A Proposed Aeromedical Disposition Flowchart for Systemic Lupus Erythematosus

Benjamin Zhi Qiang Seah; Choon Guan Chua

BACKGROUND: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by multisystem involvement. Clinical management of this condition has unique aeromedical considerations and an impact on subsequent aeromedical disposition. A comprehensive decision matrix would greatly benefit aviation medicine practitioners in the management of aircrew and personnel in flying-related vocations who are diagnosed with SLE.

CASE REPORT: We describe the aeromedical management of a military air traffic controller who was diagnosed with SLE after presenting with cutaneous lupus, nonscarring alopecia, symmetrical small joint polyarthropathy, leukopenia, and presence of SLE-specific antibody. She was treated with hydroxychloroquine and low-dose systemic glucocorticoids, and allowed to return to duties with a proximity restriction and a bar on field deployments and night duties.

DISCUSSION: Several SLE manifestations may have either incapacitating or distracting effects on aircrew and personnel in flying-related vocations. Some medications used in the treatment of SLE may similarly impact on an individual's ability to safely execute flight or air traffic control duties. We propose an aeromedical disposition decision flowchart that would guide aviation medicine practitioners in the management of individuals diagnosed with SLE to ensure optimal and safe performance in their respective occupational settings.

KEYWORDS: systemic lupus erythematosus, aeromedical disposition, aircrew, flying-related vocation.

Seah BZQ, Chua CG. *A proposed aeromedical disposition flowchart for systemic lupus erythematosus*. Aerosp Med Hum Perform. 2020; 91(10):826–832.

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease that runs a highly variable clinical course. Clinical manifestations can range from mild joint and skin involvement to severe life-threatening internal organ disease. It affects primarily women of child-bearing age and is often associated with other autoimmune diseases such as Sjogren's syndrome (SS) and antiphospholipid syndrome (APS). In addition, patients are predisposed to comorbidities such as hypertension, steroid-induced diabetes mellitus, hyperlipidemia, and glucocorticoid-induced osteoporosis. Treatment of SLE involves long-term immunosuppressants, prevention and management of comorbidities, and behavioral changes such as sun avoidance and smoking cessation. Plagued by this chronic disease, SLE patients often experience poor self-esteem and low mood, thereby requiring close psychosocial support.

In view of the variability and severity of SLE, aviators and flying-related vocation (FRV) applicants with this disease have been precluded from entry into any military or civil aviation organizations. Most organizations would also ground trained aviators and FRVs permanently upon diagnosis of SLE due to concerns over its potentially severe clinical manifestations, comorbidities, and adverse effects from treatment. However, with a better understanding of SLE and treatment advancements, many patients are now living a relatively normal life once remission is induced with initial treatment and continued on low doses of long-term immunosuppressants to maintain the remission. We note the relative paucity of guidance material for SLE in established open source civil and military aeromedical certification guides and textbooks, and hope that this article may bridge this knowledge gap and highlight the unique aeromedical considerations concerning SLE management in the context of the relevant occupational settings. Using a clinical vignette, we describe the clinical management and subsequent

From the Republic of Singapore Air Force Medical Service, Singapore, and the Department of Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital, Singapore.

This manuscript was received for review in May 2020. It was accepted for publication in July 2020.

Address correspondence to: Benjamin Zhi Qiang Seah, M.B., B.S., 492 Airport Rd., Singapore 539945, benjaminseahzq@gmail.com.

DOI: https://doi.org/10.3357/AMHP.5684.2020

aeromedical disposition of an air traffic controller (ATCO) diagnosed with SLE, focusing in particular on the aeromedical considerations when managing similar patients in the context of their unique occupational setting.

CASE REPORT

A 37-yr-old female qualified military ATCO was diagnosed with SLE in 2019 when she presented with a 5-mo history of rash located near the right nasal bridge, patchy nonscarring alopecia over her vertex, and arthralgia with early morning stiffness involving the proximal interphalangeal joints of her hands. She exhibited neither constitutional symptoms nor other symptoms suggestive of major internal organ involvement. Of note, she did not experience any neuropsychiatric symptoms of cognitive deterioration. There were no sicca symptoms and she carried three uneventful pregnancies to full-term deliveries with no history of spontaneous abortions or recurrent thrombotic episodes. She was well prior to the diagnosis of SLE and suffered from no chronic medical condition. There was no family history of rheumatic or autoimmune diseases and her physical examination was unyielding for any major organ abnormalities.

Her full blood count showed leukopenia [white blood cell count of $3.6 \times 10^9 \cdot L^{-1}$ (4.0 to 9.6)], but neither anemia (hemoglobin of $12.3\ g \cdot dL^{-1}$) nor thrombocytopenia (platelet count of $151 \times 10^9 \cdot L^{-1}$). Renal function was normal with an estimated glomerular filtration rate of $> 60\ mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ and her urine analysis revealed no proteinuria, hematuria, or cellular casts. She had a normal liver function test with no hypoalbuminemia [$39\ g \cdot L^{-1}$ (38 to 48)]. Her erythrocyte sedimentation rate was $16\ mm \cdot h^{-1}$ (3 to 15), which was normal when corrected for her age, and there was no hypocomplementemia. Serological investigations showed elevated antinuclear antibody titers (detected at dilutions $\geq$ 1:640 with a speckled pattern), elevated rheumatoid factor levels [$125\ RU \cdot mL^{-1}$ (0 to 20)], and extractable nuclear antibody positivity, in particular for anti-Sm and anti-Ro antibodies. Antidouble-stranded DNA antibody was not detected. Her coagulation profile was normal, with neither lupus anticoagulant nor anticardiolipin antibodies detected. Radiographic imaging of both hands revealed well-defined articular surfaces with no joint erosions, narrowing, or peri-articular osteopenia. Schirmer's test was normal.

Given the presence of subacute cutaneous lupus erythematosus, alopecia, symmetrical small joint polyarthropathy, leukopenia, and presence of lupus-specific antibody (anti-Sm), the patient was diagnosed with SLE. Although she tested positive for anti-Ro, she did not exhibit any other signs or symptoms suggestive of SS. The patient was commenced on hydroxychloroquine 200 mg OM and low dose glucocorticoid (prednisolone 5 mg OM) by her attending rheumatologist. In addition, she was prescribed topical tacrolimus for malar rash and monthly intralesional triamcinolone injections for alopecia. She was restricted from all control duties during the evaluation period to determine the full extent of SLE involvement. Her SLE was controlled after 3 mo with the medications prescribed, with her subsequent laboratory investigations revealing resolution of leukopenia. Her attending rheumatologist planned to gradually wean off prednisolone over time. Overall, her SLE was considered mild and the low-dose prednisolone (< 10 mg/d) was assessed to have a low risk of significant side effects. As such, the final aeromedical disposition after consulting her superiors involved a proximity restriction and permanent excuse from field deployments to minimize sun exposure. Her work schedule was optimized to preclude night duties to prevent disruptions to regular circadian rhythm that could trigger disease flares. Annual ophthalmological follow-up was also required for surveillance of bull's eye maculopathy from hydroxychloroquine use. This arrangement allowed for optimal medical management while minimizing the impact of SLE on her career and livelihood.

DISCUSSION

The aeromedical considerations in managing an aviator or FRV with SLE are complex due to the protean presentation of this condition. In view of disease chronicity and an unpredictable trajectory, applicants with SLE should continue to be precluded from selection. For trained aircrew and FRVs, waivers can potentially be considered for those with mild disease or in clinical remission to allow these trained individuals to continue to be gainfully employed. Emphasis should be placed on compliance to SLE treatment and close collaboration between the attending aviation medicine practitioner and rheumatologist in managing the patient's disease and career.

The considerations in determining aeromedical disposition can be classified into the following key domains: 1) impact of disease (including presence of other commonly associated autoimmune diseases); 2) impact of treatment; 3) impact of natural history progression and presence of comorbidities; 4) occupational considerations and potential for maximizing employability; and 5) psychosocial needs and concerns. Regardless of disease complexity, the general principles of concerns over symptom manifestations resulting in sudden incapacitation during flight controls and limitations to field deployment remain when evaluating a trained aircrew or FRV with SLE. A generic approach to the potential for waiver is to consider the manifestations individually by assessing their severity and potential impact on occupational safety. The presence of commonly associated autoimmune diseases, like SS and APS, and their severities should also be assessed. Although scoring systems such as SLEDAI can be considered for assessment of disease activity, they are complicated to administer in the clinics and should be deferred to the primary rheumatologist to perform. Refer to **Table I** for waiver potential of respective SLE manifestations for trained aircrew and FRV.

The aims of treatment in SLE are of twofold: 1) to induce disease remission, and 2) to maintain disease remission. Despite the myriad of pharmacological options available for SLE treatment in modern days, most patients would receive long term systemic glucocorticoids and hydroxychloroquine throughout

Table I. Waiver Potential of Respective SLE Manifestation for Trained Aircrew and FRV.

ORGAN SYSTEM	MANIFESTATION	CONSIDERATION(S)	WAIVER POTENTIAL		REMARKS
			YES	NO	
Mucocutaneous	Cutaneous lupus	Photosensitive nature of rash may be exacerbated by sun exposure	X		Restrict from sun exposure Topicals acceptable Stable/treated disease for waiver potential
	Aphthous ulceration	Impact on speech intelligibility Distracting	X		Subject to satisfactory functional/workplace assessment Topicals acceptable Stable/treated disease for waiver potential
	Alopecia	Impact limited to cosmesis	X		Local glucocorticoid injections acceptable Consider psychological impact concurrently
Musculoskeletal	Arthropathy	Impact of pain and reduced joint mobility/dexterity on flight and air traffic control inputs Distracting	X		Subject to satisfactory functional/workplace assessment Consider multicrew/proximity restriction Exclude personnel with moderate to severe joint disease Analgesia must be acceptable
	Myopathy and myositis	Impact of pain and weakness on flight and air traffic control inputs	X		Subject to satisfactory functional/workplace assessment Consider multicrew/proximity restriction Exclude personnel with demonstrable weakness and active disease
Renal	Lupus nephritis	Acid-base, electrolyte and fluid imbalance Uremia and accompanying manifestations (e.g., encephalopathy, pericarditis, gastroparesis) Nephrotic syndrome and accompanying manifestations (e.g., hypogammaglobulinemia)	X		Subject to severity of nephritis and residual renal function Consider multicrew/proximity restriction Exclude personnel with any biochemical derangement/clinical condition listed under "Consideration(s)" Stable/treated disease for waiver potential
Hematological	Anemia	Anemic hypoxia impacting on effort tolerance, vision, cognition and psychomotor reflexes Hyperdynamic circulation increasing myocardial oxygen consumption	X		Waiver if hemoglobin $> 11.5\ g \cdot dL^{-1}$ in men and $> 10.5\ g \cdot dL^{-1}$ in women Stable/treated disease for waiver potential
	Leukopenia	Secondary infection risk Infectious disease transmissibility at workplace due to relative lack of symptoms	X		Waiver if absolute neutrophil count > 0.5 Stable/treated disease for waiver potential
	Thrombocytopenia	Increased bleeding risk	X		Aircrew: Waiver if platelet count $> 100 \times 10^9 \cdot L^{-1}$ ATCO: Waiver if platelet count $> 75 \times 10^9 \cdot L^{-1}$ Stable/treated disease for waiver potential
Autoimmune	Sjogren's syndrome	Dry eyes and/or mouth distracting Less common presentations include neuro-Sjogren's and pulmonary cysts	X		Subject to disease severity and satisfactory functional/workplace assessment Consider multicrew/proximity restriction if mild disease Exclude personnel with severe manifestations, e.g., neuro-Sjogren's and pulmonary cysts
	Antiphospholipid syndrome	Thrombotic risk with sudden incapacitation Increased bleeding risk following treatment		X	Subject to normal coagulation profile without need for long-term treatment Consider compatibility with occupational requirements, e.g., combat deployments
Neurological	Peripheral nervous system involvement (e.g., mononeuropathy, polyneuropathy)	Impact on flight and air traffic control inputs	X		Subject to satisfactory functional/workplace assessment Consider multicrew/proximity restriction Stable/treated disease for waiver potential
	Autonomic nervous system involvement (e.g., secondary Raynaud's)	Impact on flight and air traffic control inputs Distracting	X		Subject to satisfactory functional/workplace assessment Consider multicrew/proximity restriction Stable/treated disease for waiver potential

Table I, *Continued.*

ORGAN SYSTEM	MANIFESTATION	CONSIDERATION(S)	WAIVER POTENTIAL YES	WAIVER POTENTIAL NO	REMARKS
	Central nervous system involvement (e.g., delirium, seizures, stroke)	Impact on flight and air traffic control inputs Risk of sudden incapacitation		X	Unless accredited medical conclusion opines otherwise, e.g., single episode unprovoked seizure > 10 yr ago with no recurrence and not on antiepileptics
Psychiatric	Psychiatric manifestation (e.g., psychosis)	Impact on attention and concentration Risk of sudden incapacitation		X	Unless accredited medical conclusion opines otherwise, e.g., stable depression on maintenance dose of acceptable medication
Cardiac	Acute conditions (e.g., pericarditis, myocarditis, endocarditis)	Reduced cardiac output Risk of cardiac tamponade in pericarditis Arrhythmia risk Risk of sudden incapacitation		X	Unacceptable risk profile Waiver can be considered once acute conditions resolve in the absence of long-term cardiac impairment such as residual chronic cardiac failure
	Cardiac failure (chronic)	Reduced cardiac output Arrhythmia risk Pleural effusion reducing blood oxygenation Risk of sudden incapacitation		X	Unacceptable risk profile
Respiratory	Acute conditions (e.g., pleuritis, diffuse alveolar hemorrhage)	Reduced blood oxygenation Risk of sudden incapacitation		X	Unacceptable risk profile Waiver can be considered once acute conditions resolve in the absence of long-term impairment to pulmonary function
	Pulmonary fibrosis	Increased A-a gradient reducing blood oxygenation Right heart failure and arrhythmia risk		X	Unacceptable risk profile
Gastrointestinal	Lupus gut, pancreatitis, and hepatitis	Indicative of active disease Distracting		X	Unacceptable risk profile Waiver can be considered once acute conditions resolve in the absence of long-term impairment to gastrointestinal function, e.g., impaired liver function and endocrine sequelae from pancreatitis
Ophthalmological	Episcleritis, scleritis, uveitis and retinal vasculopathy	Indicative of active disease Impact on visual acuity, field of vision and color vision		X	Unacceptable risk profile Waiver can be considered once acute conditions resolve and subjected to normal visual parameters and occupationally compatible functional vision Frequent follow-up and reassessment
Others	Constitutional symptoms (e.g., fever, malaise)	Indicative of active disease Distracting		X	Unacceptable risk profile Waiver can be considered once SLE is controlled and constitutional symptoms resolve

the induction and maintenance periods. Of note, hydroxychloroquine is an adjunct therapy that has been proven to be effective in preventing subsequent SLE flare. The remaining immunosuppressive concoctions depend on: 1) disease activity and severity, 2) treatment response, 3) side effects from treatment and contraindications, and 4) desire for family planning. In general, high doses of glucocorticoids are given at diagnosis and eventually tapered to a low dose once remission is achieved with the long-term immunosuppressants.

When considering the waiver potential, one should consider the potential side effects of the treatment at its prescribed dosage, limitations posed to extent of field deployment, and surveillances that would be required to monitor for side effects. Although occupational considerations could be taken into account in the choice of treatment, it should not deny patients from evidence-based best practices that would provide quicker response and superior health benefits. In fact, patients could switch over to a treatment regime that would be commensurate with their occupational circumstances in discussion with the primary rheumatologist once adequate clinical control over disease or remission has been achieved. Refer to **Table II** for the proposed waiver potential of drugs commonly used in the treatment of SLE.

Hydroxychloroquine is the anchor drug in this condition due to its efficacy but poses the risk of retinopathy developing from cumulative dosages. The prevalence of retinal toxicity increases from < 2% within 10 yr of use to nearly 20% after 20 yr of use.[5] As such, SLE patients are recommended to undergo yearly optical coherence tomography after receiving 5 yr of hydroxychloroquine therapy to screen for retinal toxicity. Retinal toxicity is of significance in the aviation context as it invariably impacts on visual acuity, field of vision, color vision, contrast sensitivity, and stereopsis. Good distance vision, contrast sensitivity, stereopsis, and a functional visual field are

Table II. Waiver Potential for Drugs Used in the Treatment of SLE.

DRUG	WAIVER POTENTIAL	REMARKS
Hydroxychloroquine	Yes	Regular monitoring for maculopathy
Systemic glucocorticoids	Maybe (low dose < 10 mg/d); Consider multicrew/proximity restriction	High dosages indicative of active disease with potential for neuropsychiatric side effects
Steroid-sparing agents (e.g., azathioprine, methotrexate, ciclosporin, mycophenolate mofetil and cyclophosphamide)	Maybe (if well-tolerated with long-term monitoring); Consider multicrew/proximity restriction	Regular monitoring for myelotoxicity and hepatotoxicity
Biologics (e.g., rituximab, belimumab) and intravenous immunoglobulins	No	Usage indicative of difficult disease control; increased risk of secondary infections for biologics

especially important for aviators and tower controllers in order to have a good appreciation of the external environment. Intermediate and near vision are similarly critical for gleaning information from instruments, displays, and manuals. Given the ubiquity of multifunction displays in aircraft cockpits and air traffic control stations, which use a variety of colors to denote and differentiate a wide spectrum of information, having intact color vision is of paramount importance. Hydroxychloroquine use can be waived in the USAF context with regular monitoring for development of retinopathy.

Glucocorticoids are typically prescribed upon diagnosis of SLE to establish rapid disease control, followed by gradual tapering and discontinuation if possible once a steroid-sparing agent is added on and has taken effect. This is to avoid the development of adverse effects from glucocorticoids, e.g., accelerated atherosclerosis, iatrogenic Cushing's, and glucocorticoid-induced osteoporosis. In the aviation setting, glucocorticoid usage, especially at moderate to high doses (> 10 mg/d of prednisolone and equivalent), necessitates grounding and suspension of license privileges. This is due to the fact that glucocorticoid prescriptions at such dosages: 1) indicate active disease or disease flare; and 2) are associated with adverse effects, such as neuropsychiatric sequelae, that may impair an aviator's ability to fly safely or an ATCO's ability to control effectively. Patients taking low dose glucocorticoids (prednisolone < 10 mg/d or equivalent) have been found to be at lower risk of opportunistic infections[10] and osteoporosis (in particular < 7.5 mg/d prednisolone),[4] as well as equivalent cardiovascular mortality risk compared to patients not taking glucocorticoids in rheumatological disease studies (daily doses of up to 7 mg prednisolone equivalent)[3].

Steroid-sparing agents commonly used include azathioprine, ciclosporin, mycophenolate mofetil, and cyclophosphamide. Methotrexate is occasionally used in SLE patients with musculoskeletal and cutaneous manifestations. These medications are used to accelerate glucocorticoid tapering in the event that hydroxychloroquine and prednisolone are inadequate at achieving disease control. Methotrexate or azathioprine use carries the risk of myelosuppression and hepatotoxicity, necessitating the monitoring of hematologic and hepatic parameters. The use of ciclosporin, mycophenolate mofetil and cyclophosphamide are efficacious in the treatment of major organ involvement, such as lupus nephritis, but are associated with higher risks of opportunistic infections and side effects, such as myelotoxicity and a range of gastrointestinal side effects. The use of methotrexate and azathioprine as part of maintenance therapy could potentially be permissible subject to regular monitoring and multicrew/proximity restrictions.

Biologics like rituximab and belimumab target B-cells which are vital in the pathogenesis of SLE. Commonly reported side effects include an increased infection risk and hypersensitivity reactions. Both biologics have also been noted to cause progressive multifocal leukoencephalopathy and depression, and aeromedical examiners should be aware of these reported rare adverse events for effective monitoring. Intravenous immunoglobulins are infrequently used in SLE patients who have active disease and are unable to receive other therapeutic agents due to adverse effects or severe infections. Their use should, therefore, preclude potential for licensing waiver.

The 5-yr survival rate among newly diagnosed patients has increased from 50% in one study between 1949 to 1953[6] to over 90% across several studies in Europe, the United States, Canada, and Latin America since the mid-1970s, with 15- to 20-yr survival rates of around 80%.[8] Urowitz et al.[11] described the bimodal mortality pattern of SLE, ascribing deaths in the early disease course to secondary infection from high glucocorticoid dosages and active disease, and deaths in the later disease stages to atherosclerotic heart disease, associated myocardial infarction, and the cumulative effects of long-term glucocorticoid therapy. A 300-patient cohort from University College London followed up over a period of 22 yr[7] showed that death in SLE patients was four times that of the general population, with the most common cause of death being malignancy, infection, and vascular disease. Early deaths were secondary to renal disease and late deaths due to atherosclerosis.

These findings highlight the fact that patients with SLE require follow-up on a regular basis, with particular attention paid to malignancy screening and regular assessment of cardiovascular health for possible flow-limiting disease. Detection of underlying disease should prompt management according to existing guidelines, taking into account the relevant occupational requirements. The development of Class III and IV lupus nephritis has been associated with poor prognosis.[2] Deterioration in renal function will invariably result in a need to re-evaluate the suitability of an aviator or ATCO for his/her role in view of the array of complications that may develop.

Besides mortality, the morbidity associated with SLE should not be overlooked. Functional assessments should be conducted in order to determine if the patient remains fit for duties, particularly where the musculoskeletal and neurological systems

are concerned. The ability to operate equipment and function effectively without compromising on safety and task effectiveness should be included as key evaluation outcomes. Third-party feedback from coworkers and supervisors can be obtained to assess the possibility and severity of underlying neurocognitive deficits as current cognitive screening tools fare poorly in the detection of subtle cognitive deficits.

A diagnosis of SLE usually precludes selection in view of the natural history of disease progression and the rate of complication development. However, for trained aircrew, it is usually in the organization's interests to maximize employability and retention within the field of the trained skillset in view of the sizeable investment incurred from training and professional accreditation. Assessment and subsequent aeromedical disposition should be aligned to the often-quoted 1% rule, i.e., the risk of sudden incapacitation should not exceed 1% per annum in multipilot operations, with limitations applied where appropriate. In commercial aviation and air traffic control centers where either multipilot or proximity restrictions can be applied, there is room for patients with stable disease in remission to return to duties subject to regular follow-up and monitoring. For military personnel, where such restrictions may not be available, e.g., in single-pilot fast-jet operations or field air traffic control deployments in austere environments, revocation or retraining might have to be considered.

SLE is commonly associated with depression[12] and anxiety,[9] and has a significant impact on overall quality of life.[1] The impact of SLE on an individual's career and, in turn, his/her socioeconomic status and psychological well-being, cannot be underestimated. Significant healthcare costs and disruption to employability and deployability may exert a substantial toll on financial stability. The effects of such stressors may have a bidirectional effect, with chronic disease activity influencing emotional states and mood/anxiety symptoms exacerbating disease severity and increasing the frequency of flares.

Our treatment approach involves all aspects of the biopsychosocial model. Regular communication with the attending specialists ensures that the management plan is optimal and evidence-based, yet occupationally viable from an aeromedical perspective. From an aviation medicine approach, a workplace visit was conducted in order to better understand the patient's occupational requirements. This included conversations with superiors to ensure that an appropriate aeromedical disposition could be derived while not compromising on operations. Extra effort was made to understand the potential impact of the diagnosis and treatment plan on her family and social life.

In summary, the aeromedical considerations in managing an aviator or FRV with SLE are complex. A full assessment should be performed to determine the extent of disease manifestations and a period of up to 6 mo to a year should be allowed for the disease to be controlled first before deciding on the aeromedical disposition of the patient. Aviators and FRVs who have mild disease that are controlled with therapeutic agents of acceptable risk profiles can potentially be given waivers and return to flying or control duties. Long-term close collaboration between the aviation medicine practitioners and primary rheumatologists should continue and a balanced approach should be taken in the management of personnel's medical condition and maintaining employability. **Fig. 1** shows a suggested decision flowchart in determining the waiver potential of an aviator or FRV with SLE.

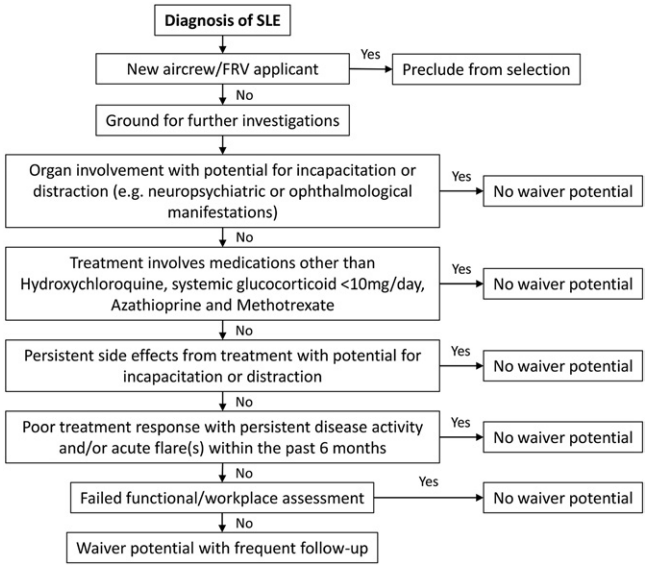

Fig. 1. SLE aeromedical disposition decision flowchart.

The chronicity, natural progression, and potential complications of SLE make it a problematic disease to manage from an aeromedical and occupational medicine perspective. Conflicting interests from the aviation medicine practitioner and organization management regarding the patient's disposition require communication and a balanced approach while not compromising on the individual's well-being. We feel that the biopsychosocial model to the management of SLE provides a robust framework to align to and from which maximum benefit to the patient may be derived.

ACKNOWLEDGMENTS

Financial Disclosure Statement: The authors have no competing interests to declare.

Authors and affiliations: Benjamin Zhi Qiang Seah, M.B.B.S. (S'pore), D.Av. Med. (UK), and Choon Guan Chua, D.Av.Med. (UK), MRCP (UK), Republic of Singapore Air Force Medical Service, Singapore; and Choon Guan Chua, Department of Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital, Singapore.

REFERENCES

1. Abu-Shakra M, Mader R, Langevitz P, Friger M, Codish S, et al. Quality of life in systemic lupus erythematosus: a controlled study. J Rheumatol. 1999; 26(2):306–309.
2. Abu-Shakra M, Urowitz MB, Gladman DD, Gough J. Mortality studies in systemic lupus erythematosus. Results from a single centre. II. Predictor variables for mortality. J Rheumatol. 1995; 22(7):1265–1270.

3. del Rincón I, Battafarano DF, Restrepo JF, Erikson JM, Escalante A. Glucocorticoid dose thresholds associated with all-cause and cardiovascular mortality in rheumatoid arthritis. Arthritis Rheumatol. 2014; 66(2):264–272.
4. McCloskey E, Kanis JA. FRAX updates 2012. Curr Opin Rheumatol. 2012; 24(5):554–560.
5. Melles RB, Marmor MF. The risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy. JAMA Ophthalmol. 2014; 132(12):1453–1460.
6. Merrell M, Shulman LE. Determination of prognosis in chronic disease, illustrated by systemic lupus erythematosus. J Chronic Dis. 1955; 1(1):12–32.
7. Moss KE, Ioannou Y, Sultan SM, Haq I, Isenberg DA. Outcome of a cohort of 300 patients with systemic lupus erythematosus attending a dedicated clinic for over two decades. Ann Rheum Dis. 2002; 61(5):409–413.
8. Pons-Estel GJ, Alarcón GS, Scofield L, Reinlib L, Cooper GS. Understanding the epidemiology and progression of systemic lupus erythematosus. Semin Arthritis Rheum. 2010; 39(4):257–268.
9. Shortall E, Isenberg D, Newman SP. Factors associated with mood and mood disorders in SLE. Lupus. 1995; 4(4):272–279.
10. Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticosteroids. Rev Infect Dis. 1989; 11(6):954–963.
11. Urowitz MB, Bookman AA, Koehler BE, Gordon DA, Smythe HA, Ogryzlo MA. The bimodal mortality pattern of systemic lupus erythematosus. Am J Med. 1976; 60(2):221–225.
12. Waterloo K, Omdal R, Husby G, Mellgren SI. Emotional status in systemic lupus erythematosus. Scand J Rheumatol. 1998; 27(6):410–414.