our series, all had normal levels of serum tumour markers except for 1 patient with HCC. On the other hand, the tumour markers were abnormal in 35.6% of the patients in whom the levels were measured, and 99.3% of them did not have an underlying

Table 2. Aetiologies of Erythroderma

Cause	Percentage (%) Out of 225 Patients
Underlying dermatoses	68.9
Endogenous eczema	47.6
Psoriasis	14.2
Others*	7.1
Idiopathic	14.2
Drugs	10.7
Malignancy	4.0
Cutaneous	1.8
Solid organ†	2.2
Others‡	2.2

*Includes acquired ichthyosis, chronic actinic dermatoses, pityriasis rubra pilaris, seborrheic dermatitis, bullous pemphigoid, pemphigus foliaceus and actinic keratosis.

†Includes 2 cases of hepatocellular carcinoma and 1 case of colorectal carcinoma, nasopharyngeal carcinoma and non-small cell lung carcinoma each.

‡Includes contact dermatitis, papuloerythroderma of Ofuji and erythema toxicum neonatorum.

Table 3. Categorical Aetiologies of Erythroderma in Previous Publications and the Present Study

Aetiologies	Relative Incidence (%)					
	Wong KS et al 1988 ⁶	Pal and Haroon 1998 ¹	Akhyani et al 2005 ⁵	Yuan XY et al 2010 ³	Li J et al 2012 ⁹	Present Study 2012
Underlying dermatoses	57.0	74.4	57.9	72.0	70.8	68.9
Drug reactions	13.0	5.5	21.6	17.0	12.7	10.7
Malignancies	0.0	5.5	11.3	4.9	2.3	4.0
Idiopathic	29.0	14.6	7.2	6.1	14.2	14.2

malignancy. Hence tumour markers are not useful as a screening tool for malignancy. The workup in such patients should instead rely on imaging and endoscopies, guided by clinical findings. Features previously noted to be suggestive of an underlying malignancy include combinations of presence of systemic symptoms, an insidious onset, lack of a pre-existing dermatosis and resistance to standard treatment.¹²

In drug-induced erythroderma, skin biopsies revealed eosinophilia in 52.4% of our patients compared to 16.6% in the study by King et al.⁸ Skin biopsy was also effective in the diagnosis of primary cutaneous malignancies in all 4 of our patients, with 3 or fewer biopsies required per patient for the diagnosis to be made.

In the literature, common drugs implicated in erythroderma include antiepileptics (such as phenobarbitone, carbamazepine, and phenytoin), antibiotics (such as penicillin, sulphonamides and antituberculous drugs), gold, lithium salts and allopurinol.^{4,5,12,13} The major causative drugs vary between studies, and appear to correlate with regional endemic diseases and cultural norms.^{3,9} In our study, antituberculosis medications including isoniazid and rifampicin, as well as traditional Chinese medicine were the most common causative drugs. This may be due to the higher prevalence of tuberculosis in Southeast Asia, and the relatively widespread use of traditional Chinese medicine in Singapore.

In contrast to some earlier studies that have quoted high mortality rates mainly attributed to drugs or lymphoma (11.0% to 64.0%),^{8,14-16} there was no mortality arising directly from erythroderma in our study population. Some other studies had also quoted low mortality rates in the range of 0.0% to 2.0%.^{5,9,17}

Conclusion

Erythroderma is commonly caused by pre-existing dermatoses and drugs. A thorough drug history should be taken including traditional medications and supplements, and if present, eosinophilia seen on skin biopsy supports a drug aetiology. However, when these have been excluded, an associated malignancy is present in a significant proportion of cases and should be actively screened for. With similar frequencies of both cutaneous and solid organ malignancies, malignancy screen should include both cutaneous and solid organ malignancies. Renal impairment and electrolyte abnormalities are commonly seen and should be monitored in patients with erythroderma.

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Hydrosurgery is Effective for Debridement of Diabetic Foot Wounds

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Abstract

Introduction: Diabetic foot wounds are serious complications of diabetes mellitus. Surgical debridement is a very important part of the management of diabetic wounds. Sharp debridement using the scalpel is normally performed. Versajet II hydrosurgery system is an alternative technique for debridement. To our knowledge, this is the first study conducted to evaluate the use of hydrosurgery debridement for diabetic foot wounds. **Materials and Methods:** This pilot study included 15 consecutive patients with diabetic foot wounds who were admitted to the National University Hospital (NUH) and were managed by the Diabetic Foot Team from June 2012 to December 2012. All wounds underwent hydrosurgery debridement. Patients' demographic details, clinical details on wound assessments, and outcome were recorded and analysed. **Results:** The Versajet II hydrosurgery system was found to show some advantages over standard surgical scalpel debridement. It allowed adequate debridement whilst preserving more viable tissue to promote rapid healing. It could be manoeuvred over complex wound terrain. The time required for debridement was short — an average of 9.5 minutes. Good wound healing was achieved in all 15 cases. Only 1 Versajet debridement was required in 13 cases and 2 required an extra debridement. Twelve wounds were healed by split thickness skin grafting (STSG) and 3 wounds by secondary healing. Two of the STSG were infected but they were subsequently healed by dressings via secondary healing. **Conclusion:** Although good wound healing was achieved in all 15 cases, further study that uses a larger cohort and a randomised controlled trial is required to fully evaluate the effectiveness, or otherwise, of the Versajet II hydrosurgery system for the debridement of diabetic foot wounds.

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Key words: Infective wounds, Versajet, Wound healing

Introduction

The prevalence of diabetes mellitus in Singapore is increasing. It was at its highest of 11.3% in the latest National Health Survey 2010 compared to 8.2% in 2004.¹ Diabetic foot wounds are serious complications of diabetes mellitus and can lead to limb loss if left untreated. Diabetics have a 10% to 25% lifetime risks of developing foot ulcers.² Neuropathy, poor circulation and injury contribute to the formation of diabetic foot ulcers and 85% of lower extremity amputations are preceded by diabetic foot ulcers.³ Nather et al found the incidence of major amputations (above and below knee) to be 27.2% for diabetics with foot complications.⁴

The commonest procedure performed for diabetic

foot surgery is surgical debridement. Debridement is the excision of necrotic, devitalised or infected tissue from a wound, leaving healthy and vascularised tissue behind. It is an essential part of wound care prior to wound healing. Sharp surgical debridement makes use of the scalpel to cut necrotic, devitalised or infected tissue from a wound.

Surgical debridement should cause only minimal damage to surrounding tissues. The preservation of viable tissue while removing necrotic tissue and slough allows wound healing to occur rapidly. Hydrosurgery debridement is a different modality described in many wound care literatures. It is used for wound bed preparation.⁵⁻¹² It enables the surgeon

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to simultaneously hold, cut and remove nonviable tissue precisely without collateral damage to healthy surrounding tissue, allowing the healing process to progress quickly.¹³ In our literature review, there are many studies that utilise hydrosurgery debridement in their wound debridement and wound bed preparation but majority of these studies reported on burn wounds, traumatic wounds like open fractures and degloving wounds, plastic surgery reconstructive wounds and chronic vascular leg ulcers.^{5-9,11,12} There are very few studies that report the usage of hydrosurgery debridement in diabetic foot wounds.^{9,11,12} Vanwijck et al in 2010 studied 167 subacute and chronic wounds using hydrosurgery debridement and only 12 of them were diabetic foot wounds.¹¹ Caputo et al in 2008 performed a prospective randomised trial comparing hydrosurgery debridement versus standard scalpel debridement in lower extremity ulcers but only had 22 diabetic foot ulcers out of 41 ulcers.¹²

To our knowledge, this is the first study that aims to report our pilot experience in using the Versajet II hydrosurgery system¹³ in the debridement of diabetic foot wounds.

Materials and Methods

This is a prospective pilot study of 15 consecutive patients treated for diabetic foot from June 2012 to December 2012. The indications for the Versajet included ray amputation wounds, wounds postdrainage for abscess, shin ulcers, and wounds postexcision of metatarsal bones. These wounds were graded according to Wagner's classification.¹⁴

Pertinent data on patients' demographics, diabetic history and control, American Society of Anaesthesiologist (ASA) grading,¹⁵ clinical assessments, operative details and complications were recorded. Peripheral neuropathy was assessed using Semmes-Weinstein 5.07/10 g monofilament test (touch/pressure) and the ability to detect 7 or less sites out of 10 sites indicated presence of peripheral neuropathy.¹⁶ Vibration perception was evaluated using the biothesiometer (Bio-Medical Instrument Company, Ohio, USA). Vascular assessment using ankle-brachial index (ABI) and toe-brachial index (TBI) were performed for each patient. Ulcer description and location were recorded. All wounds had a swab culture and sensitivity performed prior to treatment. Other parameters captured include inflammatory markers such as leukocyte count and C-reactive protein (CRP).

The Versajet was used in all 15 patients. It consisted of a disposable handpiece, power console with foot pedal activation and a waste bin. It projected a high velocity stream of sterile saline across the operating window and into the evacuation collector. This created a localised vacuum to hold and cut targeted tissue while aspirating debris from the operation site. The handpiece was held such that the waterjet was parallel to the wound so that tangential excision can be achieved. This allowed rapid removal of damaged

devitalised tissues while preserving the surrounding viable tissues. There are 2 types of handpiece available for the operator to use depending on wound type and treatment strategy. The operator can regulate the waterjet velocity using the 10 power settings that are available and visualised on the power console.

All surgeries were performed by the senior author. General or regional anaesthesia was employed. After debridement, tulle gras and Kaltostat dressings were applied. Subsequently, wound inspections were performed on postoperative day 2 and wound dressings were done using Mepilex Ag. Regular wound dressings were performed for those wounds left for secondary granulation until healing had occurred. Patients who underwent split thickness skin grafting (STSG) had a negative pressure dressing applied and the wound was inspected only on postoperative day 5 to review the state of the STSG. Following that, non-adherent dressings using Mepilex Ag were used to dress the recipient site while the donor site was dressed with tulle gras and gauze dressings.

Results

In our study, the average age of our study population was 54.5 years (range, 41 to 71 years). There were 7 males and 8 females. Our patients were followed up for an average of 10 months (range, 6 to 12 months). Majority of them were ASA grade 3 (10/15; 67%). The average glycated haemoglobin (HbA1c) reading was 9.7% (range, 6.4% to 16%). Five of the patients had severe peripheral neuropathy with zero score in the Semmes-Weinstein 5.07/10 g monofilament test and severely diminished vibration perception as indicated by the biothesiometer (Bio-Medical Instrument Company, Ohio, USA). Six patients had spinal anaesthesia, 5 patients had general anaesthesia and 4 patients underwent ankle block during the surgery. Patient demographics, operative details, diabetes control and infective markers are shown in Table 1.

There were 4 patients with shin ulcers, 5 cases for ray amputation wound, 2 cases for excision of metatarsal wound and 2 cases with wound on dorsum of foot. One patient had a wound over the plantar aspect of 5th metatarsal head from drainage of abscess while another had a wound over the base of the 5th metatarsal. These wounds were categorised according to Wagner's classification (Table 2). All the wounds were infected and the organisms cultured from the wounds were tabulated (Table 2).

An average time of 9.5 minutes (range, 5 to 20 minutes) were used for a single Versajet debridement (Table 2). Thirteen patients had a single Versajet debridement prior to wound healing while 2 patients had an additional debridement. STSG was performed in 12 patients. The graft healed successfully in 10 cases. However, in 2 patients the grafts became infected and was subsequently left to granulate with regular local dressings. The remaining 3 patients had

Table 1. Patient Demographics, Wound Site, Diabetes Control and Infective Markers

No.	Age	Gender	Wound Site	Wagner Grading	Hba1c	ABI	TBI	Infective Markers		Semmes-Weinstein 5.07/10 g Monofilament	Biothesiometer (Volts)
								WBC	CRP		
1	66	Female	Ulcer dorsum of foot	2	7.2%	1.08	0.72	12.8	342	10/10	25
2	45	Female	Wound post 5 th ray amputation	3	11.3%	1.31	0.93	10.1	18	0/9	50
3	49	Female	Ulcer shin	2	11.9%	1.23	0.62	12.1	236	5/10	22
4	48	Male	Wound post excision of 4 th and 5 th metatarsal bones	3	7.0%	1.07	0.46	8.8	22	0/10	>50
5	51	Female	Ulcer shin	2	6.4%	0.67	0.22	11.7	49	0/10	>50
6	47	Female	Wound post excision of 5 th metatarsal bone	3	7.4%	0.76	0.72	8.5	18	0/10	>50
7	49	Male	Ulcer shin	2	9.9%	1.13	0.71	6.9	17	2/10	25
8	60	Male	Wound over plantar aspect of 5 th metatarsal head	3	7.0%	1.03	0.78	7.2	34	0/10	45
9	71	Female	Wound post 1 st ray amputation	3	9.9%	0.82	0.68	22.6	206	3/9	>50
10	41	Male	Abscess dorsum of foot	2	11.1%	1.05	0.91	8.8	206	7/10	20
11	66	Female	Wound over 5 th metatarsal base	3	7.8%	0.9	1.0	7.0	16	0/10	>50
12	54	Male	Wound post 2 nd and 3 rd ray amputation	4	14.6%	1.18	0.75	25.4	133	5/7	49
13	51	Male	Wound post 5 th ray amputation	4	9.1%	2.04	0.59	8.0	88	1/10	50
14	55	Male	Wound post 5 th ray amputation	3	9.6%	1.15	0.48	7.3	73	5/10	40
15	65	Female	Ulcer shin	2	>16%	0.9	0.82	11.4	48	10/10	40

ABI: Ankle-brachial index; CRP: C-reactive protein; Hba1c: Glycated haemoglobin; TBI: Toe-brachial index; WBC: White blood cell

Table 2. Wound Culture, Versajet Debridement Details and Final Outcome

No.	ASA	Mode of Anaesthesia	Wound Swab Culture	Number of Procedures Performed Before Versajet	Number of Versajet Debridements	Duration (Minutes)	Final Outcome
1	2	Spinal	<i>Pseudomonas Aeruginosa</i> , <i>Arcanobacterium sp</i>	1	1	16	STSG
2	3	Spinal	<i>Streptococcus Agalactiae</i>	1	1	5	STSG
3	3	Spinal	<i>Streptococcus Pyogenes</i>	2	1	5	STSG
4	3	Ankle block	MRSA, <i>Pseudomonas Aeruginosa</i> , <i>Acinetobacter Baumannii</i>	3	2	11, 8	Secondary healing
5	3	Spinal	<i>Klebsiella Pneumoniae</i> , <i>Citrobacter Koseri</i> , <i>Morganella Morganii</i>	2	2	6, 5	STSG infected – left to granulate
6	3	Ankle block	<i>Escherichia Coli</i> , MRSA	3	1	12	STSG infected – left to granulate
7	2	GA	<i>Pseudomonas Aeruginosa</i> , <i>Stenotrophomonas Maltophilia</i>	2	1	8	STSG
8	2	GA	<i>Serratia Marcescens</i>	1	1	7	Secondary healing
9	3	Ankle block	<i>Streptococcus Agalactiae</i> , <i>Staphylococcus Aureus</i>	1	1	5	STSG
10	2	GA	<i>Streptococcus Agalactiae</i>	1	1	9	STSG
11	3	Spinal	<i>Streptococcus Agalactiae</i>	1	1	20	STSG
12	3	Ankle block	<i>Pseudomonas Aeruginosa</i> , <i>Klebsiella pneumoniae</i> , <i>Escherichia coli</i>	1	1	12	STSG
13	3	GA	<i>Pseudomonas Aeruginosa</i> , <i>Escherichiacoli</i> , <i>Enterococcus faecalis</i> , <i>Prevotella spp</i>	2	1	11	STSG
14	3	GA	<i>Morganella morganii</i>	1	1	8	Secondary healing
15	2	Spinal	<i>Klebsiella pneumonia</i>	0	1	7	STSG

ASA: American Society of Anaesthesiologist; GA: General anaesthesia; MRSA: Methicillin resistant *Staphylococcus Aureus*; STSG: Split thickness skin graft

regular wound dressings done to allow secondary wound granulation and healing (Table 2). Both the 2 cases that failed STSG were found to have poor vascular supply based on their respective ABI (0.67; 0.76) and TBI (0.22; 0.72) findings. These 2 cases also had severe peripheral neuropathy as shown by the monofilament test and biothesiometer.

Discussion

Treatment of diabetic foot ulcer continues to be a challenge to healthcare professionals. There are many factors affecting wound healing in a diabetic patient and it is of great importance that the wound heals quickly to minimise risk of secondary infection and subsequent amputation. One vital aspect in the management of diabetic foot ulcer is the surgical debridement. The Versajet II hydrosurgery system is a useful tool for the management of diabetic wounds. It has been described in several articles for wound management.⁵⁻¹² However, there is lack of data on its use in the treatment of diabetic foot ulcers.^{9,11,12} To our knowledge, this is the first study conducted to evaluate its effectiveness in the treatment of diabetic foot wounds.

Mosti et al in 2005 reported that 46 out of 68 (67.6%) patients who underwent the Versajet debridement required only 1 operative procedure to achieve an adequately debrided wound bed for split-skin grafting.⁹ Granick et al in 2006 showed that the Versajet helped to reduce the number of debridements required to adequately prepare the wound bed for closure.¹⁰ Similarly, we found that in our study population, 13 out of 15 patients required only one hydrosurgery debridement with Versajet while 2 patients required additional debridements prior to wound healing. A limitation of our study was to compare the results of Versajet debridement with surgical debridement using the scalpel as a control. Nevertheless, the majority of our patients only required one debridement using the Versajet to adequately prepare wound bed for eventual healing be it for secondary healing or STSG. Ten of our patients achieved complete wound healing after one debridement. The wounds were then ready for STSG similar to findings by Vanwijck et al.¹¹ In 2 patients, the split skin grafts were infected but proceeded to secondary healing with regular local dressings.

Caputo et al reported in a prospective randomised trial that hydrosurgery using the Versajet resulted in shorter debridement time without compromising wound healing.¹² In our study, the average time per procedure performed was also short; an average of 9.5 minutes (ranging from 5 to 20 minutes). The reduction in surgical time was significant as most of our patients were of ASA grade 3. A shorter anaesthetic time would be better for them. Versajet debridement could also be performed under regional anaesthesia. Four of our patients underwent Versajet

debridement under ankle block and 6 of them had spinal anaesthesia. In our experience, this waterjet debridement could also be performed under local anaesthesia. In the latter, a power setting of 5 and below was preferred.

The Versajet II hydrosurgery system was found to give good control of excisional depth in debridement. This is particularly useful in wounds with exposed neurovascular bundles and tendons. Case study 1 demonstrated the usefulness of Versajet debridement for large wound over the dorsum of foot extending from medial to lateral border of the foot and ankle. The handpiece (tip angle of 45° or 15°; working end of 8 or 14 mm in length) allowed easy navigation over the wound without having to turn the patient in multiple positions. The patient was positioned supine (Fig. 1). Case study 4 demonstrated a deep, complex, contoured wound over the lateral foot resulting from an excision of the fourth and fifth metatarsal bone. There was a deep cavity with irregular edge and surface despite performing repeated sharp debridement with a knife. The Versajet was found to be good for wound bed preparation in this complex contoured wound without further alteration of its contour and preserved more viable tissue to encourage healing (Fig. 2).



Fig. 1. 1A and 1B show a left foot dorsum ulcer while 1C and 1D show the clean and smooth surfaced wound post Versajet debridement. 1E to 1F demonstrate the successful reconstructive surgery with split thickness skin graft.



Fig. 2. 2A and 2B show the wound post excision of 4th and 5th metatarsal bones with a resultant deep cavity and irregular wound surface and edges. 2C shows the smooth surface and wound edges after Versajet debridement. 2D to 2F show the wound contraction and secondary healing via regular local dressings.

Conclusion

In this pilot study, we found that the Versajet II hydrosurgery system showed some advantages over standard surgical scalpel debridement. It allowed adequate debridement of the diabetic foot wounds without much collateral damage which can occur with standard scalpel debridement. It preserved more viable tissue to promote rapid healing. We were able to manoeuvre the hand piece over deep and complex wound terrain without much difficulty to achieve a smoother and less irregular wound surface suitable to receive STSG. The time required for surgical debridement was shorter.

However, further studies that use a larger cohort and a randomised controlled trial are required in order to fully evaluate the effectiveness, or otherwise, of the Versajet for debridement of diabetic foot wounds.

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Singapore Chapter of Rheumatologists Consensus Statement on the Eligibility for Government Subsidy of Biologic Disease Modifying Antirheumatic Agents for Treatment of Rheumatoid Arthritis (RA)

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Abstract

Introduction: Up to 30% of patients with rheumatoid arthritis (RA) respond inadequately to conventional non-biologic disease modifying antirheumatic drugs (nbDMARDs), and may benefit from therapy with biologic DMARDs (bDMARDs). However, the high cost of bDMARDs limits their widespread use. The Chapter of Rheumatologists, College of Physicians, Academy of Medicine, Singapore aims to define clinical eligibility for government-assisted funding of bDMARDs for local RA patients. **Materials and Methods:** Evidence synthesis was performed by reviewing 7 published guidelines on use of biologics for RA. Using the modified RAND/UCLA Appropriateness Method (RAM), rheumatologists rated indications for therapies for different clinical scenarios. Points reflecting the output from the formal group consensus were used to formulate the practice recommendations. **Results:** Ten recommendations including diagnosis of RA, choice of disease activity measure, initiation and continuation of bDMARD and option of first and second-line therapies were formulated. The panellists agreed that a bDMARD is indicated if a patient has (1) active RA with a Disease Activity Score in 28 joints (DAS28) score of ≥ 3.2 , (2) a minimum of 6 swollen and tender joints, and (3) has failed a minimum of 2 nbDMARD combinations of adequate dose regimen for at least 3 months each. To qualify for continued biologic therapy, a patient must have (1) documentation of DAS28 every 3 months and (2) at least a European League Against Rheumatism (EULAR) moderate response by 6 months after commencement of therapy. **Conclusion:** The recommendations developed by a formal group consensus method may be useful for clinical practice and guiding funding decisions by relevant authorities in making bDMARDs usage accessible and equitable to eligible patients in Singapore.

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Key words: Drug therapy, Funding, Management, Practice Guidelines

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease affecting 0.3% to 0.8% of the population worldwide,¹ and is the most common inflammatory arthritis in Singapore.² Suboptimally treated RA may result in irreversible joint damage,^{3,4} serious extra-articular manifestations,⁵ and comorbidities including osteoporosis⁶ and cardiovascular disease,^{7,8} with substantial adverse impact on patients' health status, health-related quality of life, employment and financial status.⁹ Evidence, both locally and from other parts of Asia highlight the substantial disease burden of RA.¹⁰⁻¹³

It is well known that up to 30% of patients do not respond to traditional non-biologic disease modifying antirheumatic drugs (nbDMARD) such as methotrexate (MTX).¹⁴ Biologic disease modifying antirheumatic drugs (bDMARD) that target specific cytokines, immune cells and signalling pathways have broadened treatment options, with the overarching principle of achieving disease remission through "treating to target". Biologics such as tumour necrosis factor (TNF) inhibitors, anti-CD20 monoclonal antibodies (rituximab), interleukin (IL)-6 receptor

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antagonists (tocilizumab) and selective co-stimulation modulator of T-cells (abatacept) can achieve rapid control of disease activity, retard radiographic progression,¹⁵ reduce functional disability,¹⁶ and improve quality of life¹⁷, and are considered cost-effective from a societal perspective¹⁸ in nbDMARD inadequate responders.

However, the high cost of biological therapies restricts their widespread use. Government-assisted subsidies in developed countries and regions such as the United Kingdom, Europe, Canada and Australia have helped patients access bDMARDs with uptake around 13% for Western European countries.¹⁵ In Asia, countries such as Taiwan, Japan, Hong Kong and Korea have policies in place to financially support the use of bDMARDs in needy patients with active disease. Unfortunately, in Singapore, patients often bear the cost of bDMARD therapy. Due to cost constraints, treatment with a bDMARD is often delayed. The Singapore government initiated the Medication Assistance Fund (MAF) in August 2010¹⁹ to provide subsidies for expensive drugs deemed clinically necessary in eligible patients with various chronic diseases. This applies primarily to the public healthcare sector in Singapore. Most biologics are available in restructured hospitals as non-standard drugs and are not available in the Standard Drug List of subsidised medications. There are currently no consistent criteria among different institutions to guide funding decisions for these therapies for RA, which are often left to the individual physician's appeal and the discretion of each institution's authority. Furthermore, given that the national budget for drug subsidies are not unlimited, there is an urgent need to develop a set of systematic national guidelines for clinical eligibility for MAF funding for bDMARD in RA. With the objective of developing eligibility criteria for funding of bDMARDs for treatment of adult patients with RA, the Chapter of Rheumatologists, College of Physicians, Academy of Medicine, Singapore formulated a consensus statement by involving a representative group of practising rheumatologists from the public and private sector through formal consensus methodology.

Materials and Methods

A modified form of the Research and Development/University of California at Los Angeles (RAND/UCLA) Appropriateness Method (RAM)²⁰ was used in the development of our recommendations. In lieu of a systematic literature review, a core working group (CWG) (GGT, PPC, ML and JAC) reviewed established international guidelines and recommendations of rheumatology societies on biologic therapies for treatment of RA. The CWG then developed common clinical scenarios simulating those seen in clinical practice and convened a task force panel (TFP) comprising 9 locally recognised rheumatologists from

various restructured government and private hospitals in Singapore who rated each scenario for appropriateness of treatment. This method has been validated and used widely to develop practice guidelines and quality indicators.^{21,22}

Review of Established Guidelines

The CWG reviewed a total of 7 guidelines from the following established institutions: British Society of Rheumatology (BSR),²³ National Institute for Health and Clinical Excellence (NICE),²⁴ Australian Rheumatology Association (ARA),²⁵ Australian Medicare,¹⁸ American College of Rheumatology (ACR)^{26,27} and European League Against Rheumatism (EULAR)^{28,29} (Table 1).

Biologics considered are those registered in Singapore as of August 2012, i.e. abatacept, adalimumab, etanercept, golimumab, infliximab, rituximab and tocilizumab. However, we approached them in classes by mode of action rather than individually. Clinical scenarios were composed of clinical determinants when biologic therapies would be clinically necessary and appropriate for RA patients: 1) RA diagnosis, 2) threshold disease activity, 3) choice of disease activity measure and 4) failure of nbDMARD (duration, number of combinations, type of nbDMARD and mode of administration of MTX). We also included factors for consideration of continuation of biologic therapy: 1) frequency of documentation of disease activity and response, 2) timing of measurement of response and 3) definition of adequate response. We did not include safety and monitoring recommendations as they ought to be standard practice and are covered extensively by others. Other scenarios added after the first rating and face-to-face meeting included the use of subcutaneous MTX in case of inefficacy or gastrointestinal (GI) intolerance with oral administration.

Discussion was limited to patients who had an appropriate use of non-steroidal anti-inflammatory drugs (NSAIDs), systemic glucocorticoids and intra-articular glucocorticoid injections by the treating physician. Scenarios regarding poor prognostic markers were omitted as these are usually used to select MTX-naïve patients for bDMARD therapy, and we were unable to justify the use of limited funds for bDMARD in this group of patients.²⁷

Rating the Appropriateness of Clinical Scenarios by the TFP

For the first round of ratings, the TFP were contacted by email, provided with evidence synthesised from recent guidelines, clinical scenarios and rating instructions. Based on the literature synthesis and their clinical judgment, the TFP individually rated the "appropriateness" of the clinical scenarios using a 9-point Likert appropriateness scale. Disagreement regarding a specific scenario was defined when one-third or more of the panellists rated a scenario

Table 1. Guidelines Reviewed For Evidence Base and Development of Clinical Scenarios

Organisation	Year of Publication	Purpose of Study	Systematic Literature Review (Search End Date)	Appraisal of Evidence/Consensus Method
American College of Rheumatology ²⁷	2012	Best practice	Yes (February 2010)	RAM
American College of Rheumatology ²⁶	2008	Best practice	Yes (February 2007)	RAM
The British Society of Rheumatology (BSR) ²³	2010	Society considered standard of care	Yes (May 2009)	No formal consensus method
European League Against Rheumatism (EULAR) ²⁹	2010	Best practice	Yes (June 2009)	EULAR standard operating procedures for the development of guidelines
National Institute for Health and Clinical Excellence (NICE) ²⁴	2009	Criteria for government reimbursement	Yes (June 2008)	NICE methodology; NCC-CC quality assurance document and systematic review chart
Australian Rheumatology Association (ARA) ²⁵	2011	Society considered standard of care	Details not available	Details not available
Australian Medicare ¹⁸	Details not available (website last updated in May 2012, no listed issue date of documents)	Criteria for government reimbursement	Details not available	Details not available

RAM: RAND/UCLA Appropriateness Method; NCC-CC: National Collaborating Centre for Chronic Conditions

in the lowest 3 points of the appropriateness scale (ordinal scores 1, 2, or 3) and one-third or more of the panellists rated the same scenario in the highest 3 points (ordinal scores 7, 8, or 9). In the absence of disagreement, a median score of 7 to 9 indicated “appropriate”, 4 to 6 indicated “equivocal” while 1 to 3 indicated “not appropriate” for the option defined in the scenario. The dispersion of scores, ranges and median scores were collated. The TFP and the CWG met under the leadership of a moderator (KHL). The results of the first round of ratings were returned to the individual panellists, with summarised results displayed throughout the discussion.

The objectives of this exercise were emphasised. The TFP agreed upon certain definitions on which they based their discussion and subsequent ratings of the scenarios. In cases of disagreement or equivocal response, there was further discussion by panellists with clarification of definitions, ambiguity and rewording of scenarios. A second round of ratings of all the scenarios by the TFP was carried out by email after the face-to-face meeting.

Conversion of Clinical Scenarios to Consensus Statement

A consensus statement was drafted based on the final agreement of appropriateness. Generally, the recommendations included only positive statements; for example, the recommendations focused on when to implement specific therapies rather than when therapies should be avoided.

Results

A total of 9 panellists in the TFP rated the clinical scenarios twice. In the first round of ratings, there was disagreement among panellists with regards to the criteria for RA diagnosis, the number of minimum swollen and tender joints and whether a uniform disease measure should be used. Disagreements also arose regarding the criteria for continued biologic therapy in patients with active RA, namely, the frequency of the Disease Activity Score in 28 joints (DAS28) documentation, the definition of an adequate response and the time frame in which the response should be seen.

During the face-to-face meeting, it was found that the majority of disagreements could be attributed to varying assumptions and different interpretations of the clinical scenarios. Moreover, it was noted that some options were mutually exclusive and some were questions pertaining to thresholds. For example, some panel members rated as “appropriate” that a patient with active RA is considered suitable for biologic therapy if DAS28 ≥ 3.2 and if DAS28 > 5.1 as the threshold of ≥ 3.2 includes the latter category. In view of this, it was clarified that the TFP should choose the minimum threshold in the second round of voting.

In the second round, panellists rerated the amended clinical scenarios. The final consensus statement is in Table 2. These recommendations are ordered by a logical sequence or procedural and chronological hierarchy rather than by importance. Of the 7 guidelines reviewed, the NICE and Australian Medicare were published for the purpose of

Table 2. Final Consensus Statement on Initiation and Continuation of a Biologic DMARD for RA Requiring Government Subsidisation

Median Agreement Score of Clinical Scenarios on Likert Scale of 9* (Clinical Threshold or Option)	
Recommendations Relating to Initiation of bDMARD Therapy	
1. The patient must fulfil either the 1987 ACR or 2010 ACR/EULAR criteria for RA diagnosis.	9
2. Only one uniform disease activity measure should be used (eg. another disease activity measure or different DAS calculations are not interchangeable).	8.5†
3. The patient must have RA of at least moderate disease activity as measured by a DAS28 score ≥3.2 and a minimum of 6 swollen and tender joints.	8.5† (DAS28 ≥3.2) 7.5† (≥6 swollen and tender joints)
4. The patient must have failed a minimum of 2 combinations of nbDMARDs with each combination at optimal dose regimen for at least 3 months (unless contraindicated by documented significant toxicity). ³⁹	9 (2 combinations) 9 (3 months)
5. Optimal combination must include MTX at a dose of ≥20 mg/week (unless contraindicated by documented significant toxicity)‡ and any of the following: • HCQ (6.5 mg/kg) • HCQ + SSZ (≥2 g/d) • LEF (≥10 mg/d) • CSA (≥2 mg/kg/d) • SSZ (≥2 g/d)	9 (include MTX) 7 (dose ≥20 mg/week) 7.5† (HCQ) 9 (HCQ + SSZ) 9† (LEF) 8.5† (CSA) 8† (SSZ)
6. If oral MTX fails due to inefficacy or gastrointestinal intolerance, subcutaneous injection of MTX must be used, and the dose must be at least 20 mg/week. If MTX is contraindicated‡, the patient must have failed a minimum of any 2 combinations of the following nbDMARDs to be considered for biologic therapy: • HCQ (6.5 mg/kg) • LEF (≥10 mg/d) • CSA (≥2 mg/kg/d) • SSZ (≥2g/d) • Sodium aurothiomalate (50 mg/week)	7 (inefficacy); 9 (intolerance); 9 (minimum dose) 9 (2 combinations)
Recommendations Relating to Continuation of bDMARD Therapy	
7. All patients on bDMARD therapy must have DAS28 documented every 3 months. bDMARD therapy cannot be continued unless the patient has at least a EULAR moderate response by 6 months bDMARD commencement. If the patient does achieve EULAR moderate response criteria but disease activity remains moderate to high (i.e. DAS28 ≥3.2), it is the rheumatologist’s discretion to switch to alternative bDMARD.	9 (3 months) 8 (6th month) 8 (EULAR moderate response) 9 (rheumatologist’s discretion to switch)
Recommendations Relating to Options of bDMARD Therapy	
8. Anti-TNF agents should be the first-line bDMARD unless contraindicated. Anti-TNF should be given with in combination with MTX unless contraindicated.	9 (anti-TNF) 9 (in combination with MTX)
9. The least expensive drug should be prescribed taking into consideration patient’s unique characteristics and preferences.	9 (least expensive)
10. Second-line bDMARD treatment, in the event of primary or secondary non-response and adverse effects, may be an alternative anti-TNF or another class of bDMARD (abatacept, rituximab, tocilizumab), taking into consideration patient’s unique characteristics and is to be determined by the treating rheumatologist.	9

ACR: American College of Rheumatology; bDMARD: Biologic disease modifying antirheumatic drug; CSA: Cyclosporin A; DAS 28: Disease Activity Score in 28 joints; EULAR: European League Against Rheumatism; HCQ: Hydroxychloroquine; LEF: Leflunomide; MTX: Methotrexate; nbDMARD: Non-biological disease modifying antirheumatic drug; RA: Rheumatoid arthritis; SSZ: Sulfasalazine; TNF: Tumour necrosis factor

*Likert scale of 9 (where 1 = very inappropriate and 9 = very appropriate).

†Fewer than 9 responses were obtained.

‡Methotrexate toxicity criteria: refer to Appendix 1.

guiding government reimbursement and clearly spelt out absolute thresholds relating to initiation and continuation of bDMARD therapy. Therefore, these 2 guidelines were discussed in greater detail.

The EULAR, ACR, BSR and ARA guidelines are referenced whenever applicable, as they provide perspectives on the best practice and standard of care in developed nations. As these recommendations are meant for practising rheumatologists both in the locales where they are published and internationally, they were not prescriptive in terms of particular disease activity criteria, monitoring schedule or specific number/type of joint cutoffs.

Consensus 1: The patient must fulfil either the 1987 ACR or 2010 ACR/EULAR criteria for RA diagnosis.

The 1987 ACR criteria for the classification of RA were used to define active RA in most clinical trials of bDMARDs³⁰⁻³⁴ and are incorporated into most established clinical guidelines. Although they distinguish RA patients with established disease from other types of inflammatory arthritis,³⁵ they are insensitive in early RA. The 2010 ACR/EULAR criteria are a validated revised classification with an increased sensitivity in early RA, introduced due to the recognition that early aggressive therapeutic intervention improves clinical outcomes.³⁵ Although it is rare for patients to only meet the 2010 ACR/EULAR criteria and have failed traditional nbDMARD therapy, the TFP voted that patients could fulfil either criteria for RA diagnosis.

Consensus 2: Only one uniform disease activity measure should be used (e.g. another disease activity measure or different DAS calculations are not interchangeable).

Monitoring of RA disease activity entails measuring the overall state of joint and systemic inflammation as well as damage. There has been a concerted effort to develop composite measures for assessing disease activity and to define response and remission. Evidence-based recommendations require clear definitions of disease activity to make rational therapeutic choices. Although it is not possible to mandate the use of a single disease activity score for the individual physician, and different studies have used different definitions, the TFP agreed that it was preferable to have one uniform scale for administrative purposes in order to achieve consistency, as this set of criteria is meant for determining the eligibility for biologics subsidisation.

One validated composite measure for RA disease activity is DAS28, which is calculated by combining information on swollen and tender joint counts, the acute phase response and patient global assessment on a visual analogue scale (VAS). The DAS28³⁶ has been widely used in clinical trials, registries and guidelines, and is suitable for clinical practice

for monitoring RA disease activity.³⁷ Discussion by the TFP concluded that DAS28 was the most appropriate measure. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) results are obtainable within a 24-hour period of the patient's visit at most local institutions. Furthermore, the panel agreed that blood test results obtained within 4 weeks of the assessment date could be used. Computer software and DAS28 online websites can be used to calculate the DAS28 score quickly and easily.

Other measures of disease activity, such as Clinical Disease Activity Index (CDAI) or Routine Assessment of Patient Index Data 3 (RAPID3), are also quantitative and informative in busy clinic settings and do not require laboratory results. However, another reason for choosing DAS28 is because it is also embedded in the assessment of EULAR response criteria. It is prudent to have a consistent measure to facilitate the processes of subsidy application for initiation as well as continuation of biologics.

Consensus 3: The patient must have RA of at least moderate disease activity as measured by a DAS28 score ≥ 3.2 and a minimum of 6 swollen and tender joints.

Both the BSR²³ and ARA²⁵ advocate the use of DAS28 to determine eligibility, and to commence bDMARD in adult patients who have active RA as defined by DAS28 ≥ 3.2 with at least 3 or more tender and 3 or more swollen joints. There was disagreement among the panellists with the cut-off of DAS28 >5.1 set as the minimal criteria for initiation of biologics. Certainly, patients with high disease activity should be given priority to biologics therapy. The ACR guideline suggested incorporating any of the 5 common composite disease activity instruments, including DAS28, to measure disease activity but did not mandate uniform use of DAS28.²⁷

There are recognised limitations with DAS28, as it excludes involvement of the feet and ankles, and can be unduly affected by ESR and patient global scores. Clinical synovitis assessed by joint counts is a more objective marker of inflammation than patient global VAS. Therefore, the TFP agreed that patients should have a minimum of 6 swollen and tender joints, in addition to a moderate disease activity of DAS28 ≥ 3.2 (Table 3). The criterion of 6 affected joints was chosen as most biologic trials used this threshold as one of the inclusion criteria; furthermore, patients with multiple joints involvement are at greater risk for progressive joint damage.^{31,32,38} Patients with less than 6 swollen and tender joints might also benefit from biological treatment in order to preserve their quality of life and work ability. The TFP debated lower cut-offs of 4 or less joints, and concluded that disease activity criteria should be more stringent for MAF subsidies.

Table 3. European League Against Rheumatism (EULAR) Response Criteria⁶⁹

Baseline DAS28	DAS28 Improvement Over Time Points		
	>1.2	0.6-1.2	<0.6
Low disease activity <3.2	Good	Moderate	No
Moderate disease activity 3.2 – 5.1	Moderate	Moderate	No
High disease activity >5.1	Moderate	No	No

DAS28: Disease Activity Score in 28 joints

Adjunctive treatments such as joint injection, synovectomy and oral steroid requirement should be taken into account in the global assessment of the patient. The Australian Medicare guideline makes a distinction between major active joints (elbows, wrist, knee, ankle, shoulder and/or hip) and other joints. The TFP decided not to discriminate between the specific joints involved, due to lack of evidence.

*Consensus 4: The patient must have failed a minimum of 2 combinations of nbDMARDs with each combination at optimal dose for at least 3 months (unless contraindicated by documented significant toxicity).*³⁹

The current practice in restructured (government-linked) hospitals is for patients to be offered multiple available nbDMARD combinations, before an application for MAF subsidy is made and granted for bDMARD. Reasons for this include lack of uniform eligibility criteria between institutions, patients' reluctance in going through financial assessment as part of the application process, and concerns over adverse effects of bDMARDs. Nonetheless, there is evidence that about a third of patients with early RA do respond to an adequate trial of MTX⁴⁰ and combination nbDMARDs have a definite role in both early and established RA.^{41,42} It has been shown that in patients who fail traditional nbDMARDs, addition of bDMARD is significantly superior in controlling joint inflammation, retarding radiological progression and improving physical function in both early and long standing RA.⁴³⁻⁴⁵

The NICE guidelines recommend anti-TNF agents (adalimumab, etanercept, infliximab, golimumab and certolizumab-pegol) for highly active RA (DAS28 >5.1) after failing a trial of 2 nbDMARDs, including MTX. An adequate treatment of 1 nbDMARD constitutes 6 months therapy, with 2 months at standard dose²⁴ but whether combination or sequential regimen should be used was not stipulated. The Australian Medicare, however, subsidises bDMARD therapy after failure or intolerance of a 6-month intensive nbDMARD trial with a minimum of 2 nbDMARD either in combination or as sequential monotherapy for at least 3 months each.¹⁸ The EULAR recommendations are less strict in that only failure of 1 or 2 nbDMARDs are required but not necessarily in combination.²⁹

The TFP agreed that 3 months at optimal dose is appropriate based on the onset of action of most nbDMARDs; however the rate of dose escalation is at the discretion of the treating physician. The ACR guideline recommends initiation of biologic agents in nbDMARD-naïve, early RA patients with high disease activity and features of poor prognosis as supported by cost-effectiveness evaluations in the US populations.²⁶ In contrast, the NICE, BSR, Australian Medicare and EULAR guidelines all do not recommend initial biologic therapy in nbDMARD naïve patients.^{23, 24, 29} The EULAR recommends biological treatment after the first failed nbDMARD treatment in case of unfavourable prognostic factors.²⁹

Consensus 5: Optimal combination must include MTX at a dose of ≥ 20 mg/week (unless contraindicated by documented significant toxicity) and any of the following: HCQ (6.5 mg/kg), HCQ + SSZ (≥ 2 g/d), LEF (≥ 10 mg/d), CSA (≥ 2 mg/kg/d), or SSZ (≥ 2 g/d).

As with most international consensus guidelines, the TFP agreed that the optimal nbDMARDs combination should include MTX at a minimum dose of 20 mg/week (agreement score of 7), unless contraindicated by documented significant toxicity.³⁹ If the patient is not able to tolerate 20 mg/week, the highest tolerated dose is considered acceptable.

The NICE guidelines do not specify any preference for nbDMARDs, beyond recommending that MTX should be included. In contrast, the Australian Medicare detailed an algorithm that all patients must receive MTX alone or in combination therapy or sequential monotherapy with the following alternative nbDMARDs: hydroxychloroquine (HCQ) or leflunomide (LEF) or sulfasalazine (SSZ). If patients cannot take MTX at the minimum dose due to contraindication or intolerance, patients may receive any 2 of HCQ, LEF or SSZ. Rarely, where treatment with MTX, HCQ, LEF or SSZ is not possible at the minimum dose due to contraindication or intolerance, third-line therapy either with azathioprine, cyclosporin or sodium aurothiomalate monotherapy or in combination can be used.¹⁸

In this consensus, the TFP agreed that the optimal combination may include MTX with any of the following: HCQ 6.5 mg/kg, HCQ + SSZ (≥ 2 g/d), LEF (≥ 10 mg/d), CSA (2 mg/kg/d) or SSZ (≥ 2 g/d). There was not sufficient evidence to support the use of azathioprine or minocycline. These are the commonly available nbDMARDs used locally. The local rheumatologists favour the use of combinations of MTX with LEF or MTX with SSZ and HCQ and would generally try to optimise these regimens where possible before escalating treatment to biologics. Evidence suggests that MTX and SSZ combination is not more effective than MTX monotherapy.^{46,47} Nonetheless, TFP surmised that this combination can be tried as it may be efficacious for

certain patients and SSZ is a relatively affordable and well-tolerated drug. Some patients may not be able to tolerate or afford other options.

Consensus 6: If oral MTX fails due to inefficacy or gastrointestinal intolerance, subcutaneous injection of MTX should be used, and the dose should be at least 20 mg/week. If MTX is contraindicated, the patient must have failed a minimum of any 2 combinations of the following nbDMARDs to be considered for biologic therapy: HCQ (6.5 mg/kg), LEF (≥ 10 mg/d), CSA (≥ 2 mg/kg/d), SSZ (≥ 2 g/d) or sodium aurothiomalate (50 mg/week).

During the face-to-face meeting, the panel discussed the efficacy of parenteral MTX based on their expert opinion. Literature review was performed by the CWG and provided to the TFP who voted on the use of subcutaneous MTX at the second round. The subcutaneous form has increased bio-availability, better efficacy and similar tolerability compared to the oral form, and evidence indicates that subcutaneous administration is significantly more effective than oral administration of the same dose, with similar tolerability and fewer GI adverse effects.^{48,49} The TFP considered subcutaneous MTX as appropriate if there is inefficacy or GI intolerance to oral MTX. The dose of subcutaneous MTX should be at least 20 mg/week, if tolerated.

In case of contraindication to MTX, the TFP agreed that an adequate nbDMARD trial would constitute 2 combinations of the following nbDMARDs: HCQ (6.5 mg/kg), LEF (≥ 10 mg/d), CSA (≥ 2 mg/kg/d), SSZ (≥ 2 g/d) or sodium aurothiomalate (50 mg/week). Intramuscular sodium aurothiomalate was included as an option as it is still used in Singapore under special circumstances in patients who are refractory to other less toxic therapies.

Consensus 7: All patients on biologic therapy should have DAS28 documented every 3 months. bDMARD therapy may be continued if the patient has at least a EULAR moderate response by 6 months after commencement. If the patient does achieve EULAR moderate response criteria but disease activity remains moderate to high (i.e. DAS28 ≥ 3.2), it is at the rheumatologist's discretion to switch to alternative bDMARD.

In order to document objective clinical response, the CWG felt it was necessary to standardise disease monitoring during bDMARD therapy. By voting, the TFP agreed that DAS28 should be documented at least every 3 months, as it was a reasonable time frame for tracking the patients' progress. Monthly documentation would be ideal, but it is not practical in busy clinic settings, while semi-annual assessment is too long for the detection of trends.

Response to treatment should be determined by 6 months after commencement of biologic therapy. The BSR guideline

recommends that although the aim should be to achieve a EULAR good response whenever possible, a EULAR moderate response is adequate for continuation of the initial biologic therapy (Table 3).²³ Panellists concurred that while a EULAR good response is the goal, some patients with refractory disease and a very high baseline disease activity may not be able to achieve this, and a EULAR moderate response should be sufficient to justify continued funding of the therapy. If the patient does achieve EULAR moderate response criteria but disease activity remains moderate-high (i.e. DAS28 ≥ 3.2), the rheumatologist retains his/her discretion to switch to alternative bDMARDs.

Consensus 8: Anti-TNF agents should be the first-line bDMARD unless contraindicated. Anti-TNF should be given in combination with MTX unless contraindicated.

Of the biologic therapies, the use of anti-TNF agents are the most established in terms of clinical experience since the first anti-TNF, etanercept, was approved in 1998. Our TFP agreed that anti-TNF therapy should be offered as first-line biologic therapy unless contraindicated, in spite of evidence of efficacy of abatacept,⁵⁰ tocilizumab³⁴ and rituximab⁵¹ compared to MTX in MTX-inadequate responders. Though abatacept and tocilizumab are now approved as first-line biologic in other countries,^{52,53} our experts opined that the extensive long-term observational data with regards to anti-TNF safety justifies their use as first-line biologics. This recommendation may change in the future when longer-term data of other bDMARDs becomes available. In general, anti-TNF agents are more efficacious when given in combination with MTX compared to monotherapy.^{32,41,54,55}

Consensus 9: The least expensive drug should be prescribed taking into consideration the patient's unique characteristics and preferences.

The administration costs, required treatment dose and product price per dose should be weighed when choosing a bDMARD. As there are differences in the modes of administration and treatment schedules, patient preferences should also be taken into consideration. The TFP also opined that escalation of the dose of anti-TNF above the starting dose is not recommended.

Consensus 10: Second-line bDMARD treatment, in the event of primary or secondary non-response and adverse effects, may be an alternative anti-TNF or another class of bDMARD (abatacept, rituximab, tocilizumab), taking into consideration the patient's unique characteristics, and is to be determined by the treating rheumatologist.

In patients who have failed an initial anti-TNF therapy,

studies have shown that switching to a second alternative anti-TNF therapy can be efficacious.^{56,57} Abatacept, rituximab and tocilizumab may be used as alternatives. The NICE guidelines allows subsidy of tocilizumab as first-line, and abatacept after TNF failure.^{58,59} Abatacept, a T-cell costimulation inhibitor, is safe and effective for the treatment of established RA in patients who fail to respond or have a contraindication to anti-TNF agents.⁶⁰ Studies found that treatment with abatacept provided significant clinical benefits regardless of whether the initial TNF inhibitor was discontinued for primary failure or secondary loss of efficacy.^{61,62} Rituximab, a chimeric monoclonal antibody that acts by depleting B cells, was found to be effective for the management of RA patients who have failed one or more anti-TNF therapies.^{33,63} Tocilizumab with MTX is efficacious in patients with RA refractory to one or more anti-TNF therapies, and has a manageable safety profile.⁶⁴

Discussion

In summary, a consensus statement was derived methodically on the use of bDMARDs for RA patients who require financial assistance in Singapore. An eligible patient should have moderately to highly active RA with a DAS28 ≥ 3.2 plus a minimum of 6 swollen and tender joints, and have failed a minimum of 2 nbDMARD combination treatments lasting at least 3 months each. To qualify for continued therapy, all patients on biologic therapy must have DAS28 documented every 3 months and should demonstrate at least a EULAR moderate response in the sixth month after commencement. Switching to an alternative biologic agent may be done at the rheumatologist's discretion if DAS28 remains ≥ 3.2 . Eligible patients should be given anti-TNF therapies as first-line, in combination with MTX, unless both agents are or either agent is absolutely or relatively contraindicated. An alternative anti-TNF or bDMARD of another class (abatacept, rituximab, tocilizumab) may be used as second-line therapy, following inadequate response.

The consensus statement this study developed may be applied as a set of eligibility criteria to guide government funding agencies in identifying patients most likely to benefit from bDMARD therapies, thereby reducing the burden of RA from active disease and joint damage in Singapore. It is recognised that some patients who do not meet the criteria set forth in this consensus may also benefit from bDMARDs. However, given the limited financial resources, the recommendations prioritised patients with the most significant impairment from active RA for biologic therapy. In general, recommendations for therapeutic intervention are not meant to be used as strict protocols. They should be applied and individualised by the treating rheumatologist according to the patient's comorbidities, unique characteristics and preference.

A modified version of the (RAND/UCLA) Appropriateness Method²⁰ was used in the development of our statement. The consensus methodology used is rigorous in that it is a systematic approach to reaching agreement through evidence-based literature and expert opinion. The original method requires a systematic literature review to be conducted. However, as several established rheumatology societies have extensively reviewed the literature and have published recommendations, we presented a comprehensive review and synthesised the evidence from these established guidelines.^{18,23,25-27,29} A limitation of our evidence review is that the most recent literature may not have been included but we believe it was incorporated in the TFP discussions by expert opinion. In addition, the foreign guidelines took into account local socioeconomic and healthcare structures, which cannot be fully generalised to the Singapore context. However, as cost-effectiveness evaluations of individual bDMARDs are not available locally, a group consensus method such as RAM enables pragmatic considerations and experiences from expert opinion to be incorporated. In addition, the scenarios created by the CWG, who are also rheumatologists, captured a good spectrum of common locally encountered situations. The CWG and TFP had rheumatologists representing both public and private healthcare sectors of Singapore and all had special interest in the treatment of inflammatory arthritis. Although there is a global trend for increased patient participation by including patient representatives in consensus committees for RA guidelines,^{65,66} a patient representative was not included in our current study. However, future consensus statements may consider inclusion of a patient representative. Approximately 10% of the scenarios were left unanswered. On clarification by the CWG, 2 members of the TFP were unaware that a response was required for every option (e.g. if they decided that the first option was appropriate, they should indicate that the other options were inappropriate, but instead they left the other options blank). A sensitivity analysis with the missing responses did not change the results.

Most importantly, the agreement on the appropriateness of intervention for each clinical scenario was generally high, with median score of 9/9 for 15 of 25 items rated (several recommendations comprised multiple items). There were 2 scenarios that were contentious with the lowest median score of 7/9, although still within the defined range of agreement. Panellists were initially divided on whether the optimal MTX dose should be at least 25 mg/week or at least 20 mg/week before failure is documented. Consensus was reached that 20 mg/week is sufficient as the effective MTX dosing in the comparator arms of most clinical trials is approximately 20 mg/week.^{41,55} The second scenario with the lowest agreement score of 7 was the use of subcutaneous MTX, if oral MTX fails due to inefficacy. Consensus was

Table 4. Comparison of Reimbursement Guidelines for the Use of Biologic Agents in RA

	Singapore Chapter of Rheumatologists Proposed Criteria	Hong Kong Samaritan Fund	Korea Reimbursement Guideline	Taiwan ⁶⁸
Criteria for Initiation				
DAS 28	≥3.2	≥5.1	Not required	≥5.1
Number of tender and swollen joints	≥6	Not required	>20 joints or >4 large joints (elbow, wrist, ankle, knee, hip, shoulder)	Not required
Lab test	(as per DAS28)	(as per DAS28)	ESR >28 or CRP >2.0	
nbDMARD trial	At least 2 combination treatments lasting at least 3 months each	At least 4 nbDMARDs for at least 3 months each	More than 2 DMARDs for 6 months (at least 3 months per DMARD)	MTX plus at least one other DMARD (given for 6 months, with at least 2 months at standard dose)
Criteria for Continuation				
Measurement of response	EULAR moderate response	A reduction of DAS28 score by >1.2 compared to baseline or ≤3.2	ESR <28 or CRP <2.0 or 20% ESR, CRP improvement and 50% decrease in number of active joint count (equal to ACR 50 response)	Improvement of DAS28 of 1.2 points or more

ACR: American College of Rheumatology; CRP: C-reactive protein; DAS28: Disease Activity Score in 28 joints; DMARD: Disease modifying antirheumatic drug; EULAR: European League Against Rheumatism; ESR: Erythrocyte sedimentation rate; MTX: Methotrexate; nbDMARD: Non-biological disease modifying antirheumatic drug; TNF: Tumour necrosis factor

reached for all scenarios, except on whether the use of sodium aurothiomalate (gold) 50 mg/week in combination with MTX constitutes an adequate trial of nbDMARD in patients. As no consensus was reached, this was not included in the consensus statement.

While consensus recommendations on best practice have been developed⁶⁷ in parts of Asia, more pragmatic guidance for the purposes of individual government subsidisation are needed. Compared to reimbursement criteria from Taiwan,⁶⁸ Hong Kong and Korea (personal communications), the criteria proposed by our Chapter has some notable differences in criteria for initiation of bDMARD (Table 4). To our knowledge, most criteria proposed by other Asian countries were adapted from either the NICE or Australian Medicare guidelines without incorporating validated consensus methodology.

Conclusion

The recommendations are not to be used in a prescriptive way or replace a physician's clinical judgment. Most importantly, the motivation of the endeavour is to provide standardised clinical eligibility criteria to aid decision for subsidy for initiation and continuation biologic treatment of RA in Singapore, in order to enhance more equitable access to effective treatments. Applicability of these recommendations may be limited to the funding structure (e.g. partial or full subsidy, means testing) and changes in the national healthcare budget. The Chapter's consensus statement will need to be periodically updated as newer evidence on treatment strategies continue to emerge.

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Appendix 1. Methotrexate Toxicity Criteria

Adverse Event	Brief Description of Minimum Grade	NIH Common Toxicity Criteria Grade
Anaemia	Haemoglobin <80 g/L	3 (or higher)
Leukopenia	Total WCC <3 x 10 ⁹ /L	2 (or higher)
Thrombocytopenia	Platelets <50 x 10 ⁹ /L	3 (or higher)
Neutropenia	Total neutrophils <1.0 x 10 ⁹ /L	3 (or higher)
Pericardial effusion/pericarditis	Pericarditis (pericardial rub, ECG changes or chest pain)	2 (or higher)
Thrombosis/embolism	Thrombosis/embolism requiring anticoagulant therapy	3 (or higher)
Alopecia	Pronounced hair loss	2 (or higher)
Rash/desquamation	Scattered macular or papular eruption or erythema with pruritis or other associated symptoms covering <50% of body surface or localised desquamation or other lesions covering <50% of body	2 (or higher)
Diarrhoea	Increase of 4 – 6 stools/day over pretreatment	2 (or higher)
Nausea	Oral intake significantly decreased, and symptoms do not improve with at least 2 of the following measures: 1. Reduction of the methotrexate dose 2. Folinic acid/folic acid supplementation 3. Switching from oral to intramuscular dosing 4. Dividing the methotrexate dose over 12 hours A minimum of 3 doses of methotrexate should have been trialled.	2 (or higher)
Pancreatitis	Abdominal pain with pancreatic enzyme elevation	3 (or higher)
Stomatitis	Painful erythema, oedema or ulcers but able to eat or swallow	2 (or higher)
Vomiting	2 or more episodes per 24 hours over pretreatment	2 (or higher)
Bilirubin	>1.5 x ULN	2 (or higher)
Transaminases	ALT and/or AST >2.5 x ULN or ALT and/or AST >1.5 x ULN on 3 occasions over a 3-month period	2 (or higher)
Increased serum alkaline phosphatase	2.5 x ULN	2 (or higher)
Osteonecrosis (avascular necrosis)	Symptomatic and interfering with function	2 (or higher)
Osteoporosis	Symptomatic and requiring treatment	3 (or higher)

ALT: Alanine transaminase; AST: Aspartate transaminase; ECG: Electrocardiogram; NIH: National Institute of Health; ULN: Upper limit of normal; WCC: White cell count

Suicidal Ideation, Suicidal Plan and Suicidal Attempts Among Those with Major Depressive Disorder

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Abstract

Introduction: The aims of the study were to identify the prevalence and sociodemographic and clinical correlates of suicidal behaviours using data from a cross-sectional survey among those with major depressive disorder (MDD) in Singapore. **Materials and Methods:** The Singapore Mental Health Study (SMHS) was a cross-sectional epidemiological study that surveyed Singapore residents (Singapore citizens and permanent residents) aged 18 years and above. The assessment of mental disorders was established using version 3.0 of the Composite International Diagnostic Interview (CIDI 3.0). For the purposes of this study, suicidal behaviour was assessed by questions which were asked to respondents who answered positively to the screening questions in the CIDI 3.0 “Depression” module. **Results:** The prevalence of suicidal ideation, plan and attempt among those with lifetime MDD was 43.6%, 13.7% and 12.3%, respectively. We found that suicidal ideation, plan and attempt were significantly associated with ethnicity, education and income. The rate of those who had sought some professional help was higher among those with suicidal plan (71.7%) and attempt (72.3%) as compared to those with suicidal ideation (48.7%) and those with MDD but no suicidal behaviour (29%). **Conclusion:** Individuals with MDD and suicidal behaviour do differ from their non-suicidal counterparts as they have a different sociodemographic and clinical profile. There is a need for more research and a better understanding of this population which in turn could lead to the development and implementation of relevant interventions.

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Key words: Composite International Diagnostic Interview, Depression, Prevalence, Singapore Mental Health Study, Suicidal behaviour

Introduction

The World Health Organization (WHO) estimates that every year, almost a million people die from suicide — a mortality rate of 16 per 100,000, or 1 death every 40 seconds.¹ WHO also posits that in some countries, suicide is one of the three leading causes of death among those aged 15 to 44 years, and the second leading cause of death among 10 to 24 year olds. Mental disorders are strongly associated with completed suicides, with studies mainly from Western populations showing that approximately 9 out of every 10 individuals appear to have had a psychiatric disorder at the time of their death.²

Studies suggest that “suicidal behaviours” occur on a

continuum of severity that progresses from less serious and more prevalent behaviours to less prevalent but more harmful and devastating behaviours.³⁻⁵ While at one end of the continuum are behaviours such as ideation without specific plans, these may progress in some individuals to a plan, and, for a very small proportion of persons at the other end of the continuum, to a completed suicide attempt with high lethality.³ Nock et al⁶ examined data across 17 countries as part of the WHO World Mental Health Surveys and established the lifetime prevalence of suicidal ideation, plan, and attempt in the overall sample to be 9.2%, 3.1% and 2.7%, respectively. The risk of each suicidal behaviour was found to be significantly associated with being female,

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in a younger age group, having fewer years of education, and never being married. They also established that presence of any mental disorder was significantly associated with the risk of suicidal behaviours, with the most robust relationship being for mood and impulse-control disorders.

Depression is a chronic mental illness, which is highly prevalent, with a high risk of recurrence if treated inadequately and it is one of the most important mental disorders in terms of public health impact.^{7,8} Prevalence of suicide among those with major depressive disorder (MDD) is considerable and suicide remains one of the most worrisome outcomes of depression. The association between suicidal behaviour and MDD is well known.^{9,10} Majority of studies have established the prevalence and risk factors of suicidal behaviour among those with MDD in clinical settings while very few studies have reported the prevalence of suicidal behaviour or its risk factors among those with MDD in population surveys.¹¹

Studies examining risk for suicidal ideation in depression have identified the following risk factors: severity of depression,^{12,13} comorbid alcohol abuse and dependence,¹² comorbid anxiety disorder,¹⁴ comorbid personality disorder,¹³ younger age,¹⁵ female gender,¹⁴ unemployment,¹² poor social support and past suicide attempts.¹⁶ Conner et al in their study on patients with MDD aged 50 years and above found that suicidal planning was associated with living alone, older age, lower scores on Physical Self-Maintenance Scale, and higher cognitive functioning.¹⁷ A study by the Office of Applied Studies (OAS) reported that males were more likely than females to have made a suicide plan and adults aged 55 or older with past year major depressive episode were less likely than their counterparts in other age groups to have made a suicide plan.¹⁸ Risk factors for suicidal attempts among those with depression are similar and include suicide attempts in the past,¹⁹ younger age,²⁰ severe depression and early age of onset of depression,^{20,21} marital discord,²² comorbid personality disorder,²³ comorbid alcohol abuse or dependence and comorbid physical illness.^{21,24,25}

Singapore is a highly urbanised and affluent city-state country with a multiracial population in South East Asia. The suicide rate in Singapore has remained relatively stable, and has been reported as 9.8 and 13.0 per 100,000 over the last 5 decades and it was higher among the elderly, men, and among Chinese and Indians.^{26,27} While several studies have analysed completed suicides and established risk factors in Singapore,²⁸ few have examined suicidal behaviours among those with MDD in a population setting.

The aims of the current study were to identify the prevalence and sociodemographic and clinical correlates of suicidal behaviours using data from a cross-sectional survey among those with MDD in Singapore. We hypothesised that

respondents diagnosed with MDD and reporting suicidal behaviour would differ significantly from those with MDD who do not report suicidal behaviour.

Methodology

Sample

The Singapore Mental Health Study (SMHS) was a cross-sectional epidemiological study that surveyed Singapore residents (Singapore citizens and permanent residents) aged 18 years and above. Disproportionate stratified sampling (by age groups and ethnicity) was used where the 3 main ethnic groups (Chinese, Malays and Indians) were sampled in an equivalent proportion of about 30% each. Individuals aged 50 and older were also oversampled. The data was adjusted accordingly, to represent the Singapore population based on the 2007 population data. Face-to-face interviews were completed with 6616 respondents from December 2009 to December 2010. The survey response rate was 75.9%. The study was approved by the ethics committee (National Healthcare Group, Domain Specific Review Board) and all participants and parents/guardians of those aged below 21 years gave written informed consent for participating in the study. The detailed methodology of the study has been described in a prior article.²⁹

Assessments

The assessment of mental disorders was established using version 3.0 of the World Mental Health Composite International Diagnostic Interview (CIDI 3.0).³⁰ Diagnostic modules for lifetime and 12-month prevalence of affective disorders, including MDD and bipolar disorder; anxiety disorders, including generalised anxiety disorder (GAD) and obsessive compulsive disorder (OCD); alcohol use disorders i.e. alcohol abuse and alcohol dependence, were included in the survey. CIDI 3.0 organic exclusion rules as well as diagnostic hierarchy rules were applied to generate the final diagnoses.

For the purposes of this study, “suicidal behaviours” included the participants’ reports of: (1) suicidal ideation (thoughts about suicide); (2) suicidal plans or intent; and (3) suicide attempts. It was assessed by the following questions which were asked to respondents who answered positively to the screening questions in the CIDI 3.0 “Depression” module:

- Did you think about committing suicide? – Suicidal Ideation
- Did you make a suicide plan? – Suicidal Plan
- Did you make a suicide attempt? – Suicidal Attempt

Help-seeking behaviour was determined using the services section of the CIDI. The key question asked from all respondents was, “Did you ever in your lifetime go to

see any of the professionals on this list for problems with your emotions, nerves, mental health or your use of alcohol or drugs?” A list of treatment providers was then presented to the participant.

The interview also gathered information on a range of chronic physical conditions. We used a modified version of the CIDI checklist of chronic medical disorders for this purpose and respondents were asked to report any of the disorders listed in the checklist. The list comprised 15 chronic medical disorders which were reclassified into 8 types of physical disorders: (1) respiratory disorders (asthma, chronic lung disease such as chronic bronchitis or emphysema), (2) diabetes, (3) hypertension and high blood pressure, (4) chronic pain (arthritis or rheumatism, back problems including disk or spine, migraine headaches), (5) cancer, (6) neurological disorders (epilepsy, convulsion, Parkinson’s disease), (7) cardiovascular disorders (stroke or major paralysis, heart attack, coronary heart disease, angina, congestive heart failure or other heart disease), and (8) ulcer and chronic inflamed bowel (stomach ulcer, chronic inflamed bowel, enteritis, or colitis).³¹ All other sociodemographic data such as age, gender, ethnicity, marital status, education, employment status, income and smoking status were collected using structured questionnaires. Nicotine dependence was established using the 6-item Modified Fagerstrom Test for Nicotine Dependence.³²

Statistical Analysis

All estimates were weighted to adjust for oversampling and post-stratified for age and ethnicity distributions between the survey sample and the Singapore resident population in 2007. Mean and standard deviations or median (if normality was not satisfied) were calculated for continuous variables, and frequencies and percentages for categorical variables. A series of logistic regression models were used to estimate odd ratios (ORs) and 95% confidence intervals (CI) using the three suicidal behaviours (ideation, plan and attempt) as the main outcome variables and sociodemographic factors, mental disorders and chronic physical conditions as predictors. Standard errors (SE) and significance tests were estimated using the Taylor series linearisation method. Multivariate significance was evaluated using Wald χ^2 tests based on design corrected coefficient variance-covariance matrices. Statistical significance was evaluated at the <0.05 level using two-sided tests. All statistical analyses were carried out using the Statistical Analysis Software (SAS) System version 9.2.

Results

Table 1 shows the sociodemographic distribution of respondents with DSM-IV lifetime major depressive

Table 1. Sociodemographic Characteristics of Respondents with DSM-IV Lifetime Major Depressive Disorder in the SMHS Study (n = 417)

	n	Weighted %	SE
Age group			
18 – 34	203	46.6	0.0
35 – 49	136	31.7	0.0
50 – 64	68	14.3	0.0
65+	10	7.3	0.0
Ethnicity			
Chinese	114	73.3	0.0
Malay	109	9.6	0.0
Indian	162	11.6	0.0
Others	32	5.5	0.0
Gender			
Male	170	36.1	3.4
Female	247	63.9	3.4
Marital status			
Single	137	31.7	2.9
Married	227	49	3.6
Divorced/ separated	43	13.7	2.4
Widowed	9	5.6	1.6
Education			
Primary	47	11.8	2.2
Secondary	111	24.3	3
Tertiary	259	63.9	3.2
Employment			
Employed	303	72.1	3
Unemployed	65	20.3	2.7
Economically inactive	31	7.6	1.9
Income			
Below \$20,000	204	48.7	3.3
\$20,000 – \$49,999	136	33.1	3.2
>\$50,000 and above	60	18.2	2.8

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition; SE: Standard error; SMHS: Singapore Mental Health Study

disorder in the SMHS study. The prevalence of suicidal ideation, plan and attempt among those with lifetime MDD was 43.6%, 13.7% and 12.3%, respectively. Among those with suicidal ideation, about 31.5% and 28.2% had made a plan and an attempt respectively. Majority of respondents with suicidal ideation and plan had made an attempt (68.3%) (Table 2). The mean age of onset of MDD among those with suicidal ideation, plan and attempt was 26.4, 28.7 and 25.8, respectively. We found that suicidal ideation, plan and attempt were significantly associated with ethnicity,

education and income; Malays and Indians were significantly less likely than Chinese to have a suicidal ideation or plan. Malays were also less likely to have a suicidal attempt than those of Chinese ethnicity. Those who were divorced/separated were significantly more likely to report suicidal attempts than those who were single. As compared to those with tertiary education, those with a primary education were significantly more likely to have suicidal ideation, plan and attempt. Those with higher annual income (\$50,000 and above) were significantly less likely to report any form of suicidal behaviours than those with lower annual income (below \$20,000). Among those with suicidal ideation, only higher annual income remained significantly related to suicidal plan (Table 3).

Table 4 shows the association between mental disorders, chronic physical conditions and suicidal behaviours. After adjusting for sociodemographic factors in the multiple logistic regression, alcohol abuse and dependence were significantly associated with suicidal plan and attempt. GAD was significantly associated with suicidal ideation, while nicotine dependence was associated with suicidal plan. The presence of any chronic physical condition, and specifically having a respiratory condition, was significantly associated with suicidal plan. Among those with suicidal ideation, nicotine dependence was significantly related to suicidal plan, while hypertension was significantly related to suicidal attempt.

The details on sources of help sought among those with suicidal ideation, plan and attempt are provided in Table 5. The most frequent source of help as indicated by those with suicidal behaviours was a “psychiatrist”. The rate of those who had sought some professional help was higher among those with suicidal plan (71.7%) and attempt (72.3%) as compared to those with suicidal ideation (48.7%) and those with MDD but no suicidal behaviour (29%). It was interesting to note that 15.7% of those with suicidal attempt had called a hotline for help versus only 1.6% with MDD but no reported suicidal behaviour.

Discussion

The prevalence of suicidal behaviour among those with MDD was considerable in our population with the prevalence of ideation, plan and attempt among those with lifetime MDD being 43.6%, 13.7% and 12.3%, respectively.

We found that suicidal behaviour was significantly associated with ethnicity. Malays and Indians were significantly less likely than Chinese to have a suicidal ideation or plan. Malays were also less likely to have a suicidal attempt than Chinese. Our findings are similar to those reported by Chan et al³³ among depressed inpatients in Malaysia. The authors reported that those of Chinese origin had a higher risk of suicidal attempts as compared to those

of Malay and Indian ethnicity. Sociocultural factors may provide a possible explanation for our findings. Ethnicity and religion are closely interrelated in Singapore as in Malaysia: almost all the Malays in Singapore are Muslims. Religious affiliation may be protective against suicide, both at the individual and societal level, and as observed in studies, religious salience may be a protective factor against suicidal behaviour and this may be more pronounced for Muslims compared to others.^{33,34} Our finding that Indians have a lower risk of suicidal ideation and plans as compared to Chinese is somewhat surprising as an earlier study in this population showed that the risk of MDD was higher in Indians as compared to those of Chinese ethnicity.³⁵ Further research on suicidal behaviour and sociocultural factors is needed to understand these differences further.

Marital status was significantly associated with suicidal behaviour; those who were divorced/separated were significantly more likely to report suicidal attempts than those who were single. While our findings are different from that reported by Hawton et al³⁶ who did not find any association of marital status with suicidal attempts, they are similar to that reported by Chan et al,³³ who found that suicidal attempts were higher among those who had experienced marital separation. Marital separation, conflict and quarrels are significant stressors and may act as significant precipitants of suicidal attempts.³⁷

Our findings that respondents with higher annual incomes had a significantly lower risk of suicidal behaviours than those with lower annual incomes replicate previous research in the field.^{38,39} Our study also found that as compared to those with tertiary education, those with a primary education were significantly more likely to have suicidal ideation, plan and attempt. Lower education and income levels are both “individual-level disadvantages” which reflect a person’s socioeconomic position that may influence suicidal behaviour. It has been suggested that low socioeconomic position may restrict the access of the individual to material, psychosocial, or institutional resources thus limiting an individual’s development of self control or strategies for managing stressful situations, seeking support and help, or it may lead to differential exposure to risk factors such as negative life events (divorce, unemployment and financial loss) thus predisposing them to adverse outcomes.⁴⁰

Comorbid mental disorders especially alcohol abuse and dependence were significantly associated with suicidal plan and attempt. Several studies have shown that suicidal behaviour is very common among subjects with co-occurring depression and alcohol use disorders.^{20,24} The mechanisms underlying this relationship are yet to be elucidated. Conner and Duberstein⁴¹ proposed a model to explain the elevated risk of suicide among alcohol dependent subjects. This model includes aggression/impulsivity, negative affect,

Table 2. Prevalence of Suicidal Behaviours

All MDD Cases			Non-suicidal Behaviour			Ideation			Plan			Attempt			Plan Among Ideators			Attempt Among Ideators			Attempt Among Ideators with a Suicide Plan			
n	%	SE	n	%	SE	n	%	SE	n	%	SE	n	%	SE	n	%	SE	n	%	SE	n	%	SE	
Total	417	100	0	281	56.4	3.6	136	43.6	3.6	37	13.7	2.7	40	12.3	2.6	37	31.5	5.4	40	28.2	5.5	24	68.3	11.4
Male	170	36.1	3.4	122	63.7	5.9	48	36.3	5.9	17	14.3	4.7	15	12.3	4.5	17	39.5	10.5	15	33.9	10.4	11	79.5	13.2
Female	247	63.9	3.4	159	47.7	4.6	88	47.7	4.6	20	13.4	3.5	25	12.3	3.3	20	28.1	6.7	25	25.8	6.5	13	61.5	15.7

MDD: Major depressive disorder; SE: Standard error

Table 3. Sociodemographic Correlates of Suicidal Behaviours

Variables	Ideation			Plan			Attempt			Plan Among Ideators			Attempt Among Ideators		
	OR*	95% CI	P Value	OR*	95% CI	P Value	OR*	95% CI	P Value	OR*	95% CI	P Value	OR*	95% CI	P Value
Age group															
18 – 34	Ref.			Ref.			Ref.			Ref.			Ref.		
35 – 49	0.5	0.2 – 1.3	0.162	0.8	0.2 – 2.9	0.796	0.5	0.1 – 2.2	0.387	2.5	0.5 – 12.5	0.256	0.8	0.1 – 4.4	0.770
50 – 64	1.1	0.4 – 3.2	0.850	0.7	0.1 – 4.0	0.682	1.2	0.1 – 10.3	0.896	0.8	0.1 – 4.2	0.786	1.2	0.2 – 7.2	0.824
65+	0.2	0.01 – 7.6	0.416	0.2	0.01 – 3.9	0.263	0.2	0.01 – 4.3	0.307	-	-	-	1.9	0.1 – 51.0	0.691
Ethnicity															
Chinese	Ref.			Ref.			Ref.			Ref.			Ref.		
Malay	0.2	0.1 – 0.4	<.0001	0.1	0.03 – 0.5	0.003	0.1	0.02 – 0.5	0.005	1.0	0.1 – 6.4	0.959	1.1	0.2 – 7.2	0.941
Indian	0.3	0.2 – 0.7	0.001	0.2	0.1 – 0.7	0.008	0.4	0.1 – 1.2	0.096	0.7	0.1 – 3.5	0.660	2.0	0.5 – 7.4	0.318
Others	0.5	0.2 – 1.5	0.217	-	-	-	-	-	-	-	-	-	-	-	-
Gender															
Male	Ref.			Ref.			Ref.			Ref.			Ref.		
Female	1.4	0.7 – 2.9	0.355	0.8	0.2 – 2.8	0.744	1.3	0.4 – 4.2	0.644	0.5	0.1 – 1.8	0.267	0.6	0.1 – 2.1	0.381

CI: Confidence interval; OR: Odds ratio; Ref: Reference category

*Derived from multiple logistic regression model adjusted for demographic variables (i.e. age, gender, ethnicity, marital status, education, employment and income).

Table 3. Sociodemographic Correlates of Suicidal Behaviours (Con't)

Variables	Ideation			Plan			Attempt			Plan Among Ideators			Attempt Among Ideators			P Value
	OR*	95% CI	P Value	OR*	95% CI	P Value	OR*	95% CI	P Value	OR*	95% CI	P Value	OR*	95% CI	P Value	
Marital status																
Single		Ref.			Ref.			Ref.			Ref.			Ref.		
Married	1.4	0.6 – 2.9	0.451	3.6	0.7 – 18.2	0.119	2.1	0.4 – 10.3	0.374	4.8	0.9 – 24.8	0.061	2.9	0.7 – 12.5	0.147	
Divorced/separated	2.8	0.8 – 9.6	0.108	3.7	0.5 – 27.3	0.198	8.3	1.1 – 61.1	0.037	2.1	0.2 – 22.1	0.547	3.4	0.5 – 22.4	0.210	
Widowed	6.5	0.1 – 283.2	0.333	22.4	0.5 – 996.8	0.109	4.1	0.1 – 142.0	0.440	-	-	-	0.2	0.01 – 5.4	0.348	
Education																
Primary	3.9	1.4 – 10.5	0.007	4.6	1.3 – 16.8	0.019	13.7	2.9 – 65.1	0.001	0.8	0.1 – 5.6	0.859	4.9	0.9 – 27.0	0.067	
Secondary	0.7	0.3 – 1.6	0.410	0.5	0.1 – 1.8	0.260	0.5	0.1 – 2.1	0.322	0.8	0.2 – 3.2	0.794	0.5	0.1 – 2.7	0.439	
Tertiary		Ref.			Ref.			Ref.			Ref.			Ref.		
Employment																
Employed		Ref.			Ref.			Ref.			Ref.			Ref.		
Unemployed	0.7	0.2 – 2.1	0.488	1.9	0.4 – 8.9	0.437	2.9	0.6 – 13.9	0.173	4.4	0.5 – 37.8	0.175	6.2	0.6 – 60.6	0.116	
Economically inactive	0.8	0.2 – 2.8	0.707	1.5	0.4 – 6.7	0.573	1.4	0.2 – 10.0	0.748	3.3	0.5 – 23.7	0.229	2.5	0.2 – 26.7	0.440	
Income																
Below \$20,000		Ref.			Ref.			Ref.			Ref.			Ref.		
\$20,000 – \$49,999	0.6	0.2 – 1.3	0.202	0.2	0.04 – 1.3	0.087	1.3	0.3 – 6.4	0.740	0.3	0.1 – 1.5	0.134	2.7	0.7 – 11.0	0.159	
>\$50,000 and above	0.3	0.1 – 0.8	0.022	0.03	0.003 – 0.2	0.001	0.1	0.01 – 0.6	0.016	0.04	0.004 – 0.4	0.005	0.1	0.02 – 1.1	0.062	

CI: Confidence interval; OR: Odds ratio; Ref: Reference category
*Derived from multiple logistic regression model adjusted for demographic variables (i.e. age, gender, ethnicity, marital status, education, employment and income).

Table 4. Correlates of Lifetime Mental Disorders and Chronic Physical Conditions with Suicidal Behaviours

	Ideation			Plan			Attempt			Plan Among Ideators			Attempt Among Ideators		
	OR	95% CI	P Value	OR	95% CI	P Value	OR	95% CI	P Value	OR	95% CI	P Value	OR	95% CI	P Value
Lifetime DSM-IV disorders															
GAD	3.7	1.1 – 12.3	0.032	2.3	0.4 – 14.0	0.361	1.7	0.3 – 10.2	0.540	0.3	0.03 – 3.5	0.352	1.01	0.1 – 7.2	0.993
OCD	0.8	0.2 – 2.5	0.662	2.3	0.6 – 9.2	0.248	1.3	0.3 – 6.3	0.754	5.8	0.8 – 41.4	0.081	4.7	0.6 – 34.1	0.129
Alcohol abuse	2.6	0.9 – 7.5	0.079	22.7	3.6 – 142.9	0.001	12.1	1.9 – 75.5	0.008	2.4	0.2 – 29.7	0.506	2.1	0.3 – 17.4	0.494
Alcohol Dependence	3.7	0.9 – 15.4	0.074	11.9	1.4 – 104.9	0.025	16.7	2.0 – 136.2	0.009	11.0	0.5 – 261.2	0.138	6.9	0.3 – 169.9	0.242
Nicotine Dependence	2.0	0.5 – 8.2	0.333	10.7	1.2 – 98.3	0.036	3.0	0.3 – 30.1	0.343	26.5	1.1 – 658.1	0.045	5.3	0.5 – 61.2	0.184
Any mental disorder	1.7	0.8 – 3.6	0.18	6.6	1.9 – 23.0	0.003	3.1	0.9 – 10.6	0.069	3.2	0.8 – 13.2	0.115	3.1	0.8 – 12.3	0.114
Lifetime chronic physical conditions															
Respiratory conditions	1.1	0.5 – 2.5	0.874	4.5	1.1 – 18.4	0.039	3.1	0.8 – 11.5	0.097	3.4	0.3 – 37.0	0.312	4.9	0.97 – 25.1	0.055
Diabetes	0.8	0.2 – 3.4	0.802	2.1	0.3 – 14.7	0.442	2.8	0.6 – 13.2	0.198				25.3	0.8 – 763.1	0.063
Hypertension	0.9	0.3 – 2.6	0.911	0.6	0.1 – 3.1	0.545	4.0	0.8 – 18.7	0.082	4.4	0.8 – 24.9	0.090	11.8	1.6 – 87.0	0.016
Chronic pain	0.8	0.4 – 1.7	0.608	1.4	0.4 – 4.8	0.601	0.9	0.3 – 2.9	0.816	1.7	0.4 – 6.7	0.473	1.6	0.5 – 5.7	0.457
Cancer										2.5	0.5 – 12.5	0.256	0.8	0.1 – 4.4	0.770
Neurological conditions	1.0	0.1 – 7.1	0.961	2.3	0.2 – 33.2	0.529	1.1	0.1 – 25.1	0.944	5.6	0.3 – 110.0	0.259	1.4	0.1 – 25.9	0.810
Cardiovascular	0.7	0.1 – 3.9	0.698	0.6	0.1 – 4.3	0.609	1.0	0.2 – 5.8	0.993	0.3	0.01 – 11.8	0.519	3.9	0.3 – 60.6	0.332
Ulcer	1.2	0.2 – 9.0	0.846	0.6	0.03 – 12.6	0.766	0.7	0.03 – 16.9	0.800				0.3	0.01 – 14.5	0.510
Any chronic physical condition	0.9	0.5 – 1.8	0.812	4.2	1.1 – 15.5	0.032	2.2	0.7 – 7.3	0.197	6.9	1.7 – 27.6	0.007	3.2	0.9 – 10.9	0.064

CI: Confidence interval; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition; GAD: Generalised anxiety disorder; OCD: Obsessive compulsive disorder; OR: Odds ratio

Table 5. Services Used Among Those With Suicidal Behaviours

	MDD with No Reported Suicidal Behaviour (n = 281)		Ideation (n = 136)		Plan (n = 37)		Attempt (n = 40)	
Professional	%	SE	%	SE	%	SE	%	SE
Any professional	29.0	3.9	48.7	5.8	71.7	9.0	72.3	9.2
Psychiatrist	7.4	2.3	25.2	5.3	42.6	11.4	58.0	10.3
Counselor	8.1	1.9	14.0	4.3	19.2	9.8	7.3	4.8
Religious/spiritual healer	2.7	1.2	10.6	3.9	14.9	9.2	3.1	1.5
GP	13.8	3.2	7.3	2.5	3.0	1.4	1.8	1.1
Psychologist	5.8	2.2	5.8	2.5	5.8	4.2	7.8	4.8
Social worker	2.9	1.3	9.1	3.7	21.6	10.0	24.8	10.7
Use a hotline	1.6	1.2	9.4	3.4	14.1	7.4	15.7	8.3
Other mental health professional	2.5	1.6	0.2	0.2	0.6	0.7	-	-
Medical doctor*	0.4	0.2	0.4	0.3	-	-	0.7	0.7
Nurse	0.3	0.2	0.4	0.3	-	-	0.6	0.6
Healer	2.7	1.6	0.6	0.5	-	-	-	-

GP: General practitioner; MDD: Major depressive disorder; SE: Standard error

*Refers to doctors with specialisation in fields other than psychiatry; does not include GPs.

and hopelessness as key predisposing factors, and major depressive episodes and stressful life events, particularly interpersonal difficulties, as key precipitating factors for suicide. Episodes of major depression are proposed to mediate the relationship between negative affect (and hopelessness) and suicidal behaviour among those with alcoholism. The authors also suggest that it is likely that depression affects the association between interpersonal difficulties and suicidal behaviour among alcoholics. This model could also partly explain the higher risk conferred by comorbid alcohol use for suicidal behaviours among those with MDD in our study.

GAD was significantly associated with suicidal ideation, while nicotine dependence was associated with suicidal plan. Our finding of an association between GAD and suicidal ideation is somewhat unique, and there is only one study reporting a similar finding (in an outpatient population with MDD).⁴² Studies have identified both smoking and nicotine dependence as risk factors for suicidal behaviour.⁴³⁻⁴⁵ Different theories have been described to explain this relation such as smoking being a non-causal marker or smoking being a psychological or physical toxin. A biological theory suggests that chronic nicotine use is associated with diminished levels of serotonin⁴⁶ and monoamine oxidase (MAO)⁴⁷ compared with unexposed populations. Low levels of serotonin and MAO activity have been linked with suicidal behaviour.^{48,49} Our findings must be interpreted cautiously as this study established current prevalence of nicotine dependence while suicidal behaviour was based on a lifetime history.

Our finding of the association between chronic physical conditions and specifically having a respiratory condition

and suicidal plan is somewhat similar to that reported by Goodwin et al.⁵⁰ The authors found that pulmonary disease with or without comorbid depression was associated with a statistically significant increased likelihood of suicidal ideation. However, those with comorbid depression and pulmonary disease had a higher risk of suicidal ideation. The mechanism of the association between respiratory disease, major depression, and suicidal behaviours is not known. The authors have suggested that “the pain, physical suffering or the limited lifestyle associated with specific physical illnesses such as asthma and chronic obstructive pulmonary disease (COPD) is severe enough to result in suicidal behaviour”. Studies conducted among the local population, i.e. among patients with chronic obstructive pulmonary disease in Singapore, have concluded that comorbid depressive symptoms are common in patients with COPD and are associated with poorer survival, longer hospitalisation stay, persistent smoking, increased symptom burden, and poorer physical and social functioning.⁵¹ These factors may be a plausible explanation for our findings. Alternatively, it may be that there are common genetic or environmental factors (or both) that are related to depression, respiratory disease and suicidal ideation, which independently predict their co-occurrence. Future research is needed to determine the nature of this link.

The rate of those who had sought some professional help was considerably higher among those with MDD and suicidal behaviour as compared to those without suicidal behaviour. These findings can be explained by Andersen's behavioural model of health services in that an increased level of evaluated need is associated with an increased likelihood of help-seeking behaviour.⁵² Individuals with

suicidal behaviours were significantly more likely than those with MDD without suicidal behaviours to seek help, suggesting that suicidal behaviours are important factors associated with help-seeking behaviour over and above the presence of mental disorders. Furthermore, individuals who had suicidal plans/attempts were even more likely than those with suicidal ideation to seek help—suggesting increasing need with the severity of the suicidal behaviour. The most frequent source of help as indicated by those with suicidal behaviours was a psychiatrist. A likely explanation for this may be that those with suicidal behaviours may interpret the ideas/plans as a clear and serious indicator of psychological distress, and are therefore more likely to seek treatment from psychiatrists. It is possible that those with attempts similarly were either self/family referred to a psychiatric facility given the seriousness of the problem. It is however, important to note that counsellors, religious and spiritual healers as well as hotlines have also been identified as sources of help seeking thus reiterating the need for care providers from different backgrounds to work in an integrated manner to support those with suicidal behaviours and avoid escalation to a completed suicide.

The strengths of our study are that it is a nationwide survey of a representative population which has lesser likelihood of sampling errors like Berkson's bias compared to those studies that examined "suicidal behaviours" in help-seeking clinical samples. It is one of the first studies in the extant literature that has examined suicidal behaviour among those with MDD in a multiethnic Asian sample. We used a structured diagnostic instrument with face-to-face interviews, and psychiatric diagnoses were made according to the DSM-IV criteria. Lastly, our response rate of 75.9% ensures reasonable generalisability of our results. There are some limitations to our study—suicide-related variables were collected with a single question; we did not assess the lethality of suicide attempts or the number of suicidal attempts and thus, were unable to compare those with single versus multiple attempts. We assessed "suicidal behaviours" only among those with MDD, however current research suggests that "suicidal behaviours" may occur independently of depressive symptoms. A stress diathesis model proposed by Mann et al⁵³ suggests that the risk for suicidal acts is determined not merely by a psychiatric illness (the stressor) but also by a diathesis. This diathesis may be reflected in a tendency to experience more suicidal ideation and to be more impulsive and, therefore, to be more likely to act on suicidal feelings. Another theory suggests that suicidal individuals are experiencing unbearable psychological pain (psychache) or suffering and that suicide may be, at least in part, an attempt to escape from the suffering.⁵⁴ Thus, the prevalence of "suicidal behaviours" in our study is not indicative of "suicidal behaviours" among the general population of Singapore. The data on suicidal behaviours was based on respondents' self-report and there could be an

element of recall bias and under-reporting especially since suicidal behaviour is a sensitive topic. Lastly, we did not establish the prevalence of personality disorders which are a significant risk factor for suicidal behaviour.

Conclusion

Individuals with MDD and suicidal behaviour do differ from their non-suicidal counterparts as they have a different sociodemographic and clinical profile. There is a need for more research and a better understanding of this population which in turn could lead to the development and implementation of relevant interventions.

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How to Bridge the “Valley of Death” Between a Research Discovery and Clinical Application?

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The Valley of Death

As physicians, one of the key questions we often ask is, “How do we bring new understanding of disease mechanisms and better treatments to our patients?” Is there a process whereby scientific discoveries are identified, assessed and adopted by physicians, healthcare providers and policy makers to ensure our patients benefit from these innovations?

In fact, this “process” of scientific discovery to actual clinical application is long, tortuous and difficult, and many bench discoveries do not actually get to the bedside. As an example, in 2008, more than 800,000 medical research papers were published, but by 2011 only 21 new drugs had been approved by the US Food and Drug Administration (FDA)¹—barely 0.003% of the “discoveries”. Of the numerous research publications, observations, clinical trials and discoveries worldwide that the public sometimes are made aware of in the lay media, how many can boast that they have actually made a real impact to improving patients’ lives and have been used by physicians in clinical practice? The answer: very, very few!

The chasm between a laboratory observation and the application of this observation to clinical care outcomes have been dubbed the “valley of death”, where basic biomedical discoveries initially generate exciting new results, are published in high profile journals and lauded as “breakthroughs” by the scientific community and the lay media, but many years later, they subsequently languish, failing to translate to actual improvements for clinical medicine and healthcare.

So how do we ensure that research endeavours, which often consume significant costs to public budgets, reach and make a tangible difference to patients?

What is Translational Medicine?

Translational medicine is the “bridge” to this valley.² Translational medicine is, essentially, the process of

applying knowledge gained from basic biomedical research to clinical practice; it involves bridging new research findings, scientific discoveries and new techniques to approaches in the prevention, diagnosis or treatment of diseases. This can be in the form of drugs, devices, biomarkers or treatment methods. Translational medicine involves the pursuit of the patient’s health as the ultimate outcome. It involves paradigm shifts such that scientific discoveries should not just be celebrated only in basic laboratories and research institutes or published (and archived) in prestigious medical journals—they also need to make their way to hospitals, clinics and into patients’ lives to be real successes. Translational medicine involves a longer term strategy for research that is beyond the immediate outcomes of a research project.

Translational medicine takes time. An example is the discovery of the treatment of age-related macular degeneration (AMD), one of the major causes of blindness.³ The observation that eyes with AMD have a higher level of a “growth factor” occurred in the early 1970s, leading to the identification of vascular endothelial growth factor (VEGF). Subsequently, this led to the design of antibodies to VEGF, testing of anti-VEGF agents in animal models and then in early phase clinical trials. The results of major phase 3 clinical trials in 2006 led to the clinical adoption of anti-VEGF treatment and for AMD as a gold standard treatment. It is now one of the major treatments for eye diseases in Singapore.⁴ In 2013, almost 4 decades later, the rate of AMD blindness has started to decline in some countries as a result of anti-VEGF treatment. So the process of translational medicine from bench to the bedside to the population took 40 years!

In the US, the National Institutes of Health (NIH) has recognised the importance of translational medicine and has made it a priority. Since 2006, the NIH has formed centres of translational research at its institutes with a budget that has reached US\$500 million a year,² and it has launched translational science awards for researchers.

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Similarly, Singapore's national biomedical sciences agenda has now shifted towards translational medicine as a priority for the future, and has refocused emphasis on such research that creates greater health and economic impact.⁵

An Example of Translational Medicine in Singapore: The Myopia Story

Because Singapore's effort in biomedical research is relatively new, there have been few successful cases to date. Nevertheless, there are encouraging signs.

An example close to home is the management of Singapore's unique problem of myopia. Myopia is a common condition and is almost a "national" problem affecting 28% of children as young as 7 years of age, with the rate hitting 83% at 18 years of age.^{6,7} Myopia may result in blindness due to myopic macular degeneration and slowing the rate of myopia progression is one way to prevent this problem.⁷

For 15 years, researchers and subsequently, clinicians at the Singapore Eye Research Institute (SERI) and the Singapore National Eye Centre (SNEC) have been trying to tackle this problem. The work over the 15 years was done with an end goal in mind—to decrease the rising incidence of myopia, and to slow down the condition in its tracks.

The SERI and SNEC research team discovered that eye drops with low-dose atropine slow down the progression of myopia in children with minimal side effects.⁸ After years of tests and clinical trials, the clinicians and researchers have transformed their findings into a solution. SNEC today now offers new eye drops with a 0.01 atropine dosage—the most effective atropine level proven to combat myopia—for children with severe myopia in a dedicated myopia clinic, and is furthering their research to meet regulatory demands. Concomitantly, community-based clinical trials efforts are underway to tackle the lack of physical and outdoor activities, which are now thought to be a major cause of myopia.⁹

With translational medicine, this major nationwide problem may become curable in the foreseeable future.¹⁰

What are the Ingredients for Successful Translational Medicine?

First, driving translational medicine requires a new model of working together. Multidisciplinary collaboration across specialties, disciplines and industries is the key to driving translational research to success. This requires teams of clinician, clinician scientists, scientists, nursing and allied health professionals.

For instance, an observation in the clinic by a doctor may give rise to a hypothesis that a scientist in the lab can work on. A scientist's discovery may translate into a biomarker

that acts as clinical tool for the clinician, or a drug target for drug development by a pharmaceutical company. A physiotherapist's inspiration may result in the invention of a rehabilitation device that could not be made possible without collaborating with an engineering or a medical technology institution. Translational medicine is not an individual event; it is a team sport that has different roles and skills for each team member. With a critical mass of research teams and sustained collaboration, drugs, treatments and care, outcomes can be brought out of the "valley of death".

Second, a strong ecosystem and culture that sustains and rewards translational medicine is critical. It involves forging a close partnership between a hospital cluster and a university, similar to the concept of the SingHealth Duke-NUS Academic Medical Centre or National University Health System.¹¹ The partnership must align the traditional divergent missions of healthcare and education, and the cultural differences between academic researchers and practising doctors. These are challenging issues that must be dealt with upfront.¹²

Third, translational medicine requires a group of people who understand both science and medicine—clinician-scientists.^{13,14} The clinician-scientist can effectively act as a connector between scientists and doctors, and must speak both "languages". To translate research, young clinician-scientists must be identified, trained, mentored and supported. Alongside a nurturing environment, supervision, guidance and advice from a sympathetic and wise mentor are essential. In the US and other countries, clinician-scientists face significant challenges in funding and career development.

The final piece of translational medicine is policy implementation. Once new discoveries and clinical evidence have been established, government agencies and healthcare systems should have a clear framework to implement healthcare policy and public health policy accordingly. The importance of policy implementation as the "final step" in the "valley of death" cannot be underestimated.^{15,16}

With these pieces in place, the "valley of death" can be bridged and research discoveries will find their way to the clinic and to our patients.

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Factors Influencing Patient's Adherence to Follow-up Postbariatric Surgery: An Asian Experience

Dear Editor,

While obesity continues to be a rising concern in the United States,¹ Singapore is not exempted from this trend and has been experiencing an uprising trend in the prevalence. A steep increase was observed between 2004 and 2010, where the obesity (BMI ≥ 30 kg/m²) prevalence among adults aged 18 to 69 years shifted from 6.9% to 10.8%, as compared to the previous 7 years, where the prevalence was at 6.0% in 1998.² Currently, bariatric surgeries are the most successful and durable intervention for obesity. There are emerging data on these procedures as treatments for individuals with Type 2 diabetes (T2D), as well as a mean to reduce cardiometabolic risk factors.¹ Postoperative follow-ups, involving a multidisciplinary approach for patients who underwent a bariatric surgery, have been recognised as essential in the management and maintenance of sustained weight loss¹ as well as minimising complications.³ However, there had been a high appointment default rate observed for postoperative follow-up appointments in Tan Tock Seng Hospital (TTSH). From 2001 to 2002, more than 90% of patients defaulted on postsurgical psychologist's appointments while more than 70% of these patients defaulted on postsurgical appointments with the dietitian. The high default rate has an influence in the patient's management and maintenance of sustained weight loss, chances of complications, as well as the economic cost and manpower borne by the hospital. The current study aimed to further explore factors that could lead to a better understanding of the poor adherence to follow-up appointments.

An online questionnaire was designed by collaborative effort between a psychologist and a dietitian to understand the reasons for a patient's non-attendance for appointments. Fifteen randomly arranged statements regarding why patients did not attend appointments were considered based on the factors highlighted by Mitchell and Selmes,⁴ who postulated that factors such as patient's "Perceived Benefit of Care", "Perceived Cost of Care", "Barrier to Care", "Doctor-Patient Factors" and "Cues to Act" were related to non-adherence.

Patient's "Perceived Benefit of Care" referred to a patient's perception that the appointment with a psychologist or

dietitian was less necessary as the patient believed that he had been coping well with weight loss and any health concerns. "Perceived Cost of Care" considered the financial cost involved, specifically referring to payments for the appointments they attend, which increase with additional appointments. "Barriers to Care" looked at barriers such as the lack of transportation and inconvenient appointments. The "Doctor-Patient Factors" included the therapeutic alliance, perceived helpfulness and communication style. "Cues to Act" referred to reminders for patients to attend the appointments.

Of the patients who attended bariatric surgery in 2011 and 2012, 21 of them had participated in the online questionnaire. As reflected on Table 1, the results suggested that the most influential factor that affected patients' adherence to attending psychologist's appointments was "Patient's Perception of Excess Benefit of Care", where patients (28.57%) thought that they were managing well without follow-up with the psychologist. This was closely followed by "Lacking Cues" to attend the appointment (26.98%), which included receiving an appointment, and/or receiving a reminder of the appointment. The reason of not being given an appointment stood out among the others. Factors such as "Financial Cost" of attending the appointment (16.67%) and "Barriers to Care" (11.43%), e.g. being unable to be away from work, and appointment scheduling challenges, also affected patient's adherence to attending psychologist's appointments.

When considering factors that affected patient's adherence to attending the appointment with the dietitian, "Patient's Perception of Excess Benefit of Care" had the most influence on their adherence (19.05%), where patients do not perceive the need to see the dietitian if they are doing well. This was closely followed by the "Barriers to Care" (18.10%); "Financial Cost" (14.29%); "Lacking Cues to Attend the Appointment" (6.35%), and "Dietitian-Patient Relationship" (1.59%).

The reasons for non-adherence to postoperative follow-up appointments were multifactorial and they differed between the psychologist's and dietitian's appointments. However, the common factor, which also surfaced as the most influencing factor among the 2 appointments, was

Table 1. Factors Influencing Psychologist's and Dietitian's Appointment

Factors	Influencing Psychologist's Appointment (%)	Influencing Dietitian's Appointment (%)
Barriers to care		
Barriers such as the lack of transportation and inconvenient appointments.	11.43	18.10
Financial cost		
The financial cost involved, referring specifically to the payments for the appointments they attend, which increases with additional appointments.	16.67	14.29
Lacking cues to attend the appointment		
Reminders to attend the appointments.	26.98	6.35
Patient's perception of excess benefit of care		
Patient's perception that the appointment with psychologist or dietitian was less necessary as the patient believed that he had been coping well with weight loss and any health concerns.	28.57	19.05
Psychologist-/dietitian-patient relationship		
This included the therapeutic alliance, perceived helpfulness and communication style.	0.00	1.59

their perception of excess benefit of care, which may be the crux of the challenge in adherence.

The perceived excess benefits of care may have stemmed from the lack of awareness of the importance of postoperative follow-up, which may possibly influence their motivation to remember and keep their appointments. Also, postoperative follow-ups may gain lesser priority, when placed on the scale with patients' work and other commitments, with their limited resources such as time and finances in consideration.

Patients could possibly have considered the bariatric surgery as the end-point to their weight and health concerns, failing to realise that bariatric surgery is a means and a beginning of a journey towards a healthier lifestyle management. Thus, patients perceived postoperative follow-up as unnecessary.

Moreover, patients lose weight significantly during the first year after the surgery.⁵ They may be pleased with the positive changes in their weight and health condition, which are visibly noticeable. These further influence their perception of benefit of care in attending to the postoperative follow-up appointments, perceiving them as excess.

Though the validity of the present study remains to be verified in studies with a larger sample size, the factors identified in the present study shed light on potential interventions that can be implemented to improve adherence to postoperative follow-up appointments. Specifically, more emphasis can be placed on educating patients during the preoperative phase, regarding the importance of postoperative follow-up and management, thus altering

the perception of excess benefit of care. With the lack of awareness of the importance of postoperative follow-up and management, manipulating other factors such as providing cues to attend the appointments, accommodating in appointment scheduling, and adjusting financial cost without educating the importance of postoperative follow-up and management would be futile in improving adherence.

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Clinical Outcomes of Ray Amputation in Diabetic Foot Patients

Dear Editor,

Diabetes mellitus is a growing problem in Singapore, with a reported incidence of 11.3% of the Singapore population, a significant increase from 8.2% in 2004.¹ With the implementation of a multidisciplinary approach combined with a clinical pathway, our major amputation rate (below- and above-knee amputation) has been reduced from 31.15% in 2002 to 11.01% in 2007.² Nather et al in 2008 identified predictive factors leading to limb loss in diabetic patients to be peripheral vascular disease and infection.³

Minor amputations in diabetic feet surgery include toe disarticulation, ray amputation, transmetatarsal amputation, Chopart's, Lisfranc's, Syme and Pirogoff amputation.⁴ The ray amputation is the commonest minor amputation performed in Singapore, and is preferred to the disarticulation of the toe.³ Several papers have studied the outcome of minor amputation in diabetic foot patients without further classifying which type of minor amputation was performed.^{5,6,7} Others have studied ray amputations in patients with and without diabetes.⁸

There are few studies in the literature on the clinical outcome of ray amputation in diabetic foot patients.^{9,10,11} These studies reported mainly selective aspects of clinical outcome such as mortality and recurrence of ulcers.^{9,10,11} The aim of this paper is to evaluate the factors that would predict a poor outcome following a ray amputation.

Materials and Methods

This is a prospective cohort study of 150 consecutive patients with diabetic foot problems undergoing ray amputation by the National University Hospital (NUH) Diabetes Foot Team from January 2007 to October 2010. Ethics approval from the hospital's ethics board was granted. Informed consent was taken. These patients were followed up for a minimum of 12 months.

Demographic data and patient profile such as age, sex, premorbid status, duration and type of diabetes, comorbidities, presence of risk factors such as smoking, alcoholism, and hyperlipidaemia were recorded. Clinical examination included the vascular status (lower limb pulses, ankle and toe-brachial indexes) and the neuropathy

status (5.07 Semmes-Weinstein Monofilament testing, Neurothesiometer reading). The presence and severity of renal failure along with cardiac status (history of acute myocardial infarction and latest ejection fraction) and the American Society of Anesthesiologists (ASA) score of the patients were documented. Preoperative blood investigations recorded included glycated haemoglobin (HbA1c), full blood count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Other investigations include wound/tissue and blood cultures. All laboratory/radiological and clinical findings were performed within 1 week of surgery by an independent observer not involved in the surgery. The indications for a ray amputation included 3 broad groups: wet gangrene of the toe, osteomyelitis of the proximal or distal phalanx, and soft tissue infection of the whole toe.

All patients were followed up for any postoperative complications. The need for any repeat operation and type of revision operation (revision of ray amputation, additional ray amputation in the affected foot, transmetatarsal amputation, syme amputation, below-knee amputation or above-knee amputation) were documented. Any mortality was also recorded.

A good clinical outcome is defined as one whose amputation healed and does not develop any complication within a year. A poor clinical outcome is defined as one who underwent proximal level reamputation within a year, and/or underwent additional ray amputation on the same foot within a year, and/or suffered mortality within a year after operation.

Statistical Analysis

All statistical analyses were performed using SPSS 18.0 with statistical significance set at $P < 0.050$. Predictive factors for clinical outcome were determined using univariate and stepwise logistic regression analysis. Mann-Whitney U test was used for numerical prognostic factors, and chi-square test was used for categorical factors.

Results

Table 1 shows the patient profile of our study population. The ages of our patients ranged between 24 to 81 years with

a median age of 56 years. Racial distribution in our study cohort was 39.3% Chinese, 38.7% Malays, 20% Indian and 2% other races, and this was compared to the national racial composition of Singapore.¹² The mean follow-up duration was 36 months (range, 13 to 62 months). No patients were lost to follow-up during the minimum follow-up period of 12 months.

Table 2 summarises the results of ray amputation. A total of 106 patients (70.7%) of ray amputations gave a good outcome. Univariate analysis showed that smoking, chronic renal failure, wet gangrene, absence of pulses, delayed capillary filling, low ankle-brachial index (ABI) and toe-brachial index (TBI), high total white blood cell count (TWC) and neutrophil count, high ESR, high urea, high creatinine (Cr) and low haemoglobin (Hb) were associated with a poor clinical outcome. Multivariate analysis showed that smoking, absence of pulses, delayed capillary filling, high ESR, high Cr and neutrophil counts were associated with a poor clinical outcome.

A total of 44 patients (29.3%) had a poor outcome. Of these patients, 22 patients (14.7%) underwent proximal level amputations, 12 patients (8.0%) underwent additional ray amputation, 7 patients (4.6%) underwent forefoot

amputation, and 3 (2.0%) patients died within 1 year. Two of the patients died of pneumonia resulting from systemic septicaemia, and 1 patient who had poor preoperative cardiac function died from postoperative acute myocardial infarction.

Discussion

The high incidence of minor amputations performed in diabetic foot patients has been well documented in existing literature.^{3,13,14} However, the significantly high rate of reamputations and significant mortality of these patients suggest that these patients should be better managed perioperatively.^{6,9,10,11,15}

Izumi et al found the cumulative rates of upper level reamputation post ray amputation to be as high as 50% after 5 years.⁹ Ohsawa et al reported a reamputation rate of 40% after 2 years.¹¹ Murdoch et al reported 60% reamputation rate, with the mean time from first to second amputation being approximately 10 months.¹⁶

Minor foot amputations have also been associated with poor outcome in terms of mortality.⁶ Jones et al have investigated the cumulative mortality rate of toe amputations and reported it to be 31.8% after 3 years and 41.4% after 5 years.⁶ A total of 70.7% of our patients had a good outcome. This is similar to results of Izumi et al in 2006, who found 73.3% good outcome after 1 year in a cohort of 277 diabetic foot patients.⁹

In our study, other significant risk factors for a poor outcome included markers of sepsis such as high ESR and high neutrophil counts. Hambleton et al have reported a similar finding in their prospective case controlled study of 205 diabetic foot patients, where sepsis was identified as one of the risk factors for poor outcome.¹⁵

Chronic renal failure and high Cr levels were associated with a poor outcome. This is similar to results published by Sheahan et al, who looked into a mixed cohort of 607 patients with 91.9% of the cohort having diabetes, and reported endstage renal failure and high Cr levels as poor prognostic indicators.⁸

Limitations of this study include a small sample size and a short follow-up period of less than 5 years. The authors aim to further follow-up the patients to report a 5-year outcome, and to generate a predictive model with an analysis of its prognostic accuracy to better guide management of ray amputations in diabetic foot infections.

Conclusion

The success rate of ray amputation was 70.7%. Smoking, absence of pulses, delayed capillary filling, high ESR, high Cr and neutrophil counts were found to be predictive factors for a poor clinical outcome.

Table 1. Patient Profile

Factors	Value (%)
Gender distribution	
Male	100 (66.7%)
Female	50 (33.3%)
Age	
≤60 years	103 (68.7%)
>60 years	47 (31.3%)
Race	
Chinese	59 (39.3%)
Malay	58 (38.7%)
Indian	30 (20.0%)
Others	3 (2.0%)
Premorbid activities of daily living	
Independent	132 (88.0%)
Walking with aid	9 (6.0%)
Wheelchair bound	8 (5.3%)
Bed bound	1 (0.7%)
Comorbidities	
Hypertension	111 (74.0%)
Ischaemic heart disease (IHD)	50 (33.3%)
Cerebrovascular accident (CVA)	12 (8.0%)
Hyperlipidaemia	90 (60.0%)
Diabetes type	
Type I	11 (7.3%)
Type II	139 (92.7%)

Table 2. Results of Evaluation of Factors as Predictives of Outcome

		Outcome		Unadjusted	Adjusted	
Risk Factors*		Good	Poor	P Value	OR (95% CI)	P Value
Age						
≤60 years		71 (68.9)	32 (31.1)	0.956		
>60 years		35 (74.5)	12 (25.5)			
Gender						
Male		71 (71.0)	29 (29.0)	0.522		
Female		35 (70.0)	15 (30.0)			
Race						
Chinese		37 (62.7)	22 (37.3)	0.222		
Malay		42 (72.4)	16 (27.6)			
Indian		24 (80.0)	6 (20.0)			
Others		3 (100.0)	0 (0.0)			
Premorbid ADL						
Independent		94 (71.2)	38 (28.8)	0.683		
Walking with aid		5 (55.6)	4 (44.4)			
Wheelchair		6 (75.0)	2 (25.0)			
Bedbound		1 (100.0)	0 (0.0)			
Smoking						
	Yes	20 (32.8)	41 (67.2)	0.022	32.1 (8.924 – 91.401)	0.040
	No	64 (71.9)	25 (28.1)		1.0	
Comorbidities						
Hypertension		Yes	76 (68.5)	35 (31.5)	0.216	
	No	30 (76.9)	9 (23.1)			
Hyperlipidaemia		Yes	61 (67.8)	29 (32.2)	0.222	
	No	45 (75.0)	15 (25.0)			
CVA		Yes	9 (75.0)	3 (25.0)	0.511	
	No	97 (70.3)	41 (29.7)			
IHD		Yes	35 (70.0)	15 (30.0)	0.522	
	No	71 (71.0)	29 (29.0)			
Previous AMI		Yes	24 (64.9)	13 (35.1)	0.221	
	No	82 (73.2)	30 (26.8)			
Renal function						
End stage renal failure		ESRF	8 (42.1)	11 (57.9)	0.006	
Chronic renal failure		CRF	7 (58.3)	5 (41.7)		
Normal renal function		Normal	91 (76.5)	28 (23.5)		
Sensory neuropathy		Yes	88 (69.3)	39 (30.7)	0.273	
	No	18 (78.3)	5 (21.7)			
Diabetes mellitus type						
Type 1		9 (81.8)	2 (18.2)	0.322		
Type 2		97 (69.8)	42 (30.2)			
Duration of diabetes						
1 – 5 years		16 (80.0)	4 (20.0)	0.485		
5 – 10 years		24 (64.9)	13 (35.1)			
>10 years		66 (71.0)	27 (29.0)			

ABI: Ankle-brachial index; ADL: Activities of daily living; AMI: Acute myocardial infarction; ASA: American Society of Anaesthesiologists; CRF: Chronic renal failure; CRP: C-reactive protein; CVA: Cerebrovascular accident/stroke; ESR: Erythrocyte sedimentation rate; ESRF: End stage renal failure; Hb: Haemoglobin; HbA1c: Glycated haemoglobin; IHD: Ischaemic heart disease; NF: Normal foot; OR: Odds ratio; PF: Pathological foot; TBI: Toe-brachial index; TWC: Total white blood cell count

*Mann-Whitney U test used for numerical prognostic factors; chi-square test used for categorical factors.

Table 2. Results of Evaluation of Factors as Predictives of Outcome (Con't)

Risk Factors*		Outcome		Unadjusted	Adjusted	
		Good	Poor	P Value	OR (95% CI)	P Value
ASA score						
1		1 (50.0)	1 (50.0)	0.363		
2		58 (73.4)	21 (26.6)			
3		47 (69.1)	21 (30.9)			
4		0 (0.0)	1 (100.0)			
Vasculopathy						
Pulses	Both pulses not palpable	26 (53.1)	23 (46.9)	0.004	1.0	0.050
	1 pulse palpable	15 (83.3)	3 (16.7)		6.337 (1.231 – 32.610)	0.027
	2 pulses palpable	65 (78.3)	18 (21.7)		2.176 (0.870 – 5.440)	0.096
Delayed capillary filling	Yes	18 (50.0)	18 (50.0)	0.002	1.0	0.031
	No	88 (77.2)	26 (22.8)		2.832 (1.102 – 7.281)	
ABI: median (range)		1.1 (0.2 – 2)	0.9 (0.2 – 3.6)	0.001		
TBI: median (range)		0.8 (0.1 – 2.9)	0.5 (0.1 – 3)	0.013		
Neuropathy						
Monofilament test (PF)	≤7/10	93 (70.5)	39 (29.5)	0.560		
	>7/10	13 (72.2)	5 (27.8)			
Monofilament test (NF)	≤7/10	87 (71.3)	35 (28.7)	0.440		
	>7/10	19 (67.9)	9 (32.1)			
Neurothesiometer (PF)	0 – 25 V	11 (61.1)	7 (38.9)	0.820		
	26 – 50 V	55 (72.4)	21 (27.6)			
	>50 V	18 (72.0)	7 (28.0)			
	Not tested	22 (71.0)	9 (29.0)			
Neurothesiometer (NF)	0 – 25 V	17 (89.5)	2 (10.5)	0.102		
	26 – 50 V	41 (69.5)	18 (30.5)			
	>50 V	16 (80.0)	4 (20.0)			
	Not tested	32 (61.5)	20 (38.5)			
Preop parameters: median (range)						
Hb (g/dL)		11.5 (6.4 – 15.7)	10 (7.4 – 15)	0.005		
TWC (x10 ⁹ /L)		13.0 (6.5 – 33)	15.6 (6.2 – 28)	0.042		
Neutrophils (x10 ⁹ /L)		10.4 (3.2 – 28.4)	14 (4.8 – 23.6)	0.000	0.880 (0.810 – 0.956)	0.002
CRP (mg/L)		120.4 (9.6)	145.4 (15.2)	0.209		
ESR (mm/hr)		94.5 (13 – 150)	157.5 (2 – 356)	0.005	0.982 (0.968 – 0.997)	0.021
Urea (mmol/L)		5.6 (1 – 76)	8.3 (1.4 – 25.9)	0.011		
Creatinine (umol/L)		82.5 (3 – 985)	139 (44 – 939)	0.000	0.997 (0.995 – 0.999)	0.004
HbA1c (%)		10.0 (5.5 – 16)	9.5 (5.9 – 73)	0.474		
Indication for surgery						
Wet gangrene		57 (62.0)	35 (38.0)	0.013		
Osteomyelitis		28 (84.8)	5 (15.2)			
Soft tissue infection of whole toe		21 (84.0)	4 (16.0)			

ABI: Ankle-brachial index; ADL: Activities of daily living; AMI: Acute myocardial infarction; ASA: American Society of Anaesthesiologists; CRF: Chronic renal failure; CRP: C-reactive protein; CVA: Cerebrovascular accident/stroke; ESR: Erythrocyte sedimentation rate; ESRF: End stage renal failure; Hb: Haemoglobin; HbA1c: Glycated haemoglobin; IHD: Ischaemic heart disease; NF: Normal foot; OR: Odds ratio; PF: Pathological foot; TBI: Toe-brachial index; TWC: Total white blood cell count

*Mann-Whitney U test used for numerical prognostic factors; chi-square test used for categorical factors

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An Uncommon Cutaneous Reaction for a Common Drug

A 72-year-old Chinese female presented with a rapidly progressing, generalised rash over a 2-week period. Her medical history includes hypertension for which nifedipine had been started 5 weeks earlier. She was otherwise well with no systemic symptoms. Physical examination showed annular, scaly, erythematous plaques with central clearing on her upper and lower limbs, neck, trunk, and back (Figs. 1A and 1B).

What is the diagnosis?

- A. Plaque psoriasis
- B. Drug-induced subacute cutaneous lupus erythematosus (DI-SCLE)
- C. Erythema annulare centrifugum
- D. Sweet's syndrome
- E. Cutaneous T-cell lymphoma

Case Report

The patient's full blood count, liver and renal biochemistry were unremarkable apart from eosinophilia ($0.9 \times 10^3/\mu\text{L}$, normal range = $0.0 - 0.4 \times 10^3/\mu\text{L}$). Her antinuclear antibody, anti-double-stranded DNA, antihistone antibody, and Ro/Sjögren syndrome-associated antigen A (Ro/SSA) autoantibodies were negative. Direct immunofluorescence was negative. A skin biopsy from a representative lesion showed focal interface activity with basal vacuolar change and lymphocytic exocytosis admixed with few eosinophils (Fig. 2). There was increased mucin on Alcian blue stain. The clinical picture and histological findings were consistent with DI-SCLE. Her lesions resolved within several weeks upon withdrawal of nifedipine.

Discussion

DI-SCLE is characterised by scaly annular skin lesions, usually in sun exposed areas. It is related to drug exposure. Antihypertensives including hydrochlorothiazide and nifedipine, and antifungals are some of the common triggers for DI-SCLE. More recently, chemotherapeutic drugs such as taxanes have been reported to cause DI-SCLE.¹ The

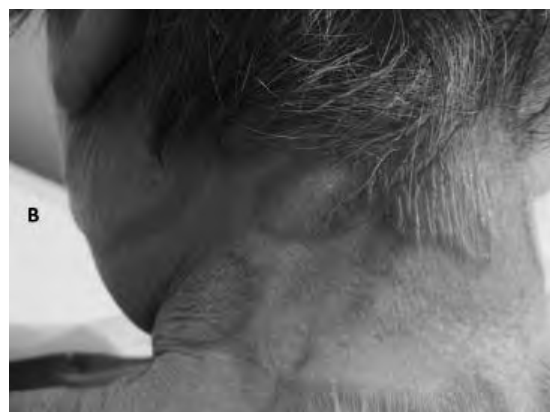


Fig. 1. A 72-year-old patient presented with rapidly progressing, generalised rash. Erythematous, annular, scaly plaques with central clearing are seen on patient's (A) upper limb and (B) neck.

Answer: B

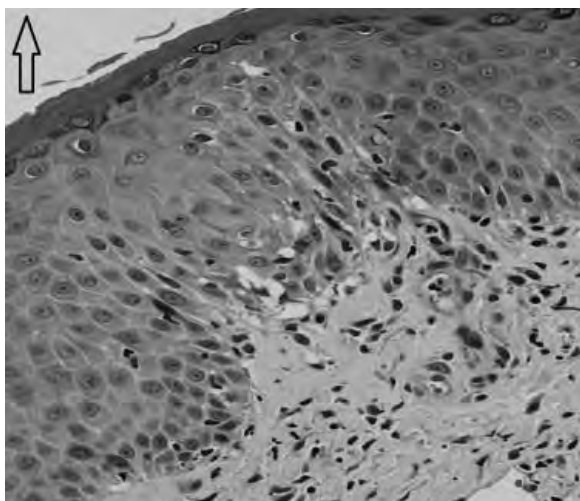


Fig. 2. Skin biopsy from thigh; H&E stain, original magnification x40.

onset of cutaneous lesions from the initiation of the culprit drug varies with different drug classes. Cutaneous lesions may appear within 5 weeks after exposure to antifungals, while calcium channel blockers may trigger a rash up to 3 years after initial exposure.² The pathogenesis of DI-SCLE is unknown. Some have suggested that DI-SCLE may be a consequence of de novo autoantibody formation after drug exposure. Others suggest DI-SCLE as a development of a condition in an already predisposed patient.³

There is a strong association with Ro/SSA autoantibodies (found in up to 90% of patients).^{2,4} However, antihistone antibody is positive in only one-third of patients of DI-SCLE.² Positive direct immunofluorescence may be found in up to 80% of cases of DI-SCLE.² The characteristic histological feature of DI-SCLE is an interface dermatitis with focal vacuolisation of the epidermal basal layer and perivascular dermal lymphocytic infiltrate.² A recent retrospective study demonstrated that tissue eosinophilia is not a differentiating histological feature of DI-SCLE, and that the diagnosis of DI-SCLE should be based largely on drug history and clinical findings.⁵

DI-SCLE is similar to idiopathic subacute cutaneous lupus erythematosus in terms of clinical, histopathological, or immunopathological features.² In contrast, patients with DI-SLE present with fever, weight loss and serositis. Antihistone antibody may be positive in 95% of patients in this group of patients.⁶

In our patient, we diagnosed DI-SCLE based on the recent introduction of typical drug, clinical features and supportive histology findings. Interestingly, Ro/SSA autoantibodies were negative in this patient. Nifedipine was withdrawn and she was treated with topical betamethasone valerate 0.1%. Five weeks after drug withdrawal, her rash had completely resolved. On the last follow-up 4 months later, there was no relapse of her symptoms.

Conclusion

Discontinuation of the offending drug usually results in resolution of the skin lesions in DI-SCLE within weeks.² However, some cases may require the use of topical or systemic corticosteroids.

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The Interface Between Medicine and Psychiatry: Neuropsychiatric Aspects of Systemic Lupus Erythematosus (SLE)

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Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease characterised epidemiologically by the preponderance of women, and pathologically by the loss of immunological tolerance to self-nuclear antigens and aberrant B- and T-cell responses.^{1,2} Similar to that of other regions around Southeast Asia, the prevalence of SLE in Singapore is 40/100,000.³ Amongst various organ involvement, neuropsychiatric SLE (NPSLE) is one of the most devastating presentations of the condition.⁴ NPSLE is likely the result of the interplay amongst the immunopathological actions of autoantibodies, intrathecal inflammatory mediators and cerebral microvasculopathy.⁵ The American College of Rheumatology (ACR) Ad Hoc Committee devised case definitions for 19 neuropsychiatric syndromes in SLE which comprise central and peripheral neurological, and psychiatric syndromes such as anxiety, depression and cognitive dysfunction.⁶ Irreversible organ damage, which potentially occurs when lupus-induced damage persists for more than 6 months, does not spare the neuropsychiatric system. Indeed, damage to the neuropsychiatric system has been dragging down the 5-year and 10-year survival rates of lupus patients over the past 50 years,⁷ in addition to the substantial socioeconomic burden it entails for those who survive.⁸

Historical Understanding of the Psychiatric Aspects of SLE

In the 1950s, reports of acute anxiety, depression, delusions and hallucinations in lupus patients started to emerge in the literature.^{9,10} Owing to the increased awareness and liaison with psychiatrists, the reported frequency of psychiatric symptoms amongst lupus patients increased from less than 20% before 1960 to 40% thereafter.¹¹ Forty-one percent of the lupus patients suffered from non-organic, non-psychotic psychopathology as compared to psychotic pathology such

as paranoid delusion and visual hallucinations.¹² Depression (39%) and anxiety (24%) are the commonest psychiatric comorbidities of SLE.¹³ Patients with SLE are susceptible to depression as a result of psychological reaction to the disease, the direct impact of inflammatory mediators on the brain, and the side effects of high-dose glucocorticoids.^{14,15} As compared to patients with other common rheumatic conditions, lupus patients are more likely to suffer from anxiety which is predicted by damage accrual, higher cumulative glucocorticoid dose and the presence of depression.¹⁶ Cognitive impairment, one of the commonest neuropsychiatric lupus manifestations, was found in 14% to 75% of lupus patients¹⁷ and associated with significant functional impairment. The ACR developed a set of standard neuropsychological tests to assess cognitive function which chiefly includes attention, executive function, memory and visuoconstructional abilities. Patients with SLE have been demonstrated inferior performance in all of these domains as compared to healthy individuals.¹⁸

In general, Asian lupus patients have more serious organ manifestations including NPSLE than their Caucasian counterparts.¹⁹ Locally, neuropsychiatric symptoms were found in 21% of Chinese lupus patients, with a female predominance and tendency to manifest early in the course of SLE.^{20,21} In this study, disturbances of orientation, perception and memory were the commonest lupus-related psychiatric comorbidities.

Some Recent Advances in the Understanding of Neuropsychiatric Aspects of Lupus

Cerebral atrophy, which can be caused by the reduction of the white and/or grey matter volume, is commonly described in lupus patients.²² Intriguingly, inflammation and atrophy of the white matter have been found to be more pronounced than those of the grey matter in lupus

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patients, especially in those with short disease duration.^{23,24} The involvement of white matter atrophy was generally correlated with anxiety, cognitive impairment, the duration of SLE and cumulative glucocorticoid dose.²⁴⁻²⁶ It is currently believed that the inciting impact of inflammation on the white matter precedes grey matter damage in lupus patients.^{24,26} Nevertheless, the differential clinical implications of white and grey matter damage remain to be elucidated in lupus patients.

A number of recent functional magnetic resonance imaging (fMRI) studies in lupus patients has generally revealed deactivations of various cortical areas responsible for working memory and executive function, accompanied by compensatory activations in other cortical areas for preserving cognitive functioning. For example, patients with childhood-onset SLE showed compensatory activations in the visual association area and the dorsolateral prefrontal cortex (attention area) but deactivations in the cingulate gyrus during the N-back working memory task.²⁷ Our recent fMRI study using the Wisconsin Card Sort Test (WCST) which probes cognitive set-shifting found that the cortico-basal ganglia-thalamic-cortical circuit, which is involved in response inhibition, was dysfunctional in adult lupus patients.²⁸ With the compensatory activations in the contralateral cerebellar and frontal areas, the performance of the WCST amongst the patients remained equivalent to that of healthy subjects despite the dysfunctional neural circuit.²⁸

The pathogenetic role of some autoantibodies in NPSLE remain controversial. For instance, high anti-ribosomal P titres were found to be associated with depression and psychosis,^{29,30} and anticardiolipin IgG was found to be related to cognitive impairment.³¹ While depression and memory impairment were noted in lupus patients with elevated serum titres of anti-NR2,³² most of the other similar studies refuted such relationships except those which studied the antibodies in the cerebrospinal fluid.^{33,34} Currently, the breach of the blood-brain barrier (BBB) is believed to be essential for the entry of pathogenic autoantibodies into the central nervous system which trigger neuropsychiatric symptoms.³⁵

Current Knowledge Gaps and Future Research Directions

The pathogenesis of neuropsychiatric symptoms in patients with SLE is still not fully elucidated. The major challenges in diagnosing and monitoring NPSLE stem from its diversity and protean clinical feature, and the lack of reliable lupus-specific neuropsychological assessment tools as well as valid diagnostic and prognostic biomarkers.³³ Targeted exploration of pathogenic autoantibodies and

inflammatory mediators leading to NPSLE coupled with longitudinal structural and functional imaging in tandem with prospective neuropsychological assessment of lupus patients are obviously paramount. Additionally, non-invasive assessment of the integrity of the BBB and its associations with neuropsychiatric symptoms and serum autoantibodies will shed more light on the pathophysiology of NPSLE.

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Causes and Features of Erythroderma

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Abstract

Introduction: Erythroderma is a generalised inflammatory reaction of the skin secondary to a variety of causes. This retrospective study aims to characterise the features of erythroderma and identify the associated causes of this condition in our population. **Materials and Methods:** We reviewed the clinical, laboratory, histological and other disease-specific investigations of 225 inpatients and outpatients with erythroderma over a 7.5-year period between January 2005 and June 2012. **Results:** The most common causative factors were underlying dermatoses (68.9%), idiopathic causes (14.2%), drug reactions (10.7%), and malignancies (4.0%). When drugs and underlying dermatoses were excluded, malignancy-associated cases constituted 19.6% of the cases. Fifty-five percent of malignancies were solid-organ malignancies, which is much higher than those previously reported (0.0% to 25%). Endogenous eczema was the most common dermatoses (69.0%), while traditional medications (20.8%) and anti-tuberculous medications (16.7%) were commonly implicated drugs. In patients with cutaneous T-cell lymphoma (CTCL), skin biopsy was suggestive or diagnostic in all cases. A total of 52.4% of patients with drug-related erythroderma had eosinophilia on skin biopsy. Electrolyte abnormalities and renal impairment were seen in 26.2% and 16.9% of patients respectively. Relapse rate at 1-year was 17.8%, with no associated mortality. **Conclusion:** Our study highlights the significant proportion of malignancy-related erythroderma in those whom common underlying causes such as dermatoses and drugs have been excluded. In cases of drug-related erythroderma, traditional medications and antituberculous medications are common causes in our population. Renal impairment and electrolyte abnormalities are commonly seen and should be monitored in patients with erythroderma.

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Key words: Cancer, Exfoliative, Malignancy

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Introduction

Erythroderma is a dermatological reaction characterised by extensive erythema and scaling of the skin secondary to a variety of causes. An improved understanding of the characteristics and aetiologies of this condition will guide management. In this retrospective study, we aim to describe the characteristics and explore the associated causes of the condition in our population.

Materials and Methods

The profile of all inpatients and outpatients with erythroderma who visited the National Skin Centre (NSC),

during a 7.5-year period from 1 January 2005 through 30 June 2012 was retrospectively analysed. Erythroderma was defined clinically as erythema and scaling involving more than 90% of the body surface. The data collected included patient demographics, drug history, past medical and dermatological history, clinical findings (skin erythema, scaling, mucosal or nail involvement, lymphadenopathy, organomegaly, pedal oedema, pruritus, fever or chills), laboratory investigations (haematologic parameters, serum electrolytes, liver and renal function, albumin and inflammatory markers), skin biopsies, cultures and other disease-specific investigations (such as imaging and bone marrow examination). The disease course was analysed, with a follow-up period of 0 to 7.5 years.

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Results

There were 225 patients diagnosed with erythroderma during the study period. The mean age of the patients was 66.0 years (range, 1 month to 95 years), median 70 years, with a male-to-female ratio of 3:1. Majority were Chinese (78.0%), followed by Malays (15.0%), Indians (3.5%) and other ethnic groups (3.5%).

The most common clinical presentations were generalised erythema (100.0%), scaling (92.4%) and pruritus (92.0%). Lymphadenopathy (32.9%), chills (24.0%) and pedal oedema (19.6%) were common, while fever (4%), nail (3.5%), mucosal involvement (2.0%) and organomegaly (1.0%) were uncommon (Table 1).

Eosinophilia (58.2%), hypoalbuminemia (45.3%), electrolyte abnormalities (26.2%) and renal impairment (16.9%) were common laboratory findings. Skin or wound cultures were done in 24.4% of the patients, in whom 92.7% (51/55) had positive cultures results, with methicillin-sensitive *Staphylococcus aureus* (MRSA) being the most frequent organism isolated (64.7%, 33/51). In patients with positive skin or wound cultures, 17.6% (9/51) had associated raised inflammatory markers (total white cell count and C-reactive protein (CRP)), 35.3% (18/51) had thermoregulation (fever or chills) and 5.9% (3/51) had bacteraemia. Bacteraemia occurred in 15.9% (7/44) of those tested.

Serum tumour markers were measured as part of the malignancy workup in 60.0% (135/225) of the patients. These included alpha-fetoprotein (AFP), carcinoembryonic antigen (CA), prostate-specific antigen (PSA) (in males), CA 19-9 and CA 125 (in females). At least 1 of these markers were abnormal in 35.6% of these patients (48/135). However, there was no associated malignancy when further investigated in these cases, except for 1 patient with raised AFP and underlying hepatocellular carcinoma (HCC).

Skin biopsy was performed in 76.0% of the patients. The most common histological findings were subacute or chronic dermatitis (35.1%), followed by psoriasiform dermatitis (29.3%). In the biopsy specimens of patients with drug-related erythroderma, 52.4% had findings of eosinophilia, 4.8% showed interface dermatitis, and 4.8% had both of these features. In all the 4 patients with cutaneous malignancies, histological analysis was suggestive or diagnostic of cutaneous T-cell lymphoma (CTCL).

The aetiology of erythroderma can be classified into 4 main categories (Table 2). The most common causative factors were pre-existing dermatoses (68.9%, 155/225), idiopathic causes (14.2%, 32/225), drug reactions (10.7%, 24/225), and malignancies (4.0%, 9/225). Among the pre-existing dermatoses, endogenous eczema was most common (69%, 107/155), followed by psoriasis (20.6%, 32/155). The most commonly implicated drugs were traditional medications (20.8%, 5/24) and antituberculous medications (16.7%, 4/24). Other implicated agents include penicillin, omeprazole, Keppra®, thiazides, calcium channel blockers and Irressa®.

Forty-five percent (4/9) of the malignancies were primary cutaneous malignancies, consisting of mycosis fungoides (3/4) and Sezary syndrome (1/4), while 55.0% (5/9) were solid-organ malignancies, with 2 cases of hepatocellular carcinoma, 1 case each of nasopharyngeal, colorectal and non-small cell lung carcinoma. Four out of 5 cases of solid-organ malignancies were diagnosed after the onset of erythroderma as part of the malignancy evaluation, while 1 patient had pre-existing HCC. The initial findings of colorectal, lung and HCC were seen on computed tomographic scans, while nasopharyngeal carcinoma (NPC) was seen on nasoendoscopy.

In the treatment of erythroderma, 48.9% of the patients received antibiotics, 42.2% received systemic steroids and

Table 1. Clinical Features of Erythroderma

Clinical Feature	Wong KS et al, 1988 ⁶ (%)	Pal and Haroon, 1998 ¹ (%)	Akhyani et al, 2005 ⁵ (%)	Li J et al, 2012 ⁹ (%)	Present Study (% Out of 225 Patients)
Erythema	100.0	100.0	100.0	100.0	100.0
Scaling	100.0	84.4	100.0	100.0	92.4
Pruritus	NA	86.0	97.5	87.7	92.0
Lymphadenopathy	22.0	55.5	21.3	19.2	32.9
Chills	NA	64.4	NA	31.1	24.0
Pedal oedema	44.0	44.4	14.4	37.7	19.6
Fever	12.0	40.0	33.6	40.0	4.0
Nail involvement	NA	80.0	NA	29.6	3.5
Mucosal involvement	NA	36.6	1.0	NA	2.0
Organomegaly	9.0	25.5	4.0	NA	1.0

NA: Not available

8.4% required other types of systemic agents, including dapsone, ciclosporin, methotrexate (MTX), azathioprine, acitretin and interferon-alpha (used in Sezary syndrome). The outcomes of the patients were fairly good with no deaths directly related to the condition. Relapse rate at 1-year was 17.8%, most commonly in patients with underlying endogenous eczema.

Discussion

In our study, patients presented at an older age, with mean age of onset at 66.0 years. This is older than figures quoted in other studies, which ranged from 41.6 to 61.0 years.¹⁻⁴ There were 3 times more males in our study, in concordance with other studies.^{1,2,5-7}

The prevalence of most clinical features, including erythema, scaling, pruritus, lymphadenopathy, oedema, chills, organomegaly and mucosal and nail involvement, were similar to other studies.^{1,5} However, the prevalence of fever (4.0%) among our patients was much lower compared to other studies (33.0% to 37.8%).^{3,5,8}

Laboratory investigations showed renal impairment in 16.9% of our patients, likely secondary to dehydration from fluid losses and poor oral intake during severe acute illness. In contrast, although King et al⁸ and Yuan et al³ reported multiple other laboratory abnormalities, renal impairment was not reported. Skin or wound cultures were positive in 92.7% of the patients tested; however, only 17.6% of these patients had associated raised inflammatory markers and 5.9% associated bacteremia. Hence, the routine use of systemic antibiotics in patients with positive skin or wound cultures is not recommended, as these may represent skin commensals.

In patients with pre-existing dermatoses that is poorly controlled, erythroderma may occur during a flare of the skin disease.^{1,3,5,9} In such cases, the diagnosis is usually obvious. Otherwise, erythroderma remains a diagnostic challenge which often entails a thorough drug history and malignancy screening. In the latter, there is no consensus of when to initiate and what investigations to conduct. In a significant number of cases, despite extensive investigations, no cause was found and these were designated to have an idiopathic aetiology.

The various categorical causes of erythroderma in our study appear similar in frequency compared to previous studies (Table 3). Although malignancies were the cause of erythroderma in only 4.0% of our patients, from a practical point of view, they constituted 19.6% of the cases when drugs and underlying dermatoses were excluded. As such, an active search for an associated malignancy should be carried out in such cases. The frequency of malignancies in our study population was comparable to other studies (1.0% to 11.3%),^{3,5,9,10} comprising of both solid-organ and cutaneous malignancies. The higher incidence of HCC associated with erythroderma might be accounted for by the prevalence of this cancer in Asia, largely due to the ubiquity of hepatitis B infection in this part of the world.¹¹

In patients diagnosed with malignancy in our series, all had normal levels of serum tumour markers except for 1 patient with HCC. On the other hand, the tumour markers were abnormal in 35.6% of the patients in whom the levels were measured, and 99.3% of them did not have an underlying

Table 2. Aetiologies of Erythroderma

Cause	Percentage (%) Out of 225 Patients
Underlying dermatoses	68.9
Endogenous eczema	47.6
Psoriasis	14.2
Others*	7.1
Idiopathic	14.2
Drugs	10.7
Malignancy	4.0
Cutaneous	1.8
Solid organ†	2.2
Others‡	2.2

*Includes acquired ichthyosis, chronic actinic dermatoses, pityriasis rubra pilaris, seborrheic dermatitis, bullous pemphigoid, pemphigus foliaceus and actinic keratosis.

†Includes 2 cases of hepatocellular carcinoma and 1 case of colorectal carcinoma, nasopharyngeal carcinoma and non-small cell lung carcinoma each.

‡Includes contact dermatitis, papuloerythroderma of Ofuji and erythema toxicum neonatorum.

Table 3. Categorical Aetiologies of Erythroderma in Previous Publications and the Present Study

Aetiologies	Relative Incidence (%)					
	Wong KS et al 1988 ⁶	Pal and Haroon 1998 ¹	Akhyani et al 2005 ⁵	Yuan XY et al 2010 ³	Li J et al 2012 ⁹	Present Study 2012
Underlying dermatoses	57.0	74.4	57.9	72.0	70.8	68.9
Drug reactions	13.0	5.5	21.6	17.0	12.7	10.7
Malignancies	0.0	5.5	11.3	4.9	2.3	4.0
Idiopathic	29.0	14.6	7.2	6.1	14.2	14.2

malignancy. Hence tumour markers are not useful as a screening tool for malignancy. The workup in such patients should instead rely on imaging and endoscopies, guided by clinical findings. Features previously noted to be suggestive of an underlying malignancy include combinations of presence of systemic symptoms, an insidious onset, lack of a pre-existing dermatosis and resistance to standard treatment.¹²

In drug-induced erythroderma, skin biopsies revealed eosinophilia in 52.4% of our patients compared to 16.6% in the study by King et al.⁸ Skin biopsy was also effective in the diagnosis of primary cutaneous malignancies in all 4 of our patients, with 3 or fewer biopsies required per patient for the diagnosis to be made.

In the literature, common drugs implicated in erythroderma include antiepileptics (such as phenobarbitone, carbamazepine, and phenytoin), antibiotics (such as penicillin, sulphonamides and antituberculous drugs), gold, lithium salts and allopurinol.^{4,5,12,13} The major causative drugs vary between studies, and appear to correlate with regional endemic diseases and cultural norms.^{3,9} In our study, antituberculosis medications including isoniazid and rifampicin, as well as traditional Chinese medicine were the most common causative drugs. This may be due to the higher prevalence of tuberculosis in Southeast Asia, and the relatively widespread use of traditional Chinese medicine in Singapore.

In contrast to some earlier studies that have quoted high mortality rates mainly attributed to drugs or lymphoma (11.0% to 64.0%),^{8,14-16} there was no mortality arising directly from erythroderma in our study population. Some other studies had also quoted low mortality rates in the range of 0.0% to 2.0%.^{5,9,17}

Conclusion

Erythroderma is commonly caused by pre-existing dermatoses and drugs. A thorough drug history should be taken including traditional medications and supplements, and if present, eosinophilia seen on skin biopsy supports a drug aetiology. However, when these have been excluded, an associated malignancy is present in a significant proportion of cases and should be actively screened for. With similar frequencies of both cutaneous and solid organ malignancies, malignancy screen should include both cutaneous and solid organ malignancies. Renal impairment and electrolyte abnormalities are commonly seen and should be monitored in patients with erythroderma.

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Hydrosurgery is Effective for Debridement of Diabetic Foot Wounds

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Abstract

Introduction: Diabetic foot wounds are serious complications of diabetes mellitus. Surgical debridement is a very important part of the management of diabetic wounds. Sharp debridement using the scalpel is normally performed. Versajet II hydrosurgery system is an alternative technique for debridement. To our knowledge, this is the first study conducted to evaluate the use of hydrosurgery debridement for diabetic foot wounds. **Materials and Methods:** This pilot study included 15 consecutive patients with diabetic foot wounds who were admitted to the National University Hospital (NUH) and were managed by the Diabetic Foot Team from June 2012 to December 2012. All wounds underwent hydrosurgery debridement. Patients' demographic details, clinical details on wound assessments, and outcome were recorded and analysed. **Results:** The Versajet II hydrosurgery system was found to show some advantages over standard surgical scalpel debridement. It allowed adequate debridement whilst preserving more viable tissue to promote rapid healing. It could be manoeuvred over complex wound terrain. The time required for debridement was short — an average of 9.5 minutes. Good wound healing was achieved in all 15 cases. Only 1 Versajet debridement was required in 13 cases and 2 required an extra debridement. Twelve wounds were healed by split thickness skin grafting (STSG) and 3 wounds by secondary healing. Two of the STSG were infected but they were subsequently healed by dressings via secondary healing. **Conclusion:** Although good wound healing was achieved in all 15 cases, further study that uses a larger cohort and a randomised controlled trial is required to fully evaluate the effectiveness, or otherwise, of the Versajet II hydrosurgery system for the debridement of diabetic foot wounds.

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Key words: Infective wounds, Versajet, Wound healing

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Introduction

The prevalence of diabetes mellitus in Singapore is increasing. It was at its highest of 11.3% in the latest National Health Survey 2010 compared to 8.2% in 2004.¹ Diabetic foot wounds are serious complications of diabetes mellitus and can lead to limb loss if left untreated. Diabetics have a 10% to 25% lifetime risks of developing foot ulcers.² Neuropathy, poor circulation and injury contribute to the formation of diabetic foot ulcers and 85% of lower extremity amputations are preceded by diabetic foot ulcers.³ Nather et al found the incidence of major amputations (above and below knee) to be 27.2% for diabetics with foot complications.⁴

The commonest procedure performed for diabetic

foot surgery is surgical debridement. Debridement is the excision of necrotic, devitalised or infected tissue from a wound, leaving healthy and vascularised tissue behind. It is an essential part of wound care prior to wound healing. Sharp surgical debridement makes use of the scalpel to cut necrotic, devitalised or infected tissue from a wound.

Surgical debridement should cause only minimal damage to surrounding tissues. The preservation of viable tissue while removing necrotic tissue and slough allows wound healing to occur rapidly. Hydrosurgery debridement is a different modality described in many wound care literatures. It is used for wound bed preparation.⁵⁻¹² It enables the surgeon

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to simultaneously hold, cut and remove nonviable tissue precisely without collateral damage to healthy surrounding tissue, allowing the healing process to progress quickly.¹³ In our literature review, there are many studies that utilise hydrosurgery debridement in their wound debridement and wound bed preparation but majority of these studies reported on burn wounds, traumatic wounds like open fractures and degloving wounds, plastic surgery reconstructive wounds and chronic vascular leg ulcers.^{5-9,11,12} There are very few studies that report the usage of hydrosurgery debridement in diabetic foot wounds.^{9,11,12} Vanwijck et al in 2010 studied 167 subacute and chronic wounds using hydrosurgery debridement and only 12 of them were diabetic foot wounds.¹¹ Caputo et al in 2008 performed a prospective randomised trial comparing hydrosurgery debridement versus standard scalpel debridement in lower extremity ulcers but only had 22 diabetic foot ulcers out of 41 ulcers.¹²

To our knowledge, this is the first study that aims to report our pilot experience in using the Versajet II hydrosurgery system¹³ in the debridement of diabetic foot wounds.

Materials and Methods

This is a prospective pilot study of 15 consecutive patients treated for diabetic foot from June 2012 to December 2012. The indications for the Versajet included ray amputation wounds, wounds postdrainage for abscess, shin ulcers, and wounds postexcision of metatarsal bones. These wounds were graded according to Wagner's classification.¹⁴

Pertinent data on patients' demographics, diabetic history and control, American Society of Anaesthesiologist (ASA) grading,¹⁵ clinical assessments, operative details and complications were recorded. Peripheral neuropathy was assessed using Semmes-Weinstein 5.07/10 g monofilament test (touch/pressure) and the ability to detect 7 or less sites out of 10 sites indicated presence of peripheral neuropathy.¹⁶ Vibration perception was evaluated using the biothesiometer (Bio-Medical Instrument Company, Ohio, USA). Vascular assessment using ankle-brachial index (ABI) and toe-brachial index (TBI) were performed for each patient. Ulcer description and location were recorded. All wounds had a swab culture and sensitivity performed prior to treatment. Other parameters captured include inflammatory markers such as leukocyte count and C-reactive protein (CRP).

The Versajet was used in all 15 patients. It consisted of a disposable handpiece, power console with foot pedal activation and a waste bin. It projected a high velocity stream of sterile saline across the operating window and into the evacuation collector. This created a localised vacuum to hold and cut targeted tissue while aspirating debris from the operation site. The handpiece was held such that the waterjet was parallel to the wound so that tangential excision can be achieved. This allowed rapid removal of damaged

devitalised tissues while preserving the surrounding viable tissues. There are 2 types of handpiece available for the operator to use depending on wound type and treatment strategy. The operator can regulate the waterjet velocity using the 10 power settings that are available and visualised on the power console.

All surgeries were performed by the senior author. General or regional anaesthesia was employed. After debridement, tulle gras and Kaltostat dressings were applied. Subsequently, wound inspections were performed on postoperative day 2 and wound dressings were done using Mepilex Ag. Regular wound dressings were performed for those wounds left for secondary granulation until healing had occurred. Patients who underwent split thickness skin grafting (STSG) had a negative pressure dressing applied and the wound was inspected only on postoperative day 5 to review the state of the STSG. Following that, non-adherent dressings using Mepilex Ag were used to dress the recipient site while the donor site was dressed with tulle gras and gauze dressings.

Results

In our study, the average age of our study population was 54.5 years (range, 41 to 71 years). There were 7 males and 8 females. Our patients were followed up for an average of 10 months (range, 6 to 12 months). Majority of them were ASA grade 3 (10/15; 67%). The average glycated haemoglobin (HbA1c) reading was 9.7% (range, 6.4% to 16%). Five of the patients had severe peripheral neuropathy with zero score in the Semmes-Weinstein 5.07/10 g monofilament test and severely diminished vibration perception as indicated by the biothesiometer (Bio-Medical Instrument Company, Ohio, USA). Six patients had spinal anaesthesia, 5 patients had general anaesthesia and 4 patients underwent ankle block during the surgery. Patient demographics, operative details, diabetes control and infective markers are shown in Table 1.

There were 4 patients with shin ulcers, 5 cases for ray amputation wound, 2 cases for excision of metatarsal wound and 2 cases with wound on dorsum of foot. One patient had a wound over the plantar aspect of 5th metatarsal head from drainage of abscess while another had a wound over the base of the 5th metatarsal. These wounds were categorised according to Wagner's classification (Table 2). All the wounds were infected and the organisms cultured from the wounds were tabulated (Table 2).

An average time of 9.5 minutes (range, 5 to 20 minutes) were used for a single Versajet debridement (Table 2). Thirteen patients had a single Versajet debridement prior to wound healing while 2 patients had an additional debridement. STSG was performed in 12 patients. The graft healed successfully in 10 cases. However, in 2 patients the grafts became infected and was subsequently left to granulate with regular local dressings. The remaining 3 patients had

Table 1. Patient Demographics, Wound Site, Diabetes Control and Infective Markers

No.	Age	Gender	Wound Site	Wagner Grading	Hba1c	ABI	TBI	Infective Markers		Semmes-Weinstein 5.07/10 g Monofilament	Biothesiometer (Volts)
								WBC	CRP		
1	66	Female	Ulcer dorsum of foot	2	7.2%	1.08	0.72	12.8	342	10/10	25
2	45	Female	Wound post 5 th ray amputation	3	11.3%	1.31	0.93	10.1	18	0/9	50
3	49	Female	Ulcer shin	2	11.9%	1.23	0.62	12.1	236	5/10	22
4	48	Male	Wound post excision of 4 th and 5 th metatarsal bones	3	7.0%	1.07	0.46	8.8	22	0/10	>50
5	51	Female	Ulcer shin	2	6.4%	0.67	0.22	11.7	49	0/10	>50
6	47	Female	Wound post excision of 5 th metatarsal bone	3	7.4%	0.76	0.72	8.5	18	0/10	>50
7	49	Male	Ulcer shin	2	9.9%	1.13	0.71	6.9	17	2/10	25
8	60	Male	Wound over plantar aspect of 5 th metatarsal head	3	7.0%	1.03	0.78	7.2	34	0/10	45
9	71	Female	Wound post 1 st ray amputation	3	9.9%	0.82	0.68	22.6	206	3/9	>50
10	41	Male	Abscess dorsum of foot	2	11.1%	1.05	0.91	8.8	206	7/10	20
11	66	Female	Wound over 5 th metatarsal base	3	7.8%	0.9	1.0	7.0	16	0/10	>50
12	54	Male	Wound post 2 nd and 3 rd ray amputation	4	14.6%	1.18	0.75	25.4	133	5/7	49
13	51	Male	Wound post 5 th ray amputation	4	9.1%	2.04	0.59	8.0	88	1/10	50
14	55	Male	Wound post 5 th ray amputation	3	9.6%	1.15	0.48	7.3	73	5/10	40
15	65	Female	Ulcer shin	2	>16%	0.9	0.82	11.4	48	10/10	40

ABI: Ankle-brachial index; CRP: C-reactive protein; Hba1c: Glycated haemoglobin; TBI: Toe-brachial index; WBC: White blood cell

Table 2. Wound Culture, Versajet Debridement Details and Final Outcome

No.	ASA	Mode of Anaesthesia	Wound Swab Culture	Number of Procedures Performed Before Versajet	Number of Versajet Debridements	Duration (Minutes)	Final Outcome
1	2	Spinal	<i>Pseudomonas Aeruginosa</i> , <i>Arcanobacterium sp</i>	1	1	16	STSG
2	3	Spinal	<i>Streptococcus Agalactiae</i>	1	1	5	STSG
3	3	Spinal	<i>Streptococcus Pyogenes</i>	2	1	5	STSG
4	3	Ankle block	MRSA, <i>Pseudomonas Aeruginosa</i> , <i>Acinetobacter Baumannii</i>	3	2	11, 8	Secondary healing
5	3	Spinal	<i>Klebsiella Pneumoniae</i> , <i>Citrobacter Koseri</i> , <i>Morganella Morganii</i>	2	2	6, 5	STSG infected – left to granulate
6	3	Ankle block	<i>Escherichia Coli</i> , MRSA	3	1	12	STSG infected – left to granulate
7	2	GA	<i>Pseudomonas Aeruginosa</i> , <i>Stenotrophomonas Maltophilia</i>	2	1	8	STSG
8	2	GA	<i>Serratia Marcescens</i>	1	1	7	Secondary healing
9	3	Ankle block	<i>Streptococcus Agalactiae</i> , <i>Staphylococcus Aureus</i>	1	1	5	STSG
10	2	GA	<i>Streptococcus Agalactiae</i>	1	1	9	STSG
11	3	Spinal	<i>Streptococcus Agalactiae</i>	1	1	20	STSG
12	3	Ankle block	<i>Pseudomonas Aeruginosa</i> , <i>Klebsiella pneumoniae</i> , <i>Escherichia coli</i>	1	1	12	STSG
13	3	GA	<i>Pseudomonas Aeruginosa</i> , <i>Escherichiacoli</i> , <i>Enterococcus faecalis</i> , <i>Prevotella spp</i>	2	1	11	STSG
14	3	GA	<i>Morganella morganii</i>	1	1	8	Secondary healing
15	2	Spinal	<i>Klebsiella pneumonia</i>	0	1	7	STSG

ASA: American Society of Anaesthesiologist; GA: General anaesthesia; MRSA: Methicillin resistant *Staphylococcus Aureus*; STSG: Split thickness skin graft

regular wound dressings done to allow secondary wound granulation and healing (Table 2). Both the 2 cases that failed STSG were found to have poor vascular supply based on their respective ABI (0.67; 0.76) and TBI (0.22; 0.72) findings. These 2 cases also had severe peripheral neuropathy as shown by the monofilament test and biothesiometer.

Discussion

Treatment of diabetic foot ulcer continues to be a challenge to healthcare professionals. There are many factors affecting wound healing in a diabetic patient and it is of great importance that the wound heals quickly to minimise risk of secondary infection and subsequent amputation. One vital aspect in the management of diabetic foot ulcer is the surgical debridement. The Versajet II hydrosurgery system is a useful tool for the management of diabetic wounds. It has been described in several articles for wound management.⁵⁻¹² However, there is lack of data on its use in the treatment of diabetic foot ulcers.^{9,11,12} To our knowledge, this is the first study conducted to evaluate its effectiveness in the treatment of diabetic foot wounds.

Mosti et al in 2005 reported that 46 out of 68 (67.6%) patients who underwent the Versajet debridement required only 1 operative procedure to achieve an adequately debrided wound bed for split-skin grafting.⁹ Granick et al in 2006 showed that the Versajet helped to reduce the number of debridements required to adequately prepare the wound bed for closure.¹⁰ Similarly, we found that in our study population, 13 out of 15 patients required only one hydrosurgery debridement with Versajet while 2 patients required additional debridements prior to wound healing. A limitation of our study was to compare the results of Versajet debridement with surgical debridement using the scalpel as a control. Nevertheless, the majority of our patients only required one debridement using the Versajet to adequately prepare wound bed for eventual healing be it for secondary healing or STSG. Ten of our patients achieved complete wound healing after one debridement. The wounds were then ready for STSG similar to findings by Vanwijck et al.¹¹ In 2 patients, the split skin grafts were infected but proceeded to secondary healing with regular local dressings.

Caputo et al reported in a prospective randomised trial that hydrosurgery using the Versajet resulted in shorter debridement time without compromising wound healing.¹² In our study, the average time per procedure performed was also short; an average of 9.5 minutes (ranging from 5 to 20 minutes). The reduction in surgical time was significant as most of our patients were of ASA grade 3. A shorter anaesthetic time would be better for them. Versajet debridement could also be performed under regional anaesthesia. Four of our patients underwent Versajet

debridement under ankle block and 6 of them had spinal anaesthesia. In our experience, this waterjet debridement could also be performed under local anaesthesia. In the latter, a power setting of 5 and below was preferred.

The Versajet II hydrosurgery system was found to give good control of excisional depth in debridement. This is particularly useful in wounds with exposed neurovascular bundles and tendons. Case study 1 demonstrated the usefulness of Versajet debridement for large wound over the dorsum of foot extending from medial to lateral border of the foot and ankle. The handpiece (tip angle of 45° or 15°; working end of 8 or 14 mm in length) allowed easy navigation over the wound without having to turn the patient in multiple positions. The patient was positioned supine (Fig. 1). Case study 4 demonstrated a deep, complex, contoured wound over the lateral foot resulting from an excision of the fourth and fifth metatarsal bone. There was a deep cavity with irregular edge and surface despite performing repeated sharp debridement with a knife. The Versajet was found to be good for wound bed preparation in this complex contoured wound without further alteration of its contour and preserved more viable tissue to encourage healing (Fig. 2).



Fig. 1. 1A and 1B show a left foot dorsum ulcer while 1C and 1D show the clean and smooth surfaced wound post Versajet debridement. 1E to 1F demonstrate the successful reconstructive surgery with split thickness skin graft.



Fig. 2. 2A and 2B show the wound post excision of 4th and 5th metatarsal bones with a resultant deep cavity and irregular wound surface and edges. 2C shows the smooth surface and wound edges after Versajet debridement. 2D to 2F show the wound contraction and secondary healing via regular local dressings.

Conclusion

In this pilot study, we found that the Versajet II hydrosurgery system showed some advantages over standard surgical scalpel debridement. It allowed adequate debridement of the diabetic foot wounds without much collateral damage which can occur with standard scalpel debridement. It preserved more viable tissue to promote rapid healing. We were able to manoeuvre the hand piece over deep and complex wound terrain without much difficulty to achieve a smoother and less irregular wound surface suitable to receive STSG. The time required for surgical debridement was shorter.

However, further studies that use a larger cohort and a randomised controlled trial are required in order to fully evaluate the effectiveness, or otherwise, of the Versajet for debridement of diabetic foot wounds.

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Singapore Chapter of Rheumatologists Consensus Statement on the Eligibility for Government Subsidy of Biologic Disease Modifying Antirheumatic Agents for Treatment of Rheumatoid Arthritis (RA)

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Abstract

Introduction: Up to 30% of patients with rheumatoid arthritis (RA) respond inadequately to conventional non-biologic disease modifying antirheumatic drugs (nbDMARDs), and may benefit from therapy with biologic DMARDs (bDMARDs). However, the high cost of bDMARDs limits their widespread use. The Chapter of Rheumatologists, College of Physicians, Academy of Medicine, Singapore aims to define clinical eligibility for government-assisted funding of bDMARDs for local RA patients. **Materials and Methods:** Evidence synthesis was performed by reviewing 7 published guidelines on use of biologics for RA. Using the modified RAND/UCLA Appropriateness Method (RAM), rheumatologists rated indications for therapies for different clinical scenarios. Points reflecting the output from the formal group consensus were used to formulate the practice recommendations. **Results:** Ten recommendations including diagnosis of RA, choice of disease activity measure, initiation and continuation of bDMARD and option of first and second-line therapies were formulated. The panellists agreed that a bDMARD is indicated if a patient has (1) active RA with a Disease Activity Score in 28 joints (DAS28) score of ≥ 3.2 , (2) a minimum of 6 swollen and tender joints, and (3) has failed a minimum of 2 nbDMARD combinations of adequate dose regimen for at least 3 months each. To qualify for continued biologic therapy, a patient must have (1) documentation of DAS28 every 3 months and (2) at least a European League Against Rheumatism (EULAR) moderate response by 6 months after commencement of therapy. **Conclusion:** The recommendations developed by a formal group consensus method may be useful for clinical practice and guiding funding decisions by relevant authorities in making bDMARDs usage accessible and equitable to eligible patients in Singapore.

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Key words: Drug therapy, Funding, Management, Practice Guidelines

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease affecting 0.3% to 0.8% of the population worldwide,¹ and is the most common inflammatory arthritis in Singapore.² Suboptimally treated RA may result in irreversible joint damage,^{3,4} serious extra-articular manifestations,⁵ and comorbidities including osteoporosis⁶ and cardiovascular disease,^{7,8} with substantial adverse impact on patients' health status, health-related quality of life, employment and financial status.⁹ Evidence, both locally and from other parts of Asia highlight the substantial disease burden of RA.¹⁰⁻¹³

It is well known that up to 30% of patients do not respond to traditional non-biologic disease modifying antirheumatic drugs (nbDMARD) such as methotrexate (MTX).¹⁴ Biologic disease modifying antirheumatic drugs (bDMARD) that target specific cytokines, immune cells and signalling pathways have broadened treatment options, with the overarching principle of achieving disease remission through "treating to target". Biologics such as tumour necrosis factor (TNF) inhibitors, anti-CD20 monoclonal antibodies (rituximab), interleukin (IL)-6 receptor

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antagonists (tocilizumab) and selective co-stimulation modulator of T-cells (abatacept) can achieve rapid control of disease activity, retard radiographic progression,¹⁵ reduce functional disability,¹⁶ and improve quality of life¹⁷, and are considered cost-effective from a societal perspective¹⁸ in nbDMARD inadequate responders.

However, the high cost of biological therapies restricts their widespread use. Government-assisted subsidies in developed countries and regions such as the United Kingdom, Europe, Canada and Australia have helped patients access bDMARDs with uptake around 13% for Western European countries.¹⁵ In Asia, countries such as Taiwan, Japan, Hong Kong and Korea have policies in place to financially support the use of bDMARDs in needy patients with active disease. Unfortunately, in Singapore, patients often bear the cost of bDMARD therapy. Due to cost constraints, treatment with a bDMARD is often delayed. The Singapore government initiated the Medication Assistance Fund (MAF) in August 2010¹⁹ to provide subsidies for expensive drugs deemed clinically necessary in eligible patients with various chronic diseases. This applies primarily to the public healthcare sector in Singapore. Most biologics are available in restructured hospitals as non-standard drugs and are not available in the Standard Drug List of subsidised medications. There are currently no consistent criteria among different institutions to guide funding decisions for these therapies for RA, which are often left to the individual physician's appeal and the discretion of each institution's authority. Furthermore, given that the national budget for drug subsidies are not unlimited, there is an urgent need to develop a set of systematic national guidelines for clinical eligibility for MAF funding for bDMARD in RA. With the objective of developing eligibility criteria for funding of bDMARDs for treatment of adult patients with RA, the Chapter of Rheumatologists, College of Physicians, Academy of Medicine, Singapore formulated a consensus statement by involving a representative group of practising rheumatologists from the public and private sector through formal consensus methodology.

Materials and Methods

A modified form of the Research and Development/University of California at Los Angeles (RAND/UCLA) Appropriateness Method (RAM)²⁰ was used in the development of our recommendations. In lieu of a systematic literature review, a core working group (CWG) (GGT, PPC, ML and JAC) reviewed established international guidelines and recommendations of rheumatology societies on biologic therapies for treatment of RA. The CWG then developed common clinical scenarios simulating those seen in clinical practice and convened a task force panel (TFP) comprising 9 locally recognised rheumatologists from

various restructured government and private hospitals in Singapore who rated each scenario for appropriateness of treatment. This method has been validated and used widely to develop practice guidelines and quality indicators.^{21,22}

Review of Established Guidelines

The CWG reviewed a total of 7 guidelines from the following established institutions: British Society of Rheumatology (BSR),²³ National Institute for Health and Clinical Excellence (NICE),²⁴ Australian Rheumatology Association (ARA),²⁵ Australian Medicare,¹⁸ American College of Rheumatology (ACR)^{26,27} and European League Against Rheumatism (EULAR)^{28,29} (Table 1).

Biologics considered are those registered in Singapore as of August 2012, i.e. abatacept, adalimumab, etanercept, golimumab, infliximab, rituximab and tocilizumab. However, we approached them in classes by mode of action rather than individually. Clinical scenarios were composed of clinical determinants when biologic therapies would be clinically necessary and appropriate for RA patients: 1) RA diagnosis, 2) threshold disease activity, 3) choice of disease activity measure and 4) failure of nbDMARD (duration, number of combinations, type of nbDMARD and mode of administration of MTX). We also included factors for consideration of continuation of biologic therapy: 1) frequency of documentation of disease activity and response, 2) timing of measurement of response and 3) definition of adequate response. We did not include safety and monitoring recommendations as they ought to be standard practice and are covered extensively by others. Other scenarios added after the first rating and face-to-face meeting included the use of subcutaneous MTX in case of inefficacy or gastrointestinal (GI) intolerance with oral administration.

Discussion was limited to patients who had an appropriate use of non-steroidal anti-inflammatory drugs (NSAIDs), systemic glucocorticoids and intra-articular glucocorticoid injections by the treating physician. Scenarios regarding poor prognostic markers were omitted as these are usually used to select MTX-naïve patients for bDMARD therapy, and we were unable to justify the use of limited funds for bDMARD in this group of patients.²⁷

Rating the Appropriateness of Clinical Scenarios by the TFP

For the first round of ratings, the TFP were contacted by email, provided with evidence synthesised from recent guidelines, clinical scenarios and rating instructions. Based on the literature synthesis and their clinical judgment, the TFP individually rated the "appropriateness" of the clinical scenarios using a 9-point Likert appropriateness scale. Disagreement regarding a specific scenario was defined when one-third or more of the panellists rated a scenario

Table 1. Guidelines Reviewed For Evidence Base and Development of Clinical Scenarios

Organisation	Year of Publication	Purpose of Study	Systematic Literature Review (Search End Date)	Appraisal of Evidence/Consensus Method
American College of Rheumatology ²⁷	2012	Best practice	Yes (February 2010)	RAM
American College of Rheumatology ²⁶	2008	Best practice	Yes (February 2007)	RAM
The British Society of Rheumatology (BSR) ²³	2010	Society considered standard of care	Yes (May 2009)	No formal consensus method
European League Against Rheumatism (EULAR) ²⁹	2010	Best practice	Yes (June 2009)	EULAR standard operating procedures for the development of guidelines
National Institute for Health and Clinical Excellence (NICE) ²⁴	2009	Criteria for government reimbursement	Yes (June 2008)	NICE methodology; NCC-CC quality assurance document and systematic review chart
Australian Rheumatology Association (ARA) ²⁵	2011	Society considered standard of care	Details not available	Details not available
Australian Medicare ¹⁸	Details not available (website last updated in May 2012, no listed issue date of documents)	Criteria for government reimbursement	Details not available	Details not available

RAM: RAND/UCLA Appropriateness Method; NCC-CC: National Collaborating Centre for Chronic Conditions

in the lowest 3 points of the appropriateness scale (ordinal scores 1, 2, or 3) and one-third or more of the panellists rated the same scenario in the highest 3 points (ordinal scores 7, 8, or 9). In the absence of disagreement, a median score of 7 to 9 indicated “appropriate”, 4 to 6 indicated “equivocal” while 1 to 3 indicated “not appropriate” for the option defined in the scenario. The dispersion of scores, ranges and median scores were collated. The TFP and the CWG met under the leadership of a moderator (KHL). The results of the first round of ratings were returned to the individual panellists, with summarised results displayed throughout the discussion.

The objectives of this exercise were emphasised. The TFP agreed upon certain definitions on which they based their discussion and subsequent ratings of the scenarios. In cases of disagreement or equivocal response, there was further discussion by panellists with clarification of definitions, ambiguity and rewording of scenarios. A second round of ratings of all the scenarios by the TFP was carried out by email after the face-to-face meeting.

Conversion of Clinical Scenarios to Consensus Statement

A consensus statement was drafted based on the final agreement of appropriateness. Generally, the recommendations included only positive statements; for example, the recommendations focused on when to implement specific therapies rather than when therapies should be avoided.

Results

A total of 9 panellists in the TFP rated the clinical scenarios twice. In the first round of ratings, there was disagreement among panellists with regards to the criteria for RA diagnosis, the number of minimum swollen and tender joints and whether a uniform disease measure should be used. Disagreements also arose regarding the criteria for continued biologic therapy in patients with active RA, namely, the frequency of the Disease Activity Score in 28 joints (DAS28) documentation, the definition of an adequate response and the time frame in which the response should be seen.

During the face-to-face meeting, it was found that the majority of disagreements could be attributed to varying assumptions and different interpretations of the clinical scenarios. Moreover, it was noted that some options were mutually exclusive and some were questions pertaining to thresholds. For example, some panel members rated as “appropriate” that a patient with active RA is considered suitable for biologic therapy if DAS28 ≥ 3.2 and if DAS28 > 5.1 as the threshold of ≥ 3.2 includes the latter category. In view of this, it was clarified that the TFP should choose the minimum threshold in the second round of voting.

In the second round, panellists rerated the amended clinical scenarios. The final consensus statement is in Table 2. These recommendations are ordered by a logical sequence or procedural and chronological hierarchy rather than by importance. Of the 7 guidelines reviewed, the NICE and Australian Medicare were published for the purpose of

Table 2. Final Consensus Statement on Initiation and Continuation of a Biologic DMARD for RA Requiring Government Subsidisation

Median Agreement Score of Clinical Scenarios on Likert Scale of 9* (Clinical Threshold or Option)	
Recommendations Relating to Initiation of bDMARD Therapy	
1. The patient must fulfil either the 1987 ACR or 2010 ACR/EULAR criteria for RA diagnosis.	9
2. Only one uniform disease activity measure should be used (eg. another disease activity measure or different DAS calculations are not interchangeable).	8.5†
3. The patient must have RA of at least moderate disease activity as measured by a DAS28 score ≥3.2 and a minimum of 6 swollen and tender joints.	8.5† (DAS28 ≥3.2) 7.5† (≥6 swollen and tender joints)
4. The patient must have failed a minimum of 2 combinations of nbDMARDs with each combination at optimal dose regimen for at least 3 months (unless contraindicated by documented significant toxicity). ³⁹	9 (2 combinations) 9 (3 months)
5. Optimal combination must include MTX at a dose of ≥20 mg/week (unless contraindicated by documented significant toxicity)‡ and any of the following: • HCQ (6.5 mg/kg) • HCQ + SSZ (≥2 g/d) • LEF (≥10 mg/d) • CSA (≥2 mg/kg/d) • SSZ (≥2 g/d)	9 (include MTX) 7 (dose ≥20 mg/week) 7.5† (HCQ) 9 (HCQ + SSZ) 9† (LEF) 8.5† (CSA) 8† (SSZ)
6. If oral MTX fails due to inefficacy or gastrointestinal intolerance, subcutaneous injection of MTX must be used, and the dose must be at least 20 mg/week. If MTX is contraindicated‡, the patient must have failed a minimum of any 2 combinations of the following nbDMARDs to be considered for biologic therapy: • HCQ (6.5 mg/kg) • LEF (≥10 mg/d) • CSA (≥2 mg/kg/d) • SSZ (≥2g/d) • Sodium aurothiomalate (50 mg/week)	7 (inefficacy); 9 (intolerance); 9 (minimum dose) 9 (2 combinations)
Recommendations Relating to Continuation of bDMARD Therapy	
7. All patients on bDMARD therapy must have DAS28 documented every 3 months. bDMARD therapy cannot be continued unless the patient has at least a EULAR moderate response by 6 months bDMARD commencement. If the patient does achieve EULAR moderate response criteria but disease activity remains moderate to high (i.e. DAS28 ≥3.2), it is the rheumatologist's discretion to switch to alternative bDMARD.	9 (3 months) 8 (6th month) 8 (EULAR moderate response) 9 (rheumatologist's discretion to switch)
Recommendations Relating to Options of bDMARD Therapy	
8. Anti-TNF agents should be the first-line bDMARD unless contraindicated. Anti-TNF should be given with in combination with MTX unless contraindicated.	9 (anti-TNF) 9 (in combination with MTX)
9. The least expensive drug should be prescribed taking into consideration patient's unique characteristics and preferences.	9 (least expensive)
10. Second-line bDMARD treatment, in the event of primary or secondary non-response and adverse effects, may be an alternative anti-TNF or another class of bDMARD (abatacept, rituximab, tocilizumab), taking into consideration patient's unique characteristics and is to be determined by the treating rheumatologist.	9

ACR: American College of Rheumatology; bDMARD: Biologic disease modifying antirheumatic drug; CSA: Cyclosporin A; DAS 28: Disease Activity Score in 28 joints; EULAR: European League Against Rheumatism; HCQ: Hydroxychloroquine; LEF: Leflunomide; MTX: Methotrexate; nbDMARD: Non-biological disease modifying antirheumatic drug; RA: Rheumatoid arthritis; SSZ: Sulfasalazine; TNF: Tumour necrosis factor

*Likert scale of 9 (where 1 = very inappropriate and 9 = very appropriate).

†Fewer than 9 responses were obtained.

‡Methotrexate toxicity criteria: refer to Appendix 1.

guiding government reimbursement and clearly spelt out absolute thresholds relating to initiation and continuation of bDMARD therapy. Therefore, these 2 guidelines were discussed in greater detail.

The EULAR, ACR, BSR and ARA guidelines are referenced whenever applicable, as they provide perspectives on the best practice and standard of care in developed nations. As these recommendations are meant for practising rheumatologists both in the locales where they are published and internationally, they were not prescriptive in terms of particular disease activity criteria, monitoring schedule or specific number/type of joint cutoffs.

Consensus 1: The patient must fulfil either the 1987 ACR or 2010 ACR/EULAR criteria for RA diagnosis.

The 1987 ACR criteria for the classification of RA were used to define active RA in most clinical trials of bDMARDs³⁰⁻³⁴ and are incorporated into most established clinical guidelines. Although they distinguish RA patients with established disease from other types of inflammatory arthritis,³⁵ they are insensitive in early RA. The 2010 ACR/EULAR criteria are a validated revised classification with an increased sensitivity in early RA, introduced due to the recognition that early aggressive therapeutic intervention improves clinical outcomes.³⁵ Although it is rare for patients to only meet the 2010 ACR/EULAR criteria and have failed traditional nbDMARD therapy, the TFP voted that patients could fulfil either criteria for RA diagnosis.

Consensus 2: Only one uniform disease activity measure should be used (e.g. another disease activity measure or different DAS calculations are not interchangeable).

Monitoring of RA disease activity entails measuring the overall state of joint and systemic inflammation as well as damage. There has been a concerted effort to develop composite measures for assessing disease activity and to define response and remission. Evidence-based recommendations require clear definitions of disease activity to make rational therapeutic choices. Although it is not possible to mandate the use of a single disease activity score for the individual physician, and different studies have used different definitions, the TFP agreed that it was preferable to have one uniform scale for administrative purposes in order to achieve consistency, as this set of criteria is meant for determining the eligibility for biologics subsidisation.

One validated composite measure for RA disease activity is DAS28, which is calculated by combining information on swollen and tender joint counts, the acute phase response and patient global assessment on a visual analogue scale (VAS). The DAS28³⁶ has been widely used in clinical trials, registries and guidelines, and is suitable for clinical practice

for monitoring RA disease activity.³⁷ Discussion by the TFP concluded that DAS28 was the most appropriate measure. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) results are obtainable within a 24-hour period of the patient's visit at most local institutions. Furthermore, the panel agreed that blood test results obtained within 4 weeks of the assessment date could be used. Computer software and DAS28 online websites can be used to calculate the DAS28 score quickly and easily.

Other measures of disease activity, such as Clinical Disease Activity Index (CDAI) or Routine Assessment of Patient Index Data 3 (RAPID3), are also quantitative and informative in busy clinic settings and do not require laboratory results. However, another reason for choosing DAS28 is because it is also embedded in the assessment of EULAR response criteria. It is prudent to have a consistent measure to facilitate the processes of subsidy application for initiation as well as continuation of biologics.

Consensus 3: The patient must have RA of at least moderate disease activity as measured by a DAS28 score ≥ 3.2 and a minimum of 6 swollen and tender joints.

Both the BSR²³ and ARA²⁵ advocate the use of DAS28 to determine eligibility, and to commence bDMARD in adult patients who have active RA as defined by DAS28 ≥ 3.2 with at least 3 or more tender and 3 or more swollen joints. There was disagreement among the panellists with the cut-off of DAS28 > 5.1 set as the minimal criteria for initiation of biologics. Certainly, patients with high disease activity should be given priority to biologics therapy. The ACR guideline suggested incorporating any of the 5 common composite disease activity instruments, including DAS28, to measure disease activity but did not mandate uniform use of DAS28.²⁷

There are recognised limitations with DAS28, as it excludes involvement of the feet and ankles, and can be unduly affected by ESR and patient global scores. Clinical synovitis assessed by joint counts is a more objective marker of inflammation than patient global VAS. Therefore, the TFP agreed that patients should have a minimum of 6 swollen and tender joints, in addition to a moderate disease activity of DAS28 ≥ 3.2 (Table 3). The criterion of 6 affected joints was chosen as most biologic trials used this threshold as one of the inclusion criteria; furthermore, patients with multiple joints involvement are at greater risk for progressive joint damage.^{31,32,38} Patients with less than 6 swollen and tender joints might also benefit from biological treatment in order to preserve their quality of life and work ability. The TFP debated lower cut-offs of 4 or less joints, and concluded that disease activity criteria should be more stringent for MAF subsidies.

Table 3. European League Against Rheumatism (EULAR) Response Criteria⁶⁹

Baseline DAS28	DAS28 Improvement Over Time Points		
	>1.2	0.6-1.2	<0.6
Low disease activity <3.2	Good	Moderate	No
Moderate disease activity 3.2 – 5.1	Moderate	Moderate	No
High disease activity >5.1	Moderate	No	No

DAS28: Disease Activity Score in 28 joints

Adjunctive treatments such as joint injection, synovectomy and oral steroid requirement should be taken into account in the global assessment of the patient. The Australian Medicare guideline makes a distinction between major active joints (elbows, wrist, knee, ankle, shoulder and/or hip) and other joints. The TFP decided not to discriminate between the specific joints involved, due to lack of evidence.

*Consensus 4: The patient must have failed a minimum of 2 combinations of nbDMARDs with each combination at optimal dose for at least 3 months (unless contraindicated by documented significant toxicity).*³⁹

The current practice in restructured (government-linked) hospitals is for patients to be offered multiple available nbDMARD combinations, before an application for MAF subsidy is made and granted for bDMARD. Reasons for this include lack of uniform eligibility criteria between institutions, patients' reluctance in going through financial assessment as part of the application process, and concerns over adverse effects of bDMARDs. Nonetheless, there is evidence that about a third of patients with early RA do respond to an adequate trial of MTX⁴⁰ and combination nbDMARDs have a definite role in both early and established RA.^{41,42} It has been shown that in patients who fail traditional nbDMARDs, addition of bDMARD is significantly superior in controlling joint inflammation, retarding radiological progression and improving physical function in both early and long standing RA.⁴³⁻⁴⁵

The NICE guidelines recommend anti-TNF agents (adalimumab, etanercept, infliximab, golimumab and certolizumab-pegol) for highly active RA (DAS28 >5.1) after failing a trial of 2 nbDMARDs, including MTX. An adequate treatment of 1 nbDMARD constitutes 6 months therapy, with 2 months at standard dose²⁴ but whether combination or sequential regimen should be used was not stipulated. The Australian Medicare, however, subsidises bDMARD therapy after failure or intolerance of a 6-month intensive nbDMARD trial with a minimum of 2 nbDMARD either in combination or as sequential monotherapy for at least 3 months each.¹⁸ The EULAR recommendations are less strict in that only failure of 1 or 2 nbDMARDs are required but not necessarily in combination.²⁹

The TFP agreed that 3 months at optimal dose is appropriate based on the onset of action of most nbDMARDs; however the rate of dose escalation is at the discretion of the treating physician. The ACR guideline recommends initiation of biologic agents in nbDMARD-naïve, early RA patients with high disease activity and features of poor prognosis as supported by cost-effectiveness evaluations in the US populations.²⁶ In contrast, the NICE, BSR, Australian Medicare and EULAR guidelines all do not recommend initial biologic therapy in nbDMARD naïve patients.^{23, 24, 29} The EULAR recommends biological treatment after the first failed nbDMARD treatment in case of unfavourable prognostic factors.²⁹

Consensus 5: Optimal combination must include MTX at a dose of ≥ 20 mg/week (unless contraindicated by documented significant toxicity) and any of the following: HCQ (6.5 mg/kg), HCQ + SSZ (≥ 2 g/d), LEF (≥ 10 mg/d), CSA (≥ 2 mg/kg/d), or SSZ (≥ 2 g/d).

As with most international consensus guidelines, the TFP agreed that the optimal nbDMARDs combination should include MTX at a minimum dose of 20 mg/week (agreement score of 7), unless contraindicated by documented significant toxicity.³⁹ If the patient is not able to tolerate 20 mg/week, the highest tolerated dose is considered acceptable.

The NICE guidelines do not specify any preference for nbDMARDs, beyond recommending that MTX should be included. In contrast, the Australian Medicare detailed an algorithm that all patients must receive MTX alone or in combination therapy or sequential monotherapy with the following alternative nbDMARDs: hydroxychloroquine (HCQ) or leflunomide (LEF) or sulfasalazine (SSZ). If patients cannot take MTX at the minimum dose due to contraindication or intolerance, patients may receive any 2 of HCQ, LEF or SSZ. Rarely, where treatment with MTX, HCQ, LEF or SSZ is not possible at the minimum dose due to contraindication or intolerance, third-line therapy either with azathioprine, cyclosporin or sodium aurothiomalate monotherapy or in combination can be used.¹⁸

In this consensus, the TFP agreed that the optimal combination may include MTX with any of the following: HCQ 6.5 mg/kg, HCQ + SSZ (≥ 2 g/d), LEF (≥ 10 mg/d), CSA (2 mg/kg/d) or SSZ (≥ 2 g/d). There was not sufficient evidence to support the use of azathioprine or minocycline. These are the commonly available nbDMARDs used locally. The local rheumatologists favour the use of combinations of MTX with LEF or MTX with SSZ and HCQ and would generally try to optimise these regimens where possible before escalating treatment to biologics. Evidence suggests that MTX and SSZ combination is not more effective than MTX monotherapy.^{46,47} Nonetheless, TFP surmised that this combination can be tried as it may be efficacious for

certain patients and SSZ is a relatively affordable and well-tolerated drug. Some patients may not be able to tolerate or afford other options.

Consensus 6: If oral MTX fails due to inefficacy or gastrointestinal intolerance, subcutaneous injection of MTX should be used, and the dose should be at least 20 mg/week. If MTX is contraindicated, the patient must have failed a minimum of any 2 combinations of the following nbDMARDs to be considered for biologic therapy: HCQ (6.5 mg/kg), LEF (≥ 10 mg/d), CSA (≥ 2 mg/kg/d), SSZ (≥ 2 g/d) or sodium aurothiomalate (50 mg/week).

During the face-to-face meeting, the panel discussed the efficacy of parenteral MTX based on their expert opinion. Literature review was performed by the CWG and provided to the TFP who voted on the use of subcutaneous MTX at the second round. The subcutaneous form has increased bio-availability, better efficacy and similar tolerability compared to the oral form, and evidence indicates that subcutaneous administration is significantly more effective than oral administration of the same dose, with similar tolerability and fewer GI adverse effects.^{48,49} The TFP considered subcutaneous MTX as appropriate if there is inefficacy or GI intolerance to oral MTX. The dose of subcutaneous MTX should be at least 20 mg/week, if tolerated.

In case of contraindication to MTX, the TFP agreed that an adequate nbDMARD trial would constitute 2 combinations of the following nbDMARDs: HCQ (6.5 mg/kg), LEF (≥ 10 mg/d), CSA (≥ 2 mg/kg/d), SSZ (≥ 2 g/d) or sodium aurothiomalate (50 mg/week). Intramuscular sodium aurothiomalate was included as an option as it is still used in Singapore under special circumstances in patients who are refractory to other less toxic therapies.

Consensus 7: All patients on biologic therapy should have DAS28 documented every 3 months. bDMARD therapy may be continued if the patient has at least a EULAR moderate response by 6 months after commencement. If the patient does achieve EULAR moderate response criteria but disease activity remains moderate to high (i.e. DAS28 ≥ 3.2), it is at the rheumatologist's discretion to switch to alternative bDMARD.

In order to document objective clinical response, the CWG felt it was necessary to standardise disease monitoring during bDMARD therapy. By voting, the TFP agreed that DAS28 should be documented at least every 3 months, as it was a reasonable time frame for tracking the patients' progress. Monthly documentation would be ideal, but it is not practical in busy clinic settings, while semi-annual assessment is too long for the detection of trends.

Response to treatment should be determined by 6 months after commencement of biologic therapy. The BSR guideline

recommends that although the aim should be to achieve a EULAR good response whenever possible, a EULAR moderate response is adequate for continuation of the initial biologic therapy (Table 3).²³ Panellists concurred that while a EULAR good response is the goal, some patients with refractory disease and a very high baseline disease activity may not be able to achieve this, and a EULAR moderate response should be sufficient to justify continued funding of the therapy. If the patient does achieve EULAR moderate response criteria but disease activity remains moderate-high (i.e. DAS28 ≥ 3.2), the rheumatologist retains his/her discretion to switch to alternative bDMARDs.

Consensus 8: Anti-TNF agents should be the first-line bDMARD unless contraindicated. Anti-TNF should be given in combination with MTX unless contraindicated.

Of the biologic therapies, the use of anti-TNF agents are the most established in terms of clinical experience since the first anti-TNF, etanercept, was approved in 1998. Our TFP agreed that anti-TNF therapy should be offered as first-line biologic therapy unless contraindicated, in spite of evidence of efficacy of abatacept,⁵⁰ tocilizumab³⁴ and rituximab⁵¹ compared to MTX in MTX-inadequate responders. Though abatacept and tocilizumab are now approved as first-line biologic in other countries,^{52,53} our experts opined that the extensive long-term observational data with regards to anti-TNF safety justifies their use as first-line biologics. This recommendation may change in the future when longer-term data of other bDMARDs becomes available. In general, anti-TNF agents are more efficacious when given in combination with MTX compared to monotherapy.^{32,41,54,55}

Consensus 9: The least expensive drug should be prescribed taking into consideration the patient's unique characteristics and preferences.

The administration costs, required treatment dose and product price per dose should be weighed when choosing a bDMARD. As there are differences in the modes of administration and treatment schedules, patient preferences should also be taken into consideration. The TFP also opined that escalation of the dose of anti-TNF above the starting dose is not recommended.

Consensus 10: Second-line bDMARD treatment, in the event of primary or secondary non-response and adverse effects, may be an alternative anti-TNF or another class of bDMARD (abatacept, rituximab, tocilizumab), taking into consideration the patient's unique characteristics, and is to be determined by the treating rheumatologist.

In patients who have failed an initial anti-TNF therapy,

studies have shown that switching to a second alternative anti-TNF therapy can be efficacious.^{56,57} Abatacept, rituximab and tocilizumab may be used as alternatives. The NICE guidelines allows subsidy of tocilizumab as first-line, and abatacept after TNF failure.^{58,59} Abatacept, a T-cell costimulation inhibitor, is safe and effective for the treatment of established RA in patients who fail to respond or have a contraindication to anti-TNF agents.⁶⁰ Studies found that treatment with abatacept provided significant clinical benefits regardless of whether the initial TNF inhibitor was discontinued for primary failure or secondary loss of efficacy.^{61,62} Rituximab, a chimeric monoclonal antibody that acts by depleting B cells, was found to be effective for the management of RA patients who have failed one or more anti-TNF therapies.^{33,63} Tocilizumab with MTX is efficacious in patients with RA refractory to one or more anti-TNF therapies, and has a manageable safety profile.⁶⁴

Discussion

In summary, a consensus statement was derived methodically on the use of bDMARDs for RA patients who require financial assistance in Singapore. An eligible patient should have moderately to highly active RA with a DAS28 ≥ 3.2 plus a minimum of 6 swollen and tender joints, and have failed a minimum of 2 nbDMARD combination treatments lasting at least 3 months each. To qualify for continued therapy, all patients on biologic therapy must have DAS28 documented every 3 months and should demonstrate at least a EULAR moderate response in the sixth month after commencement. Switching to an alternative biologic agent may be done at the rheumatologist's discretion if DAS28 remains ≥ 3.2 . Eligible patients should be given anti-TNF therapies as first-line, in combination with MTX, unless both agents are or either agent is absolutely or relatively contraindicated. An alternative anti-TNF or bDMARD of another class (abatacept, rituximab, tocilizumab) may be used as second-line therapy, following inadequate response.

The consensus statement this study developed may be applied as a set of eligibility criteria to guide government funding agencies in identifying patients most likely to benefit from bDMARD therapies, thereby reducing the burden of RA from active disease and joint damage in Singapore. It is recognised that some patients who do not meet the criteria set forth in this consensus may also benefit from bDMARDs. However, given the limited financial resources, the recommendations prioritised patients with the most significant impairment from active RA for biologic therapy. In general, recommendations for therapeutic intervention are not meant to be used as strict protocols. They should be applied and individualised by the treating rheumatologist according to the patient's comorbidities, unique characteristics and preference.

A modified version of the (RAND/UCLA) Appropriateness Method²⁰ was used in the development of our statement. The consensus methodology used is rigorous in that it is a systematic approach to reaching agreement through evidence-based literature and expert opinion. The original method requires a systematic literature review to be conducted. However, as several established rheumatology societies have extensively reviewed the literature and have published recommendations, we presented a comprehensive review and synthesised the evidence from these established guidelines.^{18,23,25-27,29} A limitation of our evidence review is that the most recent literature may not have been included but we believe it was incorporated in the TFP discussions by expert opinion. In addition, the foreign guidelines took into account local socioeconomic and healthcare structures, which cannot be fully generalised to the Singapore context. However, as cost-effectiveness evaluations of individual bDMARDs are not available locally, a group consensus method such as RAM enables pragmatic considerations and experiences from expert opinion to be incorporated. In addition, the scenarios created by the CWG, who are also rheumatologists, captured a good spectrum of common locally encountered situations. The CWG and TFP had rheumatologists representing both public and private healthcare sectors of Singapore and all had special interest in the treatment of inflammatory arthritis. Although there is a global trend for increased patient participation by including patient representatives in consensus committees for RA guidelines,^{65,66} a patient representative was not included in our current study. However, future consensus statements may consider inclusion of a patient representative. Approximately 10% of the scenarios were left unanswered. On clarification by the CWG, 2 members of the TFP were unaware that a response was required for every option (e.g. if they decided that the first option was appropriate, they should indicate that the other options were inappropriate, but instead they left the other options blank). A sensitivity analysis with the missing responses did not change the results.

Most importantly, the agreement on the appropriateness of intervention for each clinical scenario was generally high, with median score of 9/9 for 15 of 25 items rated (several recommendations comprised multiple items). There were 2 scenarios that were contentious with the lowest median score of 7/9, although still within the defined range of agreement. Panellists were initially divided on whether the optimal MTX dose should be at least 25 mg/week or at least 20 mg/week before failure is documented. Consensus was reached that 20 mg/week is sufficient as the effective MTX dosing in the comparator arms of most clinical trials is approximately 20 mg/week.^{41,55} The second scenario with the lowest agreement score of 7 was the use of subcutaneous MTX, if oral MTX fails due to inefficacy. Consensus was

Table 4. Comparison of Reimbursement Guidelines for the Use of Biologic Agents in RA

	Singapore Chapter of Rheumatologists Proposed Criteria	Hong Kong Samaritan Fund	Korea Reimbursement Guideline	Taiwan ⁶⁸
Criteria for Initiation				
DAS 28	≥3.2	≥5.1	Not required	≥5.1
Number of tender and swollen joints	≥6	Not required	>20 joints or >4 large joints (elbow, wrist, ankle, knee, hip, shoulder)	Not required
Lab test	(as per DAS28)	(as per DAS28)	ESR >28 or CRP >2.0	
nbDMARD trial	At least 2 combination treatments lasting at least 3 months each	At least 4 nbDMARDs for at least 3 months each	More than 2 DMARDs for 6 months (at least 3 months per DMARD)	MTX plus at least one other DMARD (given for 6 months, with at least 2 months at standard dose)
Criteria for Continuation				
Measurement of response	EULAR moderate response	A reduction of DAS28 score by >1.2 compared to baseline or ≤3.2	ESR <28 or CRP <2.0 or 20% ESR, CRP improvement and 50% decrease in number of active joint count (equal to ACR 50 response)	Improvement of DAS28 of 1.2 points or more

ACR: American College of Rheumatology; CRP: C-reactive protein; DAS28: Disease Activity Score in 28 joints; DMARD: Disease modifying antirheumatic drug; EULAR: European League Against Rheumatism; ESR: Erythrocyte sedimentation rate; MTX: Methotrexate; nbDMARD: Non-biological disease modifying antirheumatic drug; TNF: Tumour necrosis factor

reached for all scenarios, except on whether the use of sodium aurothiomalate (gold) 50 mg/week in combination with MTX constitutes an adequate trial of nbDMARD in patients. As no consensus was reached, this was not included in the consensus statement.

While consensus recommendations on best practice have been developed⁶⁷ in parts of Asia, more pragmatic guidance for the purposes of individual government subsidisation are needed. Compared to reimbursement criteria from Taiwan,⁶⁸ Hong Kong and Korea (personal communications), the criteria proposed by our Chapter has some notable differences in criteria for initiation of bDMARD (Table 4). To our knowledge, most criteria proposed by other Asian countries were adapted from either the NICE or Australian Medicare guidelines without incorporating validated consensus methodology.

Conclusion

The recommendations are not to be used in a prescriptive way or replace a physician's clinical judgment. Most importantly, the motivation of the endeavour is to provide standardised clinical eligibility criteria to aid decision for subsidy for initiation and continuation biologic treatment of RA in Singapore, in order to enhance more equitable access to effective treatments. Applicability of these recommendations may be limited to the funding structure (e.g. partial or full subsidy, means testing) and changes in the national healthcare budget. The Chapter's consensus statement will need to be periodically updated as newer evidence on treatment strategies continue to emerge.

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Appendix 1. Methotrexate Toxicity Criteria

Adverse Event	Brief Description of Minimum Grade	NIH Common Toxicity Criteria Grade
Anaemia	Haemoglobin <80 g/L	3 (or higher)
Leukopenia	Total WCC <3 x 10 ⁹ /L	2 (or higher)
Thrombocytopenia	Platelets <50 x 10 ⁹ /L	3 (or higher)
Neutropenia	Total neutrophils <1.0 x 10 ⁹ /L	3 (or higher)
Pericardial effusion/pericarditis	Pericarditis (pericardial rub, ECG changes or chest pain)	2 (or higher)
Thrombosis/embolism	Thrombosis/embolism requiring anticoagulant therapy	3 (or higher)
Alopecia	Pronounced hair loss	2 (or higher)
Rash/desquamation	Scattered macular or papular eruption or erythema with pruritis or other associated symptoms covering <50% of body surface or localised desquamation or other lesions covering <50% of body	2 (or higher)
Diarrhoea	Increase of 4 – 6 stools/day over pretreatment	2 (or higher)
Nausea	Oral intake significantly decreased, and symptoms do not improve with at least 2 of the following measures: 1. Reduction of the methotrexate dose 2. Folinic acid/folic acid supplementation 3. Switching from oral to intramuscular dosing 4. Dividing the methotrexate dose over 12 hours A minimum of 3 doses of methotrexate should have been trialled.	2 (or higher)
Pancreatitis	Abdominal pain with pancreatic enzyme elevation	3 (or higher)
Stomatitis	Painful erythema, oedema or ulcers but able to eat or swallow	2 (or higher)
Vomiting	2 or more episodes per 24 hours over pretreatment	2 (or higher)
Bilirubin	>1.5 x ULN	2 (or higher)
Transaminases	ALT and/or AST >2.5 x ULN or ALT and/or AST >1.5 x ULN on 3 occasions over a 3-month period	2 (or higher)
Increased serum alkaline phosphatase	2.5 x ULN	2 (or higher)
Osteonecrosis (avascular necrosis)	Symptomatic and interfering with function	2 (or higher)
Osteoporosis	Symptomatic and requiring treatment	3 (or higher)

ALT: Alanine transaminase; AST: Aspartate transaminase; ECG: Electrocardiogram; NIH: National Institute of Health; ULN: Upper limit of normal; WCC: White cell count

Suicidal Ideation, Suicidal Plan and Suicidal Attempts Among Those with Major Depressive Disorder

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Abstract

Introduction: The aims of the study were to identify the prevalence and sociodemographic and clinical correlates of suicidal behaviours using data from a cross-sectional survey among those with major depressive disorder (MDD) in Singapore. **Materials and Methods:** The Singapore Mental Health Study (SMHS) was a cross-sectional epidemiological study that surveyed Singapore residents (Singapore citizens and permanent residents) aged 18 years and above. The assessment of mental disorders was established using version 3.0 of the Composite International Diagnostic Interview (CIDI 3.0). For the purposes of this study, suicidal behaviour was assessed by questions which were asked to respondents who answered positively to the screening questions in the CIDI 3.0 “Depression” module. **Results:** The prevalence of suicidal ideation, plan and attempt among those with lifetime MDD was 43.6%, 13.7% and 12.3%, respectively. We found that suicidal ideation, plan and attempt were significantly associated with ethnicity, education and income. The rate of those who had sought some professional help was higher among those with suicidal plan (71.7%) and attempt (72.3%) as compared to those with suicidal ideation (48.7%) and those with MDD but no suicidal behaviour (29%). **Conclusion:** Individuals with MDD and suicidal behaviour do differ from their non-suicidal counterparts as they have a different sociodemographic and clinical profile. There is a need for more research and a better understanding of this population which in turn could lead to the development and implementation of relevant interventions.

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Key words: Composite International Diagnostic Interview, Depression, Prevalence, Singapore Mental Health Study, Suicidal behaviour

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Introduction

The World Health Organization (WHO) estimates that every year, almost a million people die from suicide — a mortality rate of 16 per 100,000, or 1 death every 40 seconds.¹ WHO also posits that in some countries, suicide is one of the three leading causes of death among those aged 15 to 44 years, and the second leading cause of death among 10 to 24 year olds. Mental disorders are strongly associated with completed suicides, with studies mainly from Western populations showing that approximately 9 out of every 10 individuals appear to have had a psychiatric disorder at the time of their death.²

Studies suggest that “suicidal behaviours” occur on a

continuum of severity that progresses from less serious and more prevalent behaviours to less prevalent but more harmful and devastating behaviours.³⁻⁵ While at one end of the continuum are behaviours such as ideation without specific plans, these may progress in some individuals to a plan, and, for a very small proportion of persons at the other end of the continuum, to a completed suicide attempt with high lethality.³ Nock et al⁶ examined data across 17 countries as part of the WHO World Mental Health Surveys and established the lifetime prevalence of suicidal ideation, plan, and attempt in the overall sample to be 9.2%, 3.1% and 2.7%, respectively. The risk of each suicidal behaviour was found to be significantly associated with being female,

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in a younger age group, having fewer years of education, and never being married. They also established that presence of any mental disorder was significantly associated with the risk of suicidal behaviours, with the most robust relationship being for mood and impulse-control disorders.

Depression is a chronic mental illness, which is highly prevalent, with a high risk of recurrence if treated inadequately and it is one of the most important mental disorders in terms of public health impact.^{7,8} Prevalence of suicide among those with major depressive disorder (MDD) is considerable and suicide remains one of the most worrisome outcomes of depression. The association between suicidal behaviour and MDD is well known.^{9,10} Majority of studies have established the prevalence and risk factors of suicidal behaviour among those with MDD in clinical settings while very few studies have reported the prevalence of suicidal behaviour or its risk factors among those with MDD in population surveys.¹¹

Studies examining risk for suicidal ideation in depression have identified the following risk factors: severity of depression,^{12,13} comorbid alcohol abuse and dependence,¹² comorbid anxiety disorder,¹⁴ comorbid personality disorder,¹³ younger age,¹⁵ female gender,¹⁴ unemployment,¹² poor social support and past suicide attempts.¹⁶ Conner et al in their study on patients with MDD aged 50 years and above found that suicidal planning was associated with living alone, older age, lower scores on Physical Self-Maintenance Scale, and higher cognitive functioning.¹⁷ A study by the Office of Applied Studies (OAS) reported that males were more likely than females to have made a suicide plan and adults aged 55 or older with past year major depressive episode were less likely than their counterparts in other age groups to have made a suicide plan.¹⁸ Risk factors for suicidal attempts among those with depression are similar and include suicide attempts in the past,¹⁹ younger age,²⁰ severe depression and early age of onset of depression,^{20,21} marital discord,²² comorbid personality disorder,²³ comorbid alcohol abuse or dependence and comorbid physical illness.^{21,24,25}

Singapore is a highly urbanised and affluent city-state country with a multiracial population in South East Asia. The suicide rate in Singapore has remained relatively stable, and has been reported as 9.8 and 13.0 per 100,000 over the last 5 decades and it was higher among the elderly, men, and among Chinese and Indians.^{26,27} While several studies have analysed completed suicides and established risk factors in Singapore,²⁸ few have examined suicidal behaviours among those with MDD in a population setting.

The aims of the current study were to identify the prevalence and sociodemographic and clinical correlates of suicidal behaviours using data from a cross-sectional survey among those with MDD in Singapore. We hypothesised that

respondents diagnosed with MDD and reporting suicidal behaviour would differ significantly from those with MDD who do not report suicidal behaviour.

Methodology

Sample

The Singapore Mental Health Study (SMHS) was a cross-sectional epidemiological study that surveyed Singapore residents (Singapore citizens and permanent residents) aged 18 years and above. Disproportionate stratified sampling (by age groups and ethnicity) was used where the 3 main ethnic groups (Chinese, Malays and Indians) were sampled in an equivalent proportion of about 30% each. Individuals aged 50 and older were also oversampled. The data was adjusted accordingly, to represent the Singapore population based on the 2007 population data. Face-to-face interviews were completed with 6616 respondents from December 2009 to December 2010. The survey response rate was 75.9%. The study was approved by the ethics committee (National Healthcare Group, Domain Specific Review Board) and all participants and parents/guardians of those aged below 21 years gave written informed consent for participating in the study. The detailed methodology of the study has been described in a prior article.²⁹

Assessments

The assessment of mental disorders was established using version 3.0 of the World Mental Health Composite International Diagnostic Interview (CIDI 3.0).³⁰ Diagnostic modules for lifetime and 12-month prevalence of affective disorders, including MDD and bipolar disorder; anxiety disorders, including generalised anxiety disorder (GAD) and obsessive compulsive disorder (OCD); alcohol use disorders i.e. alcohol abuse and alcohol dependence, were included in the survey. CIDI 3.0 organic exclusion rules as well as diagnostic hierarchy rules were applied to generate the final diagnoses.

For the purposes of this study, “suicidal behaviours” included the participants’ reports of: (1) suicidal ideation (thoughts about suicide); (2) suicidal plans or intent; and (3) suicide attempts. It was assessed by the following questions which were asked to respondents who answered positively to the screening questions in the CIDI 3.0 “Depression” module:

- Did you think about committing suicide? – Suicidal Ideation
- Did you make a suicide plan? – Suicidal Plan
- Did you make a suicide attempt? – Suicidal Attempt

Help-seeking behaviour was determined using the services section of the CIDI. The key question asked from all respondents was, “Did you ever in your lifetime go to

see any of the professionals on this list for problems with your emotions, nerves, mental health or your use of alcohol or drugs?” A list of treatment providers was then presented to the participant.

The interview also gathered information on a range of chronic physical conditions. We used a modified version of the CIDI checklist of chronic medical disorders for this purpose and respondents were asked to report any of the disorders listed in the checklist. The list comprised 15 chronic medical disorders which were reclassified into 8 types of physical disorders: (1) respiratory disorders (asthma, chronic lung disease such as chronic bronchitis or emphysema), (2) diabetes, (3) hypertension and high blood pressure, (4) chronic pain (arthritis or rheumatism, back problems including disk or spine, migraine headaches), (5) cancer, (6) neurological disorders (epilepsy, convulsion, Parkinson’s disease), (7) cardiovascular disorders (stroke or major paralysis, heart attack, coronary heart disease, angina, congestive heart failure or other heart disease), and (8) ulcer and chronic inflamed bowel (stomach ulcer, chronic inflamed bowel, enteritis, or colitis).³¹ All other sociodemographic data such as age, gender, ethnicity, marital status, education, employment status, income and smoking status were collected using structured questionnaires. Nicotine dependence was established using the 6-item Modified Fagerstrom Test for Nicotine Dependence.³²

Statistical Analysis

All estimates were weighted to adjust for oversampling and post-stratified for age and ethnicity distributions between the survey sample and the Singapore resident population in 2007. Mean and standard deviations or median (if normality was not satisfied) were calculated for continuous variables, and frequencies and percentages for categorical variables. A series of logistic regression models were used to estimate odd ratios (ORs) and 95% confidence intervals (CI) using the three suicidal behaviours (ideation, plan and attempt) as the main outcome variables and sociodemographic factors, mental disorders and chronic physical conditions as predictors. Standard errors (SE) and significance tests were estimated using the Taylor series linearisation method. Multivariate significance was evaluated using Wald χ^2 tests based on design corrected coefficient variance-covariance matrices. Statistical significance was evaluated at the <0.05 level using two-sided tests. All statistical analyses were carried out using the Statistical Analysis Software (SAS) System version 9.2.

Results

Table 1 shows the sociodemographic distribution of respondents with DSM-IV lifetime major depressive

Table 1. Sociodemographic Characteristics of Respondents with DSM-IV Lifetime Major Depressive Disorder in the SMHS Study (n = 417)

	n	Weighted %	SE
Age group			
18 – 34	203	46.6	0.0
35 – 49	136	31.7	0.0
50 – 64	68	14.3	0.0
65+	10	7.3	0.0
Ethnicity			
Chinese	114	73.3	0.0
Malay	109	9.6	0.0
Indian	162	11.6	0.0
Others	32	5.5	0.0
Gender			
Male	170	36.1	3.4
Female	247	63.9	3.4
Marital status			
Single	137	31.7	2.9
Married	227	49	3.6
Divorced/ separated	43	13.7	2.4
Widowed	9	5.6	1.6
Education			
Primary	47	11.8	2.2
Secondary	111	24.3	3
Tertiary	259	63.9	3.2
Employment			
Employed	303	72.1	3
Unemployed	65	20.3	2.7
Economically inactive	31	7.6	1.9
Income			
Below \$20,000	204	48.7	3.3
\$20,000 – \$49,999	136	33.1	3.2
>\$50,000 and above	60	18.2	2.8

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition; SE: Standard error; SMHS: Singapore Mental Health Study

disorder in the SMHS study. The prevalence of suicidal ideation, plan and attempt among those with lifetime MDD was 43.6%, 13.7% and 12.3%, respectively. Among those with suicidal ideation, about 31.5% and 28.2% had made a plan and an attempt respectively. Majority of respondents with suicidal ideation and plan had made an attempt (68.3%) (Table 2). The mean age of onset of MDD among those with suicidal ideation, plan and attempt was 26.4, 28.7 and 25.8, respectively. We found that suicidal ideation, plan and attempt were significantly associated with ethnicity,

education and income; Malays and Indians were significantly less likely than Chinese to have a suicidal ideation or plan. Malays were also less likely to have a suicidal attempt than those of Chinese ethnicity. Those who were divorced/separated were significantly more likely to report suicidal attempts than those who were single. As compared to those with tertiary education, those with a primary education were significantly more likely to have suicidal ideation, plan and attempt. Those with higher annual income (\$50,000 and above) were significantly less likely to report any form of suicidal behaviours than those with lower annual income (below \$20,000). Among those with suicidal ideation, only higher annual income remained significantly related to suicidal plan (Table 3).

Table 4 shows the association between mental disorders, chronic physical conditions and suicidal behaviours. After adjusting for sociodemographic factors in the multiple logistic regression, alcohol abuse and dependence were significantly associated with suicidal plan and attempt. GAD was significantly associated with suicidal ideation, while nicotine dependence was associated with suicidal plan. The presence of any chronic physical condition, and specifically having a respiratory condition, was significantly associated with suicidal plan. Among those with suicidal ideation, nicotine dependence was significantly related to suicidal plan, while hypertension was significantly related to suicidal attempt.

The details on sources of help sought among those with suicidal ideation, plan and attempt are provided in Table 5. The most frequent source of help as indicated by those with suicidal behaviours was a “psychiatrist”. The rate of those who had sought some professional help was higher among those with suicidal plan (71.7%) and attempt (72.3%) as compared to those with suicidal ideation (48.7%) and those with MDD but no suicidal behaviour (29%). It was interesting to note that 15.7% of those with suicidal attempt had called a hotline for help versus only 1.6% with MDD but no reported suicidal behaviour.

Discussion

The prevalence of suicidal behaviour among those with MDD was considerable in our population with the prevalence of ideation, plan and attempt among those with lifetime MDD being 43.6%, 13.7% and 12.3%, respectively.

We found that suicidal behaviour was significantly associated with ethnicity. Malays and Indians were significantly less likely than Chinese to have a suicidal ideation or plan. Malays were also less likely to have a suicidal attempt than Chinese. Our findings are similar to those reported by Chan et al³³ among depressed inpatients in Malaysia. The authors reported that those of Chinese origin had a higher risk of suicidal attempts as compared to those

of Malay and Indian ethnicity. Sociocultural factors may provide a possible explanation for our findings. Ethnicity and religion are closely interrelated in Singapore as in Malaysia: almost all the Malays in Singapore are Muslims. Religious affiliation may be protective against suicide, both at the individual and societal level, and as observed in studies, religious salience may be a protective factor against suicidal behaviour and this may be more pronounced for Muslims compared to others.^{33,34} Our finding that Indians have a lower risk of suicidal ideation and plans as compared to Chinese is somewhat surprising as an earlier study in this population showed that the risk of MDD was higher in Indians as compared to those of Chinese ethnicity.³⁵ Further research on suicidal behaviour and sociocultural factors is needed to understand these differences further.

Marital status was significantly associated with suicidal behaviour; those who were divorced/separated were significantly more likely to report suicidal attempts than those who were single. While our findings are different from that reported by Hawton et al³⁶ who did not find any association of marital status with suicidal attempts, they are similar to that reported by Chan et al,³³ who found that suicidal attempts were higher among those who had experienced marital separation. Marital separation, conflict and quarrels are significant stressors and may act as significant precipitants of suicidal attempts.³⁷

Our findings that respondents with higher annual incomes had a significantly lower risk of suicidal behaviours than those with lower annual incomes replicate previous research in the field.^{38,39} Our study also found that as compared to those with tertiary education, those with a primary education were significantly more likely to have suicidal ideation, plan and attempt. Lower education and income levels are both “individual-level disadvantages” which reflect a person’s socioeconomic position that may influence suicidal behaviour. It has been suggested that low socioeconomic position may restrict the access of the individual to material, psychosocial, or institutional resources thus limiting an individual’s development of self control or strategies for managing stressful situations, seeking support and help, or it may lead to differential exposure to risk factors such as negative life events (divorce, unemployment and financial loss) thus predisposing them to adverse outcomes.⁴⁰

Comorbid mental disorders especially alcohol abuse and dependence were significantly associated with suicidal plan and attempt. Several studies have shown that suicidal behaviour is very common among subjects with co-occurring depression and alcohol use disorders.^{20,24} The mechanisms underlying this relationship are yet to be elucidated. Conner and Duberstein⁴¹ proposed a model to explain the elevated risk of suicide among alcohol dependent subjects. This model includes aggression/impulsivity, negative affect,

Table 2. Prevalence of Suicidal Behaviours

All MDD Cases			Non-suicidal Behaviour			Ideation			Plan			Attempt			Plan Among Ideators			Attempt Among Ideators			Attempt Among Ideators with a Suicide Plan			
n	%	SE	n	%	SE	n	%	SE	n	%	SE	n	%	SE	n	%	SE	n	%	SE	n	%	SE	
Total	417	100	0	281	56.4	3.6	136	43.6	3.6	37	13.7	2.7	40	12.3	2.6	37	31.5	5.4	40	28.2	5.5	24	68.3	11.4
Male	170	36.1	3.4	122	63.7	5.9	48	36.3	5.9	17	14.3	4.7	15	12.3	4.5	17	39.5	10.5	15	33.9	10.4	11	79.5	13.2
Female	247	63.9	3.4	159	47.7	4.6	88	47.7	4.6	20	13.4	3.5	25	12.3	3.3	20	28.1	6.7	25	25.8	6.5	13	61.5	15.7

MDD: Major depressive disorder; SE: Standard error

Table 3. Sociodemographic Correlates of Suicidal Behaviours

Variables	Ideation			Plan			Attempt			Plan Among Ideators			Attempt Among Ideators		
	OR*	95% CI	P Value	OR*	95% CI	P Value	OR*	95% CI	P Value	OR*	95% CI	P Value	OR*	95% CI	P Value
Age group															
18 – 34	Ref.			Ref.			Ref.			Ref.			Ref.		
35 – 49	0.5	0.2 – 1.3	0.162	0.8	0.2 – 2.9	0.796	0.5	0.1 – 2.2	0.387	2.5	0.5 – 12.5	0.256	0.8	0.1 – 4.4	0.770
50 – 64	1.1	0.4 – 3.2	0.850	0.7	0.1 – 4.0	0.682	1.2	0.1 – 10.3	0.896	0.8	0.1 – 4.2	0.786	1.2	0.2 – 7.2	0.824
65+	0.2	0.01 – 7.6	0.416	0.2	0.01 – 3.9	0.263	0.2	0.01 – 4.3	0.307	-	-	-	1.9	0.1 – 51.0	0.691
Ethnicity															
Chinese	Ref.			Ref.			Ref.			Ref.			Ref.		
Malay	0.2	0.1 – 0.4	<.0001	0.1	0.03 – 0.5	0.003	0.1	0.02 – 0.5	0.005	1.0	0.1 – 6.4	0.959	1.1	0.2 – 7.2	0.941
Indian	0.3	0.2 – 0.7	0.001	0.2	0.1 – 0.7	0.008	0.4	0.1 – 1.2	0.096	0.7	0.1 – 3.5	0.660	2.0	0.5 – 7.4	0.318
Others	0.5	0.2 – 1.5	0.217	-	-	-	-	-	-	-	-	-	-	-	-
Gender															
Male	Ref.			Ref.			Ref.			Ref.			Ref.		
Female	1.4	0.7 – 2.9	0.355	0.8	0.2 – 2.8	0.744	1.3	0.4 – 4.2	0.644	0.5	0.1 – 1.8	0.267	0.6	0.1 – 2.1	0.381

CI: Confidence interval; OR: Odds ratio; Ref: Reference category

*Derived from multiple logistic regression model adjusted for demographic variables (i.e. age, gender, ethnicity, marital status, education, employment and income).

Table 3. Sociodemographic Correlates of Suicidal Behaviours (Con't)

Variables	Ideation			Plan			Attempt			Plan Among Ideators			Attempt Among Ideators		
	OR*	95% CI	P Value	OR*	95% CI	P Value	OR*	95% CI	P Value	OR*	95% CI	P Value	OR*	95% CI	P Value
Marital status															
Single		Ref.			Ref.			Ref.			Ref.			Ref.	
Married	1.4	0.6 – 2.9	0.451	3.6	0.7 – 18.2	0.119	2.1	0.4 – 10.3	0.374	4.8	0.9 – 24.8	0.061	2.9	0.7 – 12.5	0.147
Divorced/ separated	2.8	0.8 – 9.6	0.108	3.7	0.5 – 27.3	0.198	8.3	1.1 – 61.1	0.037	2.1	0.2 – 22.1	0.547	3.4	0.5 – 22.4	0.210
Widowed	6.5	0.1 – 283.2	0.333	22.4	0.5 – 996.8	0.109	4.1	0.1 – 142.0	0.440	-	-	-	0.2	0.01 – 5.4	0.348
Education															
Primary	3.9	1.4 – 10.5	0.007	4.6	1.3 – 16.8	0.019	13.7	2.9 – 65.1	0.001	0.8	0.1 – 5.6	0.859	4.9	0.9 – 27.0	0.067
Secondary	0.7	0.3 – 1.6	0.410	0.5	0.1 – 1.8	0.260	0.5	0.1 – 2.1	0.322	0.8	0.2 – 3.2	0.794	0.5	0.1 – 2.7	0.439
Tertiary		Ref.			Ref.			Ref.			Ref.			Ref.	
Employment															
Employed		Ref.			Ref.			Ref.			Ref.			Ref.	
Unemployed	0.7	0.2 – 2.1	0.488	1.9	0.4 – 8.9	0.437	2.9	0.6 – 13.9	0.173	4.4	0.5 – 37.8	0.175	6.2	0.6 – 60.6	0.116
Economically inactive	0.8	0.2 – 2.8	0.707	1.5	0.4 – 6.7	0.573	1.4	0.2 – 10.0	0.748	3.3	0.5 – 23.7	0.229	2.5	0.2 – 26.7	0.440
Income															
Below \$20,000		Ref.			Ref.			Ref.			Ref.			Ref.	
\$20,000 – \$49,999	0.6	0.2 – 1.3	0.202	0.2	0.04 – 1.3	0.087	1.3	0.3 – 6.4	0.740	0.3	0.1 – 1.5	0.134	2.7	0.7 – 11.0	0.159
>\$50,000 and above	0.3	0.1 – 0.8	0.022	0.03	0.003 – 0.2	0.001	0.1	0.01 – 0.6	0.016	0.04	0.004 – 0.4	0.005	0.1	0.02 – 1.1	0.062

CI: Confidence interval; OR: Odds ratio; Ref: Reference category
*Derived from multiple logistic regression model adjusted for demographic variables (i.e. age, gender, ethnicity, marital status, education, employment and income).

Table 4. Correlates of Lifetime Mental Disorders and Chronic Physical Conditions with Suicidal Behaviours

	Ideation			Plan			Attempt			Plan Among Ideators			Attempt Among Ideators		
	OR	95% CI	P Value	OR	95% CI	P Value	OR	95% CI	P Value	OR	95% CI	P Value	OR	95% CI	P Value
Lifetime DSM-IV disorders															
GAD	3.7	1.1 – 12.3	0.032	2.3	0.4 – 14.0	0.361	1.7	0.3 – 10.2	0.540	0.3	0.03 – 3.5	0.352	1.01	0.1 – 7.2	0.993
OCD	0.8	0.2 – 2.5	0.662	2.3	0.6 – 9.2	0.248	1.3	0.3 – 6.3	0.754	5.8	0.8 – 41.4	0.081	4.7	0.6 – 34.1	0.129
Alcohol abuse	2.6	0.9 – 7.5	0.079	22.7	3.6 – 142.9	0.001	12.1	1.9 – 75.5	0.008	2.4	0.2 – 29.7	0.506	2.1	0.3 – 17.4	0.494
Alcohol Dependence	3.7	0.9 – 15.4	0.074	11.9	1.4 – 104.9	0.025	16.7	2.0 – 136.2	0.009	11.0	0.5 – 261.2	0.138	6.9	0.3 – 169.9	0.242
Nicotine Dependence	2.0	0.5 – 8.2	0.333	10.7	1.2 – 98.3	0.036	3.0	0.3 – 30.1	0.343	26.5	1.1 – 658.1	0.045	5.3	0.5 – 61.2	0.184
Any mental disorder	1.7	0.8 – 3.6	0.18	6.6	1.9 – 23.0	0.003	3.1	0.9 – 10.6	0.069	3.2	0.8 – 13.2	0.115	3.1	0.8 – 12.3	0.114
Lifetime chronic physical conditions															
Respiratory conditions	1.1	0.5 – 2.5	0.874	4.5	1.1 – 18.4	0.039	3.1	0.8 – 11.5	0.097	3.4	0.3 – 37.0	0.312	4.9	0.97 – 25.1	0.055
Diabetes	0.8	0.2 – 3.4	0.802	2.1	0.3 – 14.7	0.442	2.8	0.6 – 13.2	0.198				25.3	0.8 – 763.1	0.063
Hypertension	0.9	0.3 – 2.6	0.911	0.6	0.1 – 3.1	0.545	4.0	0.8 – 18.7	0.082	4.4	0.8 – 24.9	0.090	11.8	1.6 – 87.0	0.016
Chronic pain	0.8	0.4 – 1.7	0.608	1.4	0.4 – 4.8	0.601	0.9	0.3 – 2.9	0.816	1.7	0.4 – 6.7	0.473	1.6	0.5 – 5.7	0.457
Cancer										2.5	0.5 – 12.5	0.256	0.8	0.1 – 4.4	0.770
Neurological conditions	1.0	0.1 – 7.1	0.961	2.3	0.2 – 33.2	0.529	1.1	0.1 – 25.1	0.944	5.6	0.3 – 110.0	0.259	1.4	0.1 – 25.9	0.810
Cardiovascular	0.7	0.1 – 3.9	0.698	0.6	0.1 – 4.3	0.609	1.0	0.2 – 5.8	0.993	0.3	0.01 – 11.8	0.519	3.9	0.3 – 60.6	0.332
Ulcer	1.2	0.2 – 9.0	0.846	0.6	0.03 – 12.6	0.766	0.7	0.03 – 16.9	0.800				0.3	0.01 – 14.5	0.510
Any chronic physical condition	0.9	0.5 – 1.8	0.812	4.2	1.1 – 15.5	0.032	2.2	0.7 – 7.3	0.197	6.9	1.7 – 27.6	0.007	3.2	0.9 – 10.9	0.064

CI: Confidence interval; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition; GAD: Generalised anxiety disorder; OCD: Obsessive compulsive disorder; OR: Odds ratio

Table 5. Services Used Among Those With Suicidal Behaviours

	MDD with No Reported Suicidal Behaviour (n = 281)		Ideation (n = 136)		Plan (n = 37)		Attempt (n = 40)	
Professional	%	SE	%	SE	%	SE	%	SE
Any professional	29.0	3.9	48.7	5.8	71.7	9.0	72.3	9.2
Psychiatrist	7.4	2.3	25.2	5.3	42.6	11.4	58.0	10.3
Counselor	8.1	1.9	14.0	4.3	19.2	9.8	7.3	4.8
Religious/spiritual healer	2.7	1.2	10.6	3.9	14.9	9.2	3.1	1.5
GP	13.8	3.2	7.3	2.5	3.0	1.4	1.8	1.1
Psychologist	5.8	2.2	5.8	2.5	5.8	4.2	7.8	4.8
Social worker	2.9	1.3	9.1	3.7	21.6	10.0	24.8	10.7
Use a hotline	1.6	1.2	9.4	3.4	14.1	7.4	15.7	8.3
Other mental health professional	2.5	1.6	0.2	0.2	0.6	0.7	-	-
Medical doctor*	0.4	0.2	0.4	0.3	-	-	0.7	0.7
Nurse	0.3	0.2	0.4	0.3	-	-	0.6	0.6
Healer	2.7	1.6	0.6	0.5	-	-	-	-

GP: General practitioner; MDD: Major depressive disorder; SE: Standard error

*Refers to doctors with specialisation in fields other than psychiatry; does not include GPs.

and hopelessness as key predisposing factors, and major depressive episodes and stressful life events, particularly interpersonal difficulties, as key precipitating factors for suicide. Episodes of major depression are proposed to mediate the relationship between negative affect (and hopelessness) and suicidal behaviour among those with alcoholism. The authors also suggest that it is likely that depression affects the association between interpersonal difficulties and suicidal behaviour among alcoholics. This model could also partly explain the higher risk conferred by comorbid alcohol use for suicidal behaviours among those with MDD in our study.

GAD was significantly associated with suicidal ideation, while nicotine dependence was associated with suicidal plan. Our finding of an association between GAD and suicidal ideation is somewhat unique, and there is only one study reporting a similar finding (in an outpatient population with MDD).⁴² Studies have identified both smoking and nicotine dependence as risk factors for suicidal behaviour.⁴³⁻⁴⁵ Different theories have been described to explain this relation such as smoking being a non-causal marker or smoking being a psychological or physical toxin. A biological theory suggests that chronic nicotine use is associated with diminished levels of serotonin⁴⁶ and monoamine oxidase (MAO)⁴⁷ compared with unexposed populations. Low levels of serotonin and MAO activity have been linked with suicidal behaviour.^{48,49} Our findings must be interpreted cautiously as this study established current prevalence of nicotine dependence while suicidal behaviour was based on a lifetime history.

Our finding of the association between chronic physical conditions and specifically having a respiratory condition

and suicidal plan is somewhat similar to that reported by Goodwin et al.⁵⁰ The authors found that pulmonary disease with or without comorbid depression was associated with a statistically significant increased likelihood of suicidal ideation. However, those with comorbid depression and pulmonary disease had a higher risk of suicidal ideation. The mechanism of the association between respiratory disease, major depression, and suicidal behaviours is not known. The authors have suggested that “the pain, physical suffering or the limited lifestyle associated with specific physical illnesses such as asthma and chronic obstructive pulmonary disease (COPD) is severe enough to result in suicidal behaviour”. Studies conducted among the local population, i.e. among patients with chronic obstructive pulmonary disease in Singapore, have concluded that comorbid depressive symptoms are common in patients with COPD and are associated with poorer survival, longer hospitalisation stay, persistent smoking, increased symptom burden, and poorer physical and social functioning.⁵¹ These factors may be a plausible explanation for our findings. Alternatively, it may be that there are common genetic or environmental factors (or both) that are related to depression, respiratory disease and suicidal ideation, which independently predict their co-occurrence. Future research is needed to determine the nature of this link.

The rate of those who had sought some professional help was considerably higher among those with MDD and suicidal behaviour as compared to those without suicidal behaviour. These findings can be explained by Andersen's behavioural model of health services in that an increased level of evaluated need is associated with an increased likelihood of help-seeking behaviour.⁵² Individuals with

suicidal behaviours were significantly more likely than those with MDD without suicidal behaviours to seek help, suggesting that suicidal behaviours are important factors associated with help-seeking behaviour over and above the presence of mental disorders. Furthermore, individuals who had suicidal plans/attempts were even more likely than those with suicidal ideation to seek help—suggesting increasing need with the severity of the suicidal behaviour. The most frequent source of help as indicated by those with suicidal behaviours was a psychiatrist. A likely explanation for this may be that those with suicidal behaviours may interpret the ideas/plans as a clear and serious indicator of psychological distress, and are therefore more likely to seek treatment from psychiatrists. It is possible that those with attempts similarly were either self/family referred to a psychiatric facility given the seriousness of the problem. It is however, important to note that counsellors, religious and spiritual healers as well as hotlines have also been identified as sources of help seeking thus reiterating the need for care providers from different backgrounds to work in an integrated manner to support those with suicidal behaviours and avoid escalation to a completed suicide.

The strengths of our study are that it is a nationwide survey of a representative population which has lesser likelihood of sampling errors like Berkson's bias compared to those studies that examined "suicidal behaviours" in help-seeking clinical samples. It is one of the first studies in the extant literature that has examined suicidal behaviour among those with MDD in a multiethnic Asian sample. We used a structured diagnostic instrument with face-to-face interviews, and psychiatric diagnoses were made according to the DSM-IV criteria. Lastly, our response rate of 75.9% ensures reasonable generalisability of our results. There are some limitations to our study—suicide-related variables were collected with a single question; we did not assess the lethality of suicide attempts or the number of suicidal attempts and thus, were unable to compare those with single versus multiple attempts. We assessed "suicidal behaviours" only among those with MDD, however current research suggests that "suicidal behaviours" may occur independently of depressive symptoms. A stress diathesis model proposed by Mann et al⁵³ suggests that the risk for suicidal acts is determined not merely by a psychiatric illness (the stressor) but also by a diathesis. This diathesis may be reflected in a tendency to experience more suicidal ideation and to be more impulsive and, therefore, to be more likely to act on suicidal feelings. Another theory suggests that suicidal individuals are experiencing unbearable psychological pain (psychache) or suffering and that suicide may be, at least in part, an attempt to escape from the suffering.⁵⁴ Thus, the prevalence of "suicidal behaviours" in our study is not indicative of "suicidal behaviours" among the general population of Singapore. The data on suicidal behaviours was based on respondents' self-report and there could be an

element of recall bias and under-reporting especially since suicidal behaviour is a sensitive topic. Lastly, we did not establish the prevalence of personality disorders which are a significant risk factor for suicidal behaviour.

Conclusion

Individuals with MDD and suicidal behaviour do differ from their non-suicidal counterparts as they have a different sociodemographic and clinical profile. There is a need for more research and a better understanding of this population which in turn could lead to the development and implementation of relevant interventions.

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How to Bridge the “Valley of Death” Between a Research Discovery and Clinical Application?

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The Valley of Death

As physicians, one of the key questions we often ask is, “How do we bring new understanding of disease mechanisms and better treatments to our patients?” Is there a process whereby scientific discoveries are identified, assessed and adopted by physicians, healthcare providers and policy makers to ensure our patients benefit from these innovations?

In fact, this “process” of scientific discovery to actual clinical application is long, tortuous and difficult, and many bench discoveries do not actually get to the bedside. As an example, in 2008, more than 800,000 medical research papers were published, but by 2011 only 21 new drugs had been approved by the US Food and Drug Administration (FDA)¹—barely 0.003% of the “discoveries”. Of the numerous research publications, observations, clinical trials and discoveries worldwide that the public sometimes are made aware of in the lay media, how many can boast that they have actually made a real impact to improving patients’ lives and have been used by physicians in clinical practice? The answer: very, very few!

The chasm between a laboratory observation and the application of this observation to clinical care outcomes have been dubbed the “valley of death”, where basic biomedical discoveries initially generate exciting new results, are published in high profile journals and lauded as “breakthroughs” by the scientific community and the lay media, but many years later, they subsequently languish, failing to translate to actual improvements for clinical medicine and healthcare.

So how do we ensure that research endeavours, which often consume significant costs to public budgets, reach and make a tangible difference to patients?

What is Translational Medicine?

Translational medicine is the “bridge” to this valley.² Translational medicine is, essentially, the process of

applying knowledge gained from basic biomedical research to clinical practice; it involves bridging new research findings, scientific discoveries and new techniques to approaches in the prevention, diagnosis or treatment of diseases. This can be in the form of drugs, devices, biomarkers or treatment methods. Translational medicine involves the pursuit of the patient’s health as the ultimate outcome. It involves paradigm shifts such that scientific discoveries should not just be celebrated only in basic laboratories and research institutes or published (and archived) in prestigious medical journals—they also need to make their way to hospitals, clinics and into patients’ lives to be real successes. Translational medicine involves a longer term strategy for research that is beyond the immediate outcomes of a research project.

Translational medicine takes time. An example is the discovery of the treatment of age-related macular degeneration (AMD), one of the major causes of blindness.³ The observation that eyes with AMD have a higher level of a “growth factor” occurred in the early 1970s, leading to the identification of vascular endothelial growth factor (VEGF). Subsequently, this led to the design of antibodies to VEGF, testing of anti-VEGF agents in animal models and then in early phase clinical trials. The results of major phase 3 clinical trials in 2006 led to the clinical adoption of anti-VEGF treatment and for AMD as a gold standard treatment. It is now one of the major treatments for eye diseases in Singapore.⁴ In 2013, almost 4 decades later, the rate of AMD blindness has started to decline in some countries as a result of anti-VEGF treatment. So the process of translational medicine from bench to the bedside to the population took 40 years!

In the US, the National Institutes of Health (NIH) has recognised the importance of translational medicine and has made it a priority. Since 2006, the NIH has formed centres of translational research at its institutes with a budget that has reached US\$500 million a year,² and it has launched translational science awards for researchers.

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Similarly, Singapore's national biomedical sciences agenda has now shifted towards translational medicine as a priority for the future, and has refocused emphasis on such research that creates greater health and economic impact.⁵

An Example of Translational Medicine in Singapore: The Myopia Story

Because Singapore's effort in biomedical research is relatively new, there have been few successful cases to date. Nevertheless, there are encouraging signs.

An example close to home is the management of Singapore's unique problem of myopia. Myopia is a common condition and is almost a "national" problem affecting 28% of children as young as 7 years of age, with the rate hitting 83% at 18 years of age.^{6,7} Myopia may result in blindness due to myopic macular degeneration and slowing the rate of myopia progression is one way to prevent this problem.⁷

For 15 years, researchers and subsequently, clinicians at the Singapore Eye Research Institute (SERI) and the Singapore National Eye Centre (SNEC) have been trying to tackle this problem. The work over the 15 years was done with an end goal in mind—to decrease the rising incidence of myopia, and to slow down the condition in its tracks.

The SERI and SNEC research team discovered that eye drops with low-dose atropine slow down the progression of myopia in children with minimal side effects.⁸ After years of tests and clinical trials, the clinicians and researchers have transformed their findings into a solution. SNEC today now offers new eye drops with a 0.01 atropine dosage—the most effective atropine level proven to combat myopia—for children with severe myopia in a dedicated myopia clinic, and is furthering their research to meet regulatory demands. Concomitantly, community-based clinical trials efforts are underway to tackle the lack of physical and outdoor activities, which are now thought to be a major cause of myopia.⁹

With translational medicine, this major nationwide problem may become curable in the foreseeable future.¹⁰

What are the Ingredients for Successful Translational Medicine?

First, driving translational medicine requires a new model of working together. Multidisciplinary collaboration across specialties, disciplines and industries is the key to driving translational research to success. This requires teams of clinician, clinician scientists, scientists, nursing and allied health professionals.

For instance, an observation in the clinic by a doctor may give rise to a hypothesis that a scientist in the lab can work on. A scientist's discovery may translate into a biomarker

that acts as clinical tool for the clinician, or a drug target for drug development by a pharmaceutical company. A physiotherapist's inspiration may result in the invention of a rehabilitation device that could not be made possible without collaborating with an engineering or a medical technology institution. Translational medicine is not an individual event; it is a team sport that has different roles and skills for each team member. With a critical mass of research teams and sustained collaboration, drugs, treatments and care, outcomes can be brought out of the "valley of death".

Second, a strong ecosystem and culture that sustains and rewards translational medicine is critical. It involves forging a close partnership between a hospital cluster and a university, similar to the concept of the SingHealth Duke-NUS Academic Medical Centre or National University Health System.¹¹ The partnership must align the traditional divergent missions of healthcare and education, and the cultural differences between academic researchers and practising doctors. These are challenging issues that must be dealt with upfront.¹²

Third, translational medicine requires a group of people who understand both science and medicine—clinician-scientists.^{13,14} The clinician-scientist can effectively act as a connector between scientists and doctors, and must speak both "languages". To translate research, young clinician-scientists must be identified, trained, mentored and supported. Alongside a nurturing environment, supervision, guidance and advice from a sympathetic and wise mentor are essential. In the US and other countries, clinician-scientists face significant challenges in funding and career development.

The final piece of translational medicine is policy implementation. Once new discoveries and clinical evidence have been established, government agencies and healthcare systems should have a clear framework to implement healthcare policy and public health policy accordingly. The importance of policy implementation as the "final step" in the "valley of death" cannot be underestimated.^{15,16}

With these pieces in place, the "valley of death" can be bridged and research discoveries will find their way to the clinic and to our patients.

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Factors Influencing Patient's Adherence to Follow-up Postbariatric Surgery: An Asian Experience

Dear Editor,

While obesity continues to be a rising concern in the United States,¹ Singapore is not exempted from this trend and has been experiencing an uprising trend in the prevalence. A steep increase was observed between 2004 and 2010, where the obesity (BMI ≥ 30 kg/m²) prevalence among adults aged 18 to 69 years shifted from 6.9% to 10.8%, as compared to the previous 7 years, where the prevalence was at 6.0% in 1998.² Currently, bariatric surgeries are the most successful and durable intervention for obesity. There are emerging data on these procedures as treatments for individuals with Type 2 diabetes (T2D), as well as a mean to reduce cardiometabolic risk factors.¹ Postoperative follow-ups, involving a multidisciplinary approach for patients who underwent a bariatric surgery, have been recognised as essential in the management and maintenance of sustained weight loss¹ as well as minimising complications.³ However, there had been a high appointment default rate observed for postoperative follow-up appointments in Tan Tock Seng Hospital (TTSH). From 2001 to 2002, more than 90% of patients defaulted on postsurgical psychologist's appointments while more than 70% of these patients defaulted on postsurgical appointments with the dietitian. The high default rate has an influence in the patient's management and maintenance of sustained weight loss, chances of complications, as well as the economic cost and manpower borne by the hospital. The current study aimed to further explore factors that could lead to a better understanding of the poor adherence to follow-up appointments.

An online questionnaire was designed by collaborative effort between a psychologist and a dietitian to understand the reasons for a patient's non-attendance for appointments. Fifteen randomly arranged statements regarding why patients did not attend appointments were considered based on the factors highlighted by Mitchell and Selmes,⁴ who postulated that factors such as patient's "Perceived Benefit of Care", "Perceived Cost of Care", "Barrier to Care", "Doctor-Patient Factors" and "Cues to Act" were related to non-adherence.

Patient's "Perceived Benefit of Care" referred to a patient's perception that the appointment with a psychologist or

dietitian was less necessary as the patient believed that he had been coping well with weight loss and any health concerns. "Perceived Cost of Care" considered the financial cost involved, specifically referring to payments for the appointments they attend, which increase with additional appointments. "Barriers to Care" looked at barriers such as the lack of transportation and inconvenient appointments. The "Doctor-Patient Factors" included the therapeutic alliance, perceived helpfulness and communication style. "Cues to Act" referred to reminders for patients to attend the appointments.

Of the patients who attended bariatric surgery in 2011 and 2012, 21 of them had participated in the online questionnaire. As reflected on Table 1, the results suggested that the most influential factor that affected patients' adherence to attending psychologist's appointments was "Patient's Perception of Excess Benefit of Care", where patients (28.57%) thought that they were managing well without follow-up with the psychologist. This was closely followed by "Lacking Cues" to attend the appointment (26.98%), which included receiving an appointment, and/or receiving a reminder of the appointment. The reason of not being given an appointment stood out among the others. Factors such as "Financial Cost" of attending the appointment (16.67%) and "Barriers to Care" (11.43%), e.g. being unable to be away from work, and appointment scheduling challenges, also affected patient's adherence to attending psychologist's appointments.

When considering factors that affected patient's adherence to attending the appointment with the dietitian, "Patient's Perception of Excess Benefit of Care" had the most influence on their adherence (19.05%), where patients do not perceive the need to see the dietitian if they are doing well. This was closely followed by the "Barriers to Care" (18.10%); "Financial Cost" (14.29%); "Lacking Cues to Attend the Appointment" (6.35%), and "Dietitian-Patient Relationship" (1.59%).

The reasons for non-adherence to postoperative follow-up appointments were multifactorial and they differed between the psychologist's and dietitian's appointments. However, the common factor, which also surfaced as the most influencing factor among the 2 appointments, was

Table 1. Factors Influencing Psychologist's and Dietitian's Appointment

Factors	Influencing Psychologist's Appointment (%)	Influencing Dietitian's Appointment (%)
Barriers to care		
Barriers such as the lack of transportation and inconvenient appointments.	11.43	18.10
Financial cost		
The financial cost involved, referring specifically to the payments for the appointments they attend, which increases with additional appointments.	16.67	14.29
Lacking cues to attend the appointment		
Reminders to attend the appointments.	26.98	6.35
Patient's perception of excess benefit of care		
Patient's perception that the appointment with psychologist or dietitian was less necessary as the patient believed that he had been coping well with weight loss and any health concerns.	28.57	19.05
Psychologist-/dietitian-patient relationship		
This included the therapeutic alliance, perceived helpfulness and communication style.	0.00	1.59

their perception of excess benefit of care, which may be the crux of the challenge in adherence.

The perceived excess benefits of care may have stemmed from the lack of awareness of the importance of postoperative follow-up, which may possibly influence their motivation to remember and keep their appointments. Also, postoperative follow-ups may gain lesser priority, when placed on the scale with patients' work and other commitments, with their limited resources such as time and finances in consideration.

Patients could possibly have considered the bariatric surgery as the end-point to their weight and health concerns, failing to realise that bariatric surgery is a means and a beginning of a journey towards a healthier lifestyle management. Thus, patients perceived postoperative follow-up as unnecessary.

Moreover, patients lose weight significantly during the first year after the surgery.⁵ They may be pleased with the positive changes in their weight and health condition, which are visibly noticeable. These further influence their perception of benefit of care in attending to the postoperative follow-up appointments, perceiving them as excess.

Though the validity of the present study remains to be verified in studies with a larger sample size, the factors identified in the present study shed light on potential interventions that can be implemented to improve adherence to postoperative follow-up appointments. Specifically, more emphasis can be placed on educating patients during the preoperative phase, regarding the importance of postoperative follow-up and management, thus altering

the perception of excess benefit of care. With the lack of awareness of the importance of postoperative follow-up and management, manipulating other factors such as providing cues to attend the appointments, accommodating in appointment scheduling, and adjusting financial cost without educating the importance of postoperative follow-up and management would be futile in improving adherence.

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Clinical Outcomes of Ray Amputation in Diabetic Foot Patients

Dear Editor,

Diabetes mellitus is a growing problem in Singapore, with a reported incidence of 11.3% of the Singapore population, a significant increase from 8.2% in 2004.¹ With the implementation of a multidisciplinary approach combined with a clinical pathway, our major amputation rate (below- and above-knee amputation) has been reduced from 31.15% in 2002 to 11.01% in 2007.² Nather et al in 2008 identified predictive factors leading to limb loss in diabetic patients to be peripheral vascular disease and infection.³

Minor amputations in diabetic feet surgery include toe disarticulation, ray amputation, transmetatarsal amputation, Chopart's, Lisfranc's, Syme and Pirogoff amputation.⁴ The ray amputation is the commonest minor amputation performed in Singapore, and is preferred to the disarticulation of the toe.³ Several papers have studied the outcome of minor amputation in diabetic foot patients without further classifying which type of minor amputation was performed.^{5,6,7} Others have studied ray amputations in patients with and without diabetes.⁸

There are few studies in the literature on the clinical outcome of ray amputation in diabetic foot patients.^{9,10,11} These studies reported mainly selective aspects of clinical outcome such as mortality and recurrence of ulcers.^{9,10,11} The aim of this paper is to evaluate the factors that would predict a poor outcome following a ray amputation.

Materials and Methods

This is a prospective cohort study of 150 consecutive patients with diabetic foot problems undergoing ray amputation by the National University Hospital (NUH) Diabetes Foot Team from January 2007 to October 2010. Ethics approval from the hospital's ethics board was granted. Informed consent was taken. These patients were followed up for a minimum of 12 months.

Demographic data and patient profile such as age, sex, premorbid status, duration and type of diabetes, comorbidities, presence of risk factors such as smoking, alcoholism, and hyperlipidaemia were recorded. Clinical examination included the vascular status (lower limb pulses, ankle and toe-brachial indexes) and the neuropathy

status (5.07 Semmes-Weinstein Monofilament testing, Neurothesiometer reading). The presence and severity of renal failure along with cardiac status (history of acute myocardial infarction and latest ejection fraction) and the American Society of Anesthesiologists (ASA) score of the patients were documented. Preoperative blood investigations recorded included glycated haemoglobin (HbA1c), full blood count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Other investigations include wound/tissue and blood cultures. All laboratory/radiological and clinical findings were performed within 1 week of surgery by an independent observer not involved in the surgery. The indications for a ray amputation included 3 broad groups: wet gangrene of the toe, osteomyelitis of the proximal or distal phalanx, and soft tissue infection of the whole toe.

All patients were followed up for any postoperative complications. The need for any repeat operation and type of revision operation (revision of ray amputation, additional ray amputation in the affected foot, transmetatarsal amputation, syme amputation, below-knee amputation or above-knee amputation) were documented. Any mortality was also recorded.

A good clinical outcome is defined as one whose amputation healed and does not develop any complication within a year. A poor clinical outcome is defined as one who underwent proximal level reamputation within a year, and/or underwent additional ray amputation on the same foot within a year, and/or suffered mortality within a year after operation.

Statistical Analysis

All statistical analyses were performed using SPSS 18.0 with statistical significance set at $P < 0.050$. Predictive factors for clinical outcome were determined using univariate and stepwise logistic regression analysis. Mann-Whitney U test was used for numerical prognostic factors, and chi-square test was used for categorical factors.

Results

Table 1 shows the patient profile of our study population. The ages of our patients ranged between 24 to 81 years with

a median age of 56 years. Racial distribution in our study cohort was 39.3% Chinese, 38.7% Malays, 20% Indian and 2% other races, and this was compared to the national racial composition of Singapore.¹² The mean follow-up duration was 36 months (range, 13 to 62 months). No patients were lost to follow-up during the minimum follow-up period of 12 months.

Table 2 summarises the results of ray amputation. A total of 106 patients (70.7%) of ray amputations gave a good outcome. Univariate analysis showed that smoking, chronic renal failure, wet gangrene, absence of pulses, delayed capillary filling, low ankle-brachial index (ABI) and toe-brachial index (TBI), high total white blood cell count (TWC) and neutrophil count, high ESR, high urea, high creatinine (Cr) and low haemoglobin (Hb) were associated with a poor clinical outcome. Multivariate analysis showed that smoking, absence of pulses, delayed capillary filling, high ESR, high Cr and neutrophil counts were associated with a poor clinical outcome.

A total of 44 patients (29.3%) had a poor outcome. Of these patients, 22 patients (14.7%) underwent proximal level amputations, 12 patients (8.0%) underwent additional ray amputation, 7 patients (4.6%) underwent forefoot

amputation, and 3 (2.0%) patients died within 1 year. Two of the patients died of pneumonia resulting from systemic septicaemia, and 1 patient who had poor preoperative cardiac function died from postoperative acute myocardial infarction.

Discussion

The high incidence of minor amputations performed in diabetic foot patients has been well documented in existing literature.^{3,13,14} However, the significantly high rate of reamputations and significant mortality of these patients suggest that these patients should be better managed perioperatively.^{6,9,10,11,15}

Izumi et al found the cumulative rates of upper level reamputation post ray amputation to be as high as 50% after 5 years.⁹ Ohsawa et al reported a reamputation rate of 40% after 2 years.¹¹ Murdoch et al reported 60% reamputation rate, with the mean time from first to second amputation being approximately 10 months.¹⁶

Minor foot amputations have also been associated with poor outcome in terms of mortality.⁶ Jones et al have investigated the cumulative mortality rate of toe amputations and reported it to be 31.8% after 3 years and 41.4% after 5 years.⁶ A total of 70.7% of our patients had a good outcome. This is similar to results of Izumi et al in 2006, who found 73.3% good outcome after 1 year in a cohort of 277 diabetic foot patients.⁹

In our study, other significant risk factors for a poor outcome included markers of sepsis such as high ESR and high neutrophil counts. Hambleton et al have reported a similar finding in their prospective case controlled study of 205 diabetic foot patients, where sepsis was identified as one of the risk factors for poor outcome.¹⁵

Chronic renal failure and high Cr levels were associated with a poor outcome. This is similar to results published by Sheahan et al, who looked into a mixed cohort of 607 patients with 91.9% of the cohort having diabetes, and reported endstage renal failure and high Cr levels as poor prognostic indicators.⁸

Limitations of this study include a small sample size and a short follow-up period of less than 5 years. The authors aim to further follow-up the patients to report a 5-year outcome, and to generate a predictive model with an analysis of its prognostic accuracy to better guide management of ray amputations in diabetic foot infections.

Conclusion

The success rate of ray amputation was 70.7%. Smoking, absence of pulses, delayed capillary filling, high ESR, high Cr and neutrophil counts were found to be predictive factors for a poor clinical outcome.

Table 1. Patient Profile

Factors	Value (%)
Gender distribution	
Male	100 (66.7%)
Female	50 (33.3%)
Age	
≤60 years	103 (68.7%)
>60 years	47 (31.3%)
Race	
Chinese	59 (39.3%)
Malay	58 (38.7%)
Indian	30 (20.0%)
Others	3 (2.0%)
Premorbid activities of daily living	
Independent	132 (88.0%)
Walking with aid	9 (6.0%)
Wheelchair bound	8 (5.3%)
Bed bound	1 (0.7%)
Comorbidities	
Hypertension	111 (74.0%)
Ischaemic heart disease (IHD)	50 (33.3%)
Cerebrovascular accident (CVA)	12 (8.0%)
Hyperlipidaemia	90 (60.0%)
Diabetes type	
Type I	11 (7.3%)
Type II	139 (92.7%)

Table 2. Results of Evaluation of Factors as Predictives of Outcome

		Outcome		Unadjusted	Adjusted	
Risk Factors*		Good	Poor	P Value	OR (95% CI)	P Value
Age						
≤60 years		71 (68.9)	32 (31.1)	0.956		
>60 years		35 (74.5)	12 (25.5)			
Gender						
Male		71 (71.0)	29 (29.0)	0.522		
Female		35 (70.0)	15 (30.0)			
Race						
Chinese		37 (62.7)	22 (37.3)	0.222		
Malay		42 (72.4)	16 (27.6)			
Indian		24 (80.0)	6 (20.0)			
Others		3 (100.0)	0 (0.0)			
Premorbid ADL						
Independent		94 (71.2)	38 (28.8)	0.683		
Walking with aid		5 (55.6)	4 (44.4)			
Wheelchair		6 (75.0)	2 (25.0)			
Bedbound		1 (100.0)	0 (0.0)			
Smoking						
	Yes	20 (32.8)	41 (67.2)	0.022	32.1 (8.924 – 91.401)	0.040
	No	64 (71.9)	25 (28.1)		1.0	
Comorbidities						
Hypertension		Yes	76 (68.5)	35 (31.5)	0.216	
	No	30 (76.9)	9 (23.1)			
Hyperlipidaemia		Yes	61 (67.8)	29 (32.2)	0.222	
	No	45 (75.0)	15 (25.0)			
CVA		Yes	9 (75.0)	3 (25.0)	0.511	
	No	97 (70.3)	41 (29.7)			
IHD		Yes	35 (70.0)	15 (30.0)	0.522	
	No	71 (71.0)	29 (29.0)			
Previous AMI		Yes	24 (64.9)	13 (35.1)	0.221	
	No	82 (73.2)	30 (26.8)			
Renal function						
End stage renal failure		ESRF	8 (42.1)	11 (57.9)	0.006	
Chronic renal failure		CRF	7 (58.3)	5 (41.7)		
Normal renal function		Normal	91 (76.5)	28 (23.5)		
Sensory neuropathy		Yes	88 (69.3)	39 (30.7)	0.273	
	No	18 (78.3)	5 (21.7)			
Diabetes mellitus type						
Type 1		9 (81.8)	2 (18.2)	0.322		
Type 2		97 (69.8)	42 (30.2)			
Duration of diabetes						
1 – 5 years		16 (80.0)	4 (20.0)	0.485		
5 – 10 years		24 (64.9)	13 (35.1)			
>10 years		66 (71.0)	27 (29.0)			

ABI: Ankle-brachial index; ADL: Activities of daily living; AMI: Acute myocardial infarction; ASA: American Society of Anaesthesiologists; CRF: Chronic renal failure; CRP: C-reactive protein; CVA: Cerebrovascular accident/stroke; ESR: Erythrocyte sedimentation rate; ESRF: End stage renal failure; Hb: Haemoglobin; HbA1c: Glycated haemoglobin; IHD: Ischaemic heart disease; NF: Normal foot; OR: Odds ratio; PF: Pathological foot; TBI: Toe-brachial index; TWC: Total white blood cell count

*Mann-Whitney U test used for numerical prognostic factors; chi-square test used for categorical factors.

Table 2. Results of Evaluation of Factors as Predictives of Outcome (Con't)

Risk Factors*		Outcome		Unadjusted	Adjusted	
		Good	Poor	P Value	OR (95% CI)	P Value
ASA score						
1		1 (50.0)	1 (50.0)	0.363		
2		58 (73.4)	21 (26.6)			
3		47 (69.1)	21 (30.9)			
4		0 (0.0)	1 (100.0)			
Vasculopathy						
Pulses	Both pulses not palpable	26 (53.1)	23 (46.9)	0.004	1.0	0.050
	1 pulse palpable	15 (83.3)	3 (16.7)		6.337 (1.231 – 32.610)	0.027
	2 pulses palpable	65 (78.3)	18 (21.7)		2.176 (0.870 – 5.440)	0.096
Delayed capillary filling	Yes	18 (50.0)	18 (50.0)	0.002	1.0	0.031
	No	88 (77.2)	26 (22.8)		2.832 (1.102 – 7.281)	
ABI: median (range)		1.1 (0.2 – 2)	0.9 (0.2 – 3.6)	0.001		
TBI: median (range)		0.8 (0.1 – 2.9)	0.5 (0.1 – 3)	0.013		
Neuropathy						
Monofilament test (PF)	≤7/10	93 (70.5)	39 (29.5)	0.560		
	>7/10	13 (72.2)	5 (27.8)			
Monofilament test (NF)	≤7/10	87 (71.3)	35 (28.7)	0.440		
	>7/10	19 (67.9)	9 (32.1)			
Neurothesiometer (PF)	0 – 25 V	11 (61.1)	7 (38.9)	0.820		
	26 – 50 V	55 (72.4)	21 (27.6)			
	>50 V	18 (72.0)	7 (28.0)			
	Not tested	22 (71.0)	9 (29.0)			
Neurothesiometer (NF)	0 – 25 V	17 (89.5)	2 (10.5)	0.102		
	26 – 50 V	41 (69.5)	18 (30.5)			
	>50 V	16 (80.0)	4 (20.0)			
	Not tested	32 (61.5)	20 (38.5)			
Preop parameters: median (range)						
Hb (g/dL)		11.5 (6.4 – 15.7)	10 (7.4 – 15)	0.005		
TWC (x10 ⁹ /L)		13.0 (6.5 – 33)	15.6 (6.2 – 28)	0.042		
Neutrophils (x10 ⁹ /L)		10.4 (3.2 – 28.4)	14 (4.8 – 23.6)	0.000	0.880 (0.810 – 0.956)	0.002
CRP (mg/L)		120.4 (9.6)	145.4 (15.2)	0.209		
ESR (mm/hr)		94.5 (13 – 150)	157.5 (2 – 356)	0.005	0.982 (0.968 – 0.997)	0.021
Urea (mmol/L)		5.6 (1 – 76)	8.3 (1.4 – 25.9)	0.011		
Creatinine (umol/L)		82.5 (3 – 985)	139 (44 – 939)	0.000	0.997 (0.995 – 0.999)	0.004
HbA1c (%)		10.0 (5.5 – 16)	9.5 (5.9 – 73)	0.474		
Indication for surgery						
Wet gangrene		57 (62.0)	35 (38.0)	0.013		
Osteomyelitis		28 (84.8)	5 (15.2)			
Soft tissue infection of whole toe		21 (84.0)	4 (16.0)			

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An Uncommon Cutaneous Reaction for a Common Drug

A 72-year-old Chinese female presented with a rapidly progressing, generalised rash over a 2-week period. Her medical history includes hypertension for which nifedipine had been started 5 weeks earlier. She was otherwise well with no systemic symptoms. Physical examination showed annular, scaly, erythematous plaques with central clearing on her upper and lower limbs, neck, trunk, and back (Figs. 1A and 1B).

What is the diagnosis?

- A. Plaque psoriasis
- B. Drug-induced subacute cutaneous lupus erythematosus (DI-SCLE)
- C. Erythema annulare centrifugum
- D. Sweet's syndrome
- E. Cutaneous T-cell lymphoma

Case Report

The patient's full blood count, liver and renal biochemistry were unremarkable apart from eosinophilia ($0.9 \times 10^3/\mu\text{L}$, normal range = $0.0 - 0.4 \times 10^3/\mu\text{L}$). Her antinuclear antibody, anti-double-stranded DNA, antihistone antibody, and Ro/Sjögren syndrome-associated antigen A (Ro/SSA) autoantibodies were negative. Direct immunofluorescence was negative. A skin biopsy from a representative lesion showed focal interface activity with basal vacuolar change and lymphocytic exocytosis admixed with few eosinophils (Fig. 2). There was increased mucin on Alcian blue stain. The clinical picture and histological findings were consistent with DI-SCLE. Her lesions resolved within several weeks upon withdrawal of nifedipine.

Discussion

DI-SCLE is characterised by scaly annular skin lesions, usually in sun exposed areas. It is related to drug exposure. Antihypertensives including hydrochlorothiazide and nifedipine, and antifungals are some of the common triggers for DI-SCLE. More recently, chemotherapeutic drugs such as taxanes have been reported to cause DI-SCLE.¹ The



Fig. 1. A 72-year-old patient presented with rapidly progressing, generalised rash. Erythematous, annular, scaly plaques with central clearing are seen on patient's (A) upper limb and (B) neck.

Answer: B

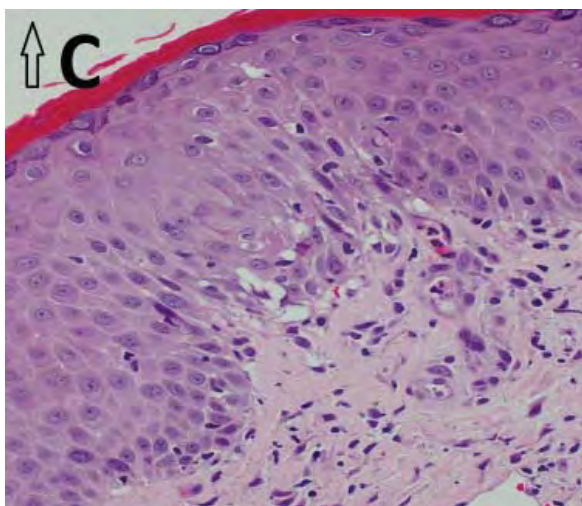


Fig. 2. Skin biopsy from thigh; H&E stain, original magnification x40.

onset of cutaneous lesions from the initiation of the culprit drug varies with different drug classes. Cutaneous lesions may appear within 5 weeks after exposure to antifungals, while calcium channel blockers may trigger a rash up to 3 years after initial exposure.² The pathogenesis of DI-SCLE is unknown. Some have suggested that DI-SCLE may be a consequence of de novo autoantibody formation after drug exposure. Others suggest DI-SCLE as a development of a condition in an already predisposed patient.³

There is a strong association with Ro/SSA autoantibodies (found in up to 90% of patients).^{2,4} However, antihistone antibody is positive in only one-third of patients of DI-SCLE.² Positive direct immunofluorescence may be found in up to 80% of cases of DI-SCLE.² The characteristic histological feature of DI-SCLE is an interface dermatitis with focal vacuolisation of the epidermal basal layer and perivascular dermal lymphocytic infiltrate.² A recent retrospective study demonstrated that tissue eosinophilia is not a differentiating histological feature of DI-SCLE, and that the diagnosis of DI-SCLE should be based largely on drug history and clinical findings.⁵

DI-SCLE is similar to idiopathic subacute cutaneous lupus erythematosus in terms of clinical, histopathological, or immunopathological features.² In contrast, patients with DI-SLE present with fever, weight loss and serositis. Antihistone antibody may be positive in 95% of patients in this group of patients.⁶

In our patient, we diagnosed DI-SCLE based on the recent introduction of typical drug, clinical features and supportive histology findings. Interestingly, Ro/SSA autoantibodies were negative in this patient. Nifedipine was withdrawn and she was treated with topical betamethasone valerate 0.1%. Five weeks after drug withdrawal, her rash had completely resolved. On the last follow-up 4 months later, there was no relapse of her symptoms.

Conclusion

Discontinuation of the offending drug usually results in resolution of the skin lesions in DI-SCLE within weeks.² However, some cases may require the use of topical or systemic corticosteroids.

Acknowledgement

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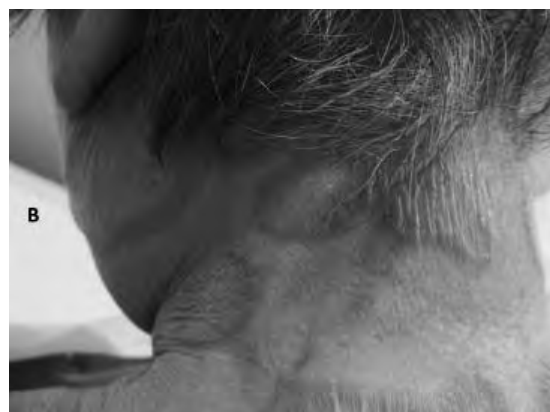


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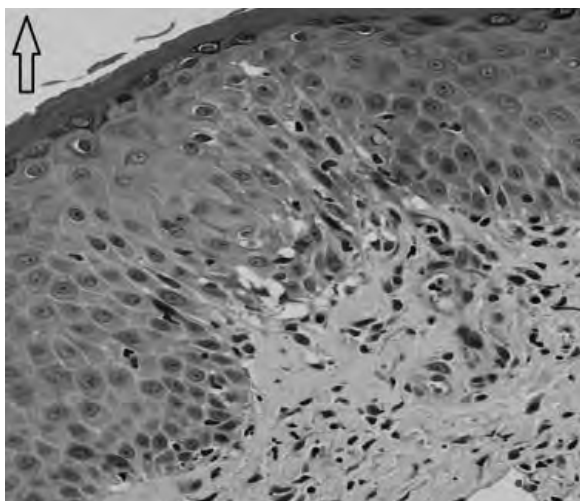


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