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"Men who wish to know about the world must learn about it in its particular details."

Heraclitus (535 BC – 475 BC)
Greek philosopher

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Editorial on Guidelines for the Management of Atopic Dermatitis in Singapore

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As a chronic relapsing inflammatory skin disorder affecting 1 in 5 of school children by 16 years of age in Singapore, atopic dermatitis (AD) poses a significant burden of disease.[1] The pruritus can cause sleeplessness and sleep deprivation, leading to psychosocial problems that disrupt the quality of life for the child and the family. While the childhood prevalence here of AD is similar to that in most developed countries, adult-onset AD appeared to be more common in Singapore, comprising 14% of all cases of AD seen at the National Skin Centre.[2] It is estimated that close to 50% of early onset AD children may have persistent AD in adulthood. Given that AD can be managed by primary care practitioners, paediatricians, allergists and dermatologists, the Guidelines for the Management of Atopic Dermatitis in Singapore by Tay et al,[3] in this issue of Annals, is timely as best practice guidelines, that are developed by a group of experienced dermatologists.

Since the growth of the internet revolution, it is not uncommon to find that many AD patients have tried alternative treatments, sensing that current treatments do not get to its "root" cause.[4] Indeed, steroid phobia leading to under-treatment is more of an issue than its overuse, in the management of AD in developed countries. It should be noted that there is no evidence from randomised controlled trials (RCTs) to suggest that skin thinning is a problem from the intermittent use of topical corticosteroids (TCS). The reality of under-treatment is that weak steroids may not clear the skin and patients develop flare ups because they stop using TCS, expecting the treatment to be curative. In these guidelines, a stepped approach to management with appropriate potency of TCS based on severity is provided, escalating to the use of phototherapy and systemic therapy with immunosuppressive drugs such as cyclosporine and azathioprine in severe AD. This stratification by disease severity also provides a guide on when patients need to be referred to a dermatologist.

The use of topical calcineurin inhibitors (TCIs) has witnessed a decade of experience and black box warnings. Despite safety data from long-term registries and large studies in infants, there have been conflicting results on the cost-effectiveness of TCIs as first-line therapy in mild to moderate AD.[5,6] Therefore, the use of TCIs in AD is best reserved for: 1) maintenance therapy in patients who have steroid phobia; and 2) steroid-sensitive areas, for e.g. eyelids, face and skin folds where TCIs may be considered as first-line treatment, as proposed by the authors. For maintenance therapy, it should be noted that proactive treatment with twice weekly mild-to-mid potency TCS and even the use of moisturisers alone can help in the maintenance of improvement. What has not been evaluated is which of these strategies would be most cost-effective and safe for patients.

The article alluded to the lack of benefit from topical antibiotics and antiseptics in either clinically infected or uninfected skin, which we concur with. A recent RCT study showed a worsening of both subjective and objective eczema scores when topical/oral antibiotics were used in mild-moderate AD.[7] Use of topical fusidic acid (FA) has also been shown to be associated with an increased risk of antibiotic-resistant *S. aureus* locally and should be avoided.[8] Another common clinical practice is the use of a TCS/antibiotic combination. Although *S. aureus* load on the skin can be decreased with TCS/antibiotic combination,[9,10] none of the studies have shown superior clinical efficacy in AD. The use of combination topical, e.g. betamethasone 17-valerate plus FA should therefore be discouraged in the light of potential antibiotic resistance.[8,11] In disease flares caused by secondary infection with *S. aureus*, we share a differing view from the authors in that oral antibiotics are preferred over topical antimicrobial agents. Cultures are also recommended when patients do not respond to standard treatment. Though the benefits of diluted bleach baths have

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been recommended as an anti-infective measure for AD, we find this option rather unacceptable for the parents of our patients in the local context. This is echoed by a recent finding of high non-adherence rate in a Hong Kong study.[12] Other antiseptic washes like triclosan can be used instead.

Food allergy is the other controversial area in AD. In this respect, there is evidence that food allergy may play a role only in infants and young children younger than 3 years with extensive, recalcitrant AD. This group of patients should be evaluated by a paediatric dermatologist or a paediatric allergist as the interpretation of skin prick testing and specific IgE tests needs correlation with the clinical history. These tests should not be performed "routinely" in other patients with AD. Sensitivity to inhalant allergens may instead be more common.[13] The authors have also enunciated that the exclusion of foods during pregnancy and breastfeeding has not been shown to have a preventive role. However, daily application of full-body emollients in neonates at high risk of AD within 3 weeks of birth can prevent the disease.[14]

In the institutional setting, where more complex or severe AD patients are being managed, it is also critical to provide patient and caregiver education beyond medical treatment. Adequate time for education and demonstration of treatments has been shown to be crucial in the management of AD.[15] Nurse-led educational clinics and implementation of the eczema action plan can provide positive steps towards patient or caregiver empowerment and self-management. Written plans can be used in any clinic setting to help patients or caregivers know the practicalities of topical therapy, and reduce call-backs and walk-ins.

In conclusion, these guidelines would serve well for primary care practitioners, dermatologists and other specialists who manage AD patients. Not only should there be a tiered approach to therapy, there should be appropriateness in where patients are best managed based on disease severity. In this respect, primary care practitioners, particularly those equipped with dermatology skills, may be better placed to manage the great majority of mild AD in the community.

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Original Article

Guidelines for the Management of Atopic Dermatitis in Singapore

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Abstract

Introduction: Atopic dermatitis is a common, chronic pruritic condition affecting both children and adults, which has a negative impact on the quality of life. These guidelines were developed by an expert workgroup appointed by the Dermatological Society of Singapore, to provide doctors with information to assist in the management of their patients with atopic dermatitis. The workgroup members are experienced dermatologists with interest and expertise in eczemas. Materials and Methods: Workgroup members arrived at a consensus on the topics to be included. Relevant studies from the literature were assessed for best evidence, supplemented by the collective experience of the workgroup. Results: For mild atopic dermatitis, emollients, mild potency topical steroids and topical calcineurin inhibitors are recommended. For moderate-to-severe atopic dermatitis, the use of emollients, moderate-to-potent topical steroids, topical calcineurin inhibitors, wet dressings, antimicrobials for secondary skin infection, phototherapy, and systemic therapy (e.g. prednisolone, cyclosporine, azathioprine or methotrexate) may be warranted. Patients with moderate-to-severe atopic dermatitis should be managed in conjunction with a dermatologist. Conclusion: Good outcomes can be achieved with an individualised therapeutic approach combined with adequate patient and parental education.

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Key words: Antimicrobials, Calcineurin inhibitors, Corticosteroids, Eczema, Moisturisers

Introduction

Atopic dermatitis (AD) or atopic eczema is a common, chronic pruritic inflammatory disorder affecting 20.8% of school children and teenagers aged 7 to 16 years in Singapore, with an equal gender ratio.[1] Many children (about 70%) improve as they grow older. Adult onset after the age of 21 years is uncommon, constituting about 2.4% of cases.[2] However, in Singapore, a significant proportion of patients (13.6%) have a later onset, after the age of 21 years.[3] AD is thought to arise as a result of skin barrier defects (e.g. loss of function mutations of the filaggrin gene, defects in ceramides, protease inhibitors) immune dysfunction and environmental factors.[4] A damaged skin barrier increases transepidermal water loss, causing dry skin and facilitates the penetration of allergens and microorganisms.

Diagnosis

AD is a clinical diagnosis, which cannot be confirmed by any laboratory tests. Based on the original Hanifin and Rajka criteria, a UK Working Party has established a minimum set of diagnostic criteria.[5] A patient must have a history of an itchy skin condition plus 3 or more of: 1) history of rash in the skin creases, including cheeks in children <10 years; 2) personal history of asthma or hay fever, or history of atopic disease in a first-degree relative in children <4 years; 3)

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history of dry skin in the last year; 4) onset under the age of 2 years; and 5) presence of visible flexural dermatitis, e.g. eczema affecting the neck, folds of the elbows, behind the knees, fronts of the ankles.

Identification of Trigger Factors

Identification of possible aggravating factors such as excessive heat and sweating, exercise, infections, rough fabrics, house dust mites and stress is an important part of the assessment. Other possible triggers include irritants (medicated soaps, detergents, bubble baths, grass) and allergens (contact, foods).[1] These aggravating factors should be minimised.

Management

The goals of management include control of symptoms, reduction of flares and improvement in quality of life. This is achieved via the maintenance of an optimal skin barrier function with the use of emollients, reduction of skin inflammation with anti-inflammatory therapy in combination with adequate patient education. Tailoring the treatment stages to the severity of the AD is recommended (Table 1).[6]

Moisturisers

The mainstay of the general management of AD is the regular use of moisturisers, as severe xerosis is a key feature caused by dysfunction of the skin barrier with increased transepidermal water loss.[7] The term "emollient" implies a material designed to soften the skin, making the surface smooth.[8] Humectants are substances introduced into the stratum corneum to increase its moisture retaining capacity.[9] Occlusive ingredients provide a layer of lipid on the skin to slow water loss.[10] Common moisturiser ingredients are outlined in Table 2.

Studies have shown that the concomitant use of moisturisers significantly improves xerosis and pruritus during corticosteroid treatment of AD compared to corticosteroid treatment without any moisturisers.[11] A greater improvement in disease severity and a short-term steroid-sparing effect have been demonstrated. The use of moisturisers is also important for the maintenance of improvement after therapy discontinuation.[12] Sufficient moisturiser should be applied liberally including on normal skin, at least twice a day or as frequently as required.[13] There is no evidence on which to base the order of application of either the topical steroid or moisturiser.[14] The moisturiser should be applied in the direction of hair growth to reduce the risk of folliculitis. Although newer moisturisers containing ceramides have been developed, further clinical studies are required to assess the efficacy and acceptability of these products.[15]

Role of Moisturisers in Atopic Dermatitis Prevention

Preliminary research has shown that moisturiser therapy

Table 1. Stepped Approach to Management[6]

Severity	Symptoms and Signs	Impact on Quality of Life	Treatment
Mild	Infrequent itching, dry skin, limited areas of eczema	Little impact on every day activities and sleep	• Gentle skincare • Emollients • Mild potency topical steroids • Topical calcineurin inhibitors
Moderate	Frequent itching, dry skin, redness, excoriations and localised lichenification	Moderate impact on every day activities, frequently disturbed sleep	• Gentle skincare • Emollients • Moderate potency topical steroids • Topical calcineurin inhibitors • Antimicrobials for secondary skin infections • Wet dressings
Severe	Incessant itching, dry skin, extensive eczema, excoriations, oozing, cracking, lichenification	Severe limitation of every day activities, psychological functioning, nightly loss of sleep	• Gentle skincare • Emollients • Potent topical steroids • Topical calcineurin inhibitors • Wet dressings • Antimicrobials • Phototherapy • Systemic therapy e.g. cyclosporine azathioprine, methotrexate

Note: Daily bathing with non-soap cleansers to remove crusts, with application of a moisturiser soon after, is recommended.

Table 2. Common Moisturiser Ingredients with Mechanisms

Active Ingredient	Major Category	Notes
Ceramide	Emollient	Repairs stratum corneum integrity and function.
Shea butter	Emollient	Provides a stable carrier of antioxidant substances and supplies lipids to the skin.
Palmitoyl-ethanolamine	Emollient and humectant with anti-inflammatory properties	Cannabinoid receptor agonist with anti-inflammatory, analgesic and antioxidant effects.
Glycrrhetinic acid	Emollient with anti-inflammatory properties	Potentiates action of steroids on the skin due to its structural similarity with cortisone.
Glycerin	Humectant	Hastens maturity of corneocytes Reduces scaling associated with xerosis.
Colloidal oatmeal	Humectant	Provides a hydrophilic film on the skin surface. Oat triglycerides and phospholipids are important stratum corneum components.
Hyaluronic acid	Humectant Emollient	Very hygroscopic. Has a major organisational role within the collagen bundles. Expensive.
Lactic acid	Humectant Emollient	Decreases transepidermal water loss. Reduces dryness and scaling.
Propylene glycol	Humectant Emollient	Makes skin supple and smooth. Absorbs moisture into the skin.
Urea	Humectant	Moisturises the skin by decreasing transepidermal water loss.
Liquid paraffin/mineral oil	Occlusive	Semi-occlusive layer that retards water evaporation. Penetrates upper layers of stratum corneum.
Olive oil	Occlusive	Semi-occlusive layer that retards water evaporation.
White soft paraffin/ petrolatum	Occlusive	Prevents transepidermal water loss. Useful when the skin is very dry.
Coconut oil	Occlusive	Decreases transepidermal water loss. Increases fibroblast proliferation and neovascularisation. Antioxidant, anti-inflammatory.

Adapted from 'Asian Atopic Dermatitis Summit 2014 Consensus. Understanding the Role of Emollients in Atopic Dermatitis Management' with permission from MIMS MedComms and the Pediatric Dermatology Subspecialty Core Group, Philippine Dermatological Society.

from birth represents a feasible, safe, and effective approach for AD prevention. Two recent multicentre studies have shown that daily application of full-body emollients for 6 to 8 months in neonates at high risk of AD reduces the cumulative incidence of AD by 32% to 50%.[16,17] The proposed theory is that moisturisers correct subclinical skin barrier dysfunction and early inflammation in predisposed infants before AD development by improving skin hydration and reducing skin permeability.

Topical Corticosteroids

Topical corticosteroids (TCS) which have anti-inflammatory and vasoconstrictive properties remain the mainstay of treatment in AD. Safe use of TCS depends on their appropriate potency and formulation for the age of the patient, degree of inflammation, appropriate amount and duration of use. The lowest potency TCS to produce adequate clearance should be chosen. Table 3 shows the potency of various formulations of TCS available in Singapore.

Potent TCS should generally not be used in children under 12 months of age and is used with caution on the face, eyelids and flexures.[7] There may be occasions where a 1- to 2-week course of a potent TCS is helpful for severe facial and flexural infantile AD; once better, a milder TCS is used. Potent TCS can be used on thick, lichenified eczema on other parts of the body. Ointments are more potent than creams, and lotions are preferred on hairy areas. TCS are often applied twice daily, but once daily application of moderate-to-potent TCS has been found to be as effective, and may be associated with fewer side effects and better patient compliance.[18]

When TCS are used for the treatment of eczema flares, treatment can be continued until resolution of inflammation. It is generally recommended that potent TCS should not be used for more than 2 weeks without supervision. However, after the stabilisation of an acute flare, proactive treatment with twice weekly mild-to-mid potency TCS can be used to reduce relapse.[19] This strategy should be reviewed within 3 to 6 months to assess effectiveness.[6]

Local adverse effects such as skin atrophy, folliculitis or perioral dermatitis can be avoided if appropriate use of TCS is adhered to. Systemic absorption of TCS with resultant

Table 3. Potency of Various Formulations of Topical Corticosteroids Available in Singapore

Potency	Generic Name	Strength	Steroid Only		Steroid with Additive		
		%	Dosage Form	Examples of Some Brands	Additive	Dosage Form	Examples of Some Brands
Super potent	Betamethasone dipropionate (optimised vehicle)	0.05	ointment	Diprocel®			
	Clobetasol propionate	0.05	ointment	Cloderm®, Univate®			
			cream	Cloderm®, Dermovate®, Dermosol®, Univate®, Dhabesol®			
			lotion	Cloderm®			
			shampoo	Clobex®			
	Betamethasone dipropionate	0.05	ointment	Beprosone®	Betamethasone dipropionate + salicylic acid 3%	ointment, lotion	Beprosalic®
	Mometasone furoate	0.1	ointment	Elomet®, Elosone®			
Potent	Betamethasone dipropionate	0.05	cream	Beprosone®, Diproderma	Betamethasone dipropionate + fusidic acid 2%	cream	Fobancort®
					Betamethasone dipropionate + gentamicin + clotrimazole	cream	Neoderm®, Gentriderm®, Triderm®
					Betamethasone dipropionate + gentamicin	cream, ointment	Diprogenta®
	Betamethasone valerate	0.1	ointment, cream, lotion	Dermasone®, Medobeta®, Betasone®, Uniflex®, Betacorten®	Betamethasone valerate + clioquinol 3%	cream	Dermanol-C®
					Betamethasone valerate + fusidic acid 2%		Fucicort®
	Mometasone furoate	0.1	cream, lotion	Elomet®, Elosone®			
	Hydrocortisone aceponate	0.127	lipocream	Efficort®			
	Fluticasone propionate	0.05	cream	Cutivate®			
	Fluocinolone acetonide	0.025	cream	Cutivate®			
	Diflucortolone valerate	0.1	-	-	Diflucortolone + isoconazole 1%	cream	Travocort®
	Triamcinolone acetonide	0.1	oral paste	Trinolone®	Triamcinolone + lignocaine 3%	oral paste	Oracort E®
Moderate	Betamethasone valerate	0.025	cream, ointment	Dermasone®			
	Fluocinolone acetonide	0.0125	cream	Diluted Flunolone-V®			
	Clobetasone butyrate	0.05	cream	Eumovate®			
	Desonide	0.05	cream, lotion	Desowen®			
Mild	Hydrocortisone	1	cream	Dhacort®, Hydrocortisone®, Hydroderm®	Hydrocortisone + clioquinol 3% Hydrocortisone + fusidic acid 2%	cream	Hydroderm-C® Fucidin H
			ointment	H-Cort®	Hydrocortisone + miconazole 2%	Hydrocortisone + miconazole 2%	Daktacort®, Decocort®, Zaricort®

Source:
AHFS Drug Information. Drug Assignments and reassignments 2013.
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hypothalamic-pituitary-adrenal (HPA) axis suppression, growth retardation, diabetes, hypertension or osteoporosis is rare. Although the risk of developing glaucoma and cataracts from application of TCS to the eyelids and peri-orbital region over longer periods of time is extremely low, TCS should be used with caution in the peri-ocular region.[20] Patients or caregivers may express fear and anxiety about using TCS. It is thus important to allay any fears, as steroid phobia can lead to poor control of AD.[21]

Topical Calcineurin Inhibitors

Topical calcineurin inhibitors (TCI) are non-steroidal immunomodulatory agents approved for use in the treatment of moderate-to-severe AD for patients aged 2 years and above. There are 2 TCIs, namely tacrolimus and pimecrolimus. Tacrolimus is available as either a 0.1% or 0.03% ointment, and pimecrolimus is available as a 1% cream. A recent large international multicentre study compared the use of 1% pimecrolimus cream versus TCS in infants aged 3 to 12 months with mild-to-moderate AD. The 5-year study showed that pimecrolimus was safe, had similar efficacy to TCS and was steroid-sparing.[22] These data suggest that pimecrolimus 1% cream may be considered as a first-line treatment of AD in infants and children. The use of pimecrolimus 1% cream is accepted for use in children aged 3 months and older in some countries such as Hong Kong, Australia and New Zealand.

There is a lack of epidemiological evidence to infer whether TCIs cause malignancy (skin cancers and lymphomas).[23] However, a recent longitudinal cohort study of children with AD involving more than 25,000 person-years of follow-up concluded that, at least for topical pimecrolimus, there seemed to be no associated increased risk of malignancy.[24] On areas where skin atrophy may be a concern with long-term TCS use (e.g., eyelids, face, neck and skin folds), our workgroup agrees that TCI can be considered as a first-line treatment.

Topical calcineurin inhibitors can be used in the treatment of inflamed eczema, as well as maintenance therapy. Proactive treatment with twice weekly TCI for up to 1 year can be used to reduce relapse. The common side effects of TCI include transient burning sensation and erythema, which often resolve after a few days with continued use. TCI use should be avoided on skin that appears clinically infected and it should not be used under occlusion, e.g. wet wraps.

Bathing Practices Including Additives

Daily bathing to remove serous crusts and to apply a moisturiser soon after is recommended.[25] Use of non-soap cleansers with a neutral-to-low pH that are hypoallergenic and fragrance-free is advisable. High pH soaps increase the level of proteases, disrupting the skin barrier.

Wet Wrap Treatment

Wet wrap treatment is a relatively safe and efficacious intervention in children with severe AD.[26] This aids skin barrier recovery, increases the efficacy of topical steroids and protects the skin from scratching.[27] Wet wrap treatment uses a double layer of tubular bandages, gauze or pyjamas, with a moist first layer and a dry second layer.[26] The use of wet wraps is limited up to 1 week with once daily application to minimise potential adverse effects of steroid absorption. Wet wraps should not be used if overt infection is present.

Antimicrobials

Atopic patients are predisposed to skin infections due to a dysfunctional physical barrier and impaired immune defences. *Staphylococcus aureus* (the majority of which secretes superantigens), has an important role in the pathophysiology of AD, with up to 90% colonisation rates in the skin of patients.[28]

Topical Antimicrobials

Cochrane reviews in 2008 and 2010 concluded that there was a lack of benefit for topical antibiotics/antiseptics, antibacterial soaps, or antibacterial bath additives in the setting of clinically infected or uninfected AD, with poor reporting of details of positive findings in some studies.[29] Despite the decrease in load of *S. aureus* on the skin with the addition of a topical antibiotic to a TCS, the combination has not shown improvement in severity of skin disease when compared to TCS or TCI alone.[30] There is also a possibility of allergic contact dermatitis to the antibiotic component.

However, our workgroup members feel that disease flares caused by secondary infection with *S. aureus* respond to treatment with topical antimicrobial agents. In particular, certain regimes of topical antimicrobial agents have shown benefit in AD. The use of twice-weekly bleach baths (0.5 cups of 6% bleach to a full bathtub of water [final concentration, 0.005%]) with intranasal topical mupirocin (5 consecutive days per month) in children with moderate-to-severe clinically infected AD resulted in clinical improvement in severity of skin disease at 1 and 3 months.[31]

The role of prophylactic use of antimicrobials in the setting of clinically uninfected skin in AD or in patients with recurring bacterial infection is controversial. Antiseptics used for this purpose may be more appropriate given their lower potential to induce bacterial resistance and contact allergy.[32] Antiseptics other than bleach include triclosan, potassium permanganate and chlorhexidine gluconate.

Systemic Antimicrobials

Systemic antibiotics used in the treatment of AD include cloxacillin, cephalexin, erythromycin, clindamycin and amoxicillin-clavulanic acid.

The use of systemic antibiotics in the treatment of clinically non-infected AD is not recommended. Judicious use of systemic antibiotics are appropriate in AD with clinical evidence of bacterial infection.[29,33,34] Systemic antibiotics for 1 to 2 weeks may be administered concurrently with standard treatment for AD, including application of TCS or TCI. However, despite extensive antibacterial treatment, eradication of *S. aureus* is only transient, with recurrence rates of up to 100%.[35] Bacterial cultures from skin with antibiotic susceptibility profiling are indicated when skin infections are recurrent or non-responsive.

Eczema herpeticum is caused by infection with herpes simplex virus (HSV) and potentially fatal. Systemic antiviral agents include oral acyclovir and valacyclovir for 1 to 2 weeks.[36] If there is a high index of suspicion of eczema herpeticum (e.g. presence of punched-out erosions), therapy should be instituted without delay while awaiting investigations such as cultures or polymerase chain reaction tests. Table 4 shows the doses for systemic antibiotics and antivirals.

Table 4. Doses of Systemic Antibiotics and Antivirals

Drug	Adult Dose	Paediatric Dose
Cloxacillin	500 mg qds	50 mg/kg/day in 4 divided doses
Cephalexin	500 mg tds	50 mg/kg/day in 3 divided doses
Erythromycin	500 mg qds (erythromycin stearate) 800 mg bd (erythromycin ethylsuccinate)	50 mg/kg/day in 4 divided doses (erythromycin ethylsuccinate) (not for children less than 2 months old)
Clindamycin	150 – 450 mg qds	30 mg/kg/day in 3 divided doses
Amoxicillin-clavulanic acid	625 mg bd	50 mg/kg/day in 2 divided doses (doses expressed in amoxicillin-clavulanic dose)
Acyclovir	Severe disease or in immunocompromised patients: IV 5 – 15 mg/kg/dose q8h Less severe disease: PO 200 – 400 mg 5 times daily	Severe disease or in immunocompromised patients: IV 10 mg/kg q8h Less severe disease: PO 30 – 60 mg/kg/day in 3 divided doses
Valacyclovir	1 g tds No IV dose	Not applicable

bd: Twice daily; IV: Intravenously; PO: Per oral; qds: Four times daily, tds: Three times daily, q8h: Every 8 hourly

Oral Antihistamines

There is little evidence that antihistamines alone are beneficial in the control of pruritus in AD. However, intermittent use of sedating antihistamines, for example, hydroxyzine, chlorpheniramine for patients older than 6 months may be beneficial where there is sleep loss at night, secondary to itch.[37] As sedating antihistamines in children may negatively affect school performance, a less sedative antihistamine such as cetirizine may be warranted. Non-sedating antihistamines are not recommended routinely for AD in the absence of urticaria or allergic rhinitis. The dosages of hydroxyzine, chlorpheniramine and cetirizine are as follows: Hydroxyzine (adults: 10-25 mg at night; children: 1-2 mg/kg/day in 2 to 3 divided doses); Chlorpheniramine (adults: 4-8 mg at night; children: 0.35 mg/kg/day in 2 to 3 divided doses); Cetirizine (adults: 10 mg at night; children: 2.5-5 mg twice a day).

Phototherapy

Phototherapy is a second-line treatment, after failure of first-line treatments. Multiple forms of phototherapy are beneficial for the control of AD, including broad band-ultraviolet B, narrow band-ultraviolet B, ultraviolet A and B (UVAB) and topical and systemic psoralen plus UVA (PUVA). Narrow band-ultraviolet B (NB-UVB) and ultraviolet (UV)-A1 are effective treatment modalities for severe AD in both children and adults.[38,39] While the exact mechanism of action of phototherapy in AD is not fully known, local immunosuppressive and anti-inflammatory effects are thought to be important. Erythema and dryness are common side effects and the risk associated with skin cancer is unknown. Treatment regimen and dosing should be guided by a dermatologist experienced in phototherapy techniques.

Systemic Immunosuppressive Therapy in Atopic Dermatitis[37,40 41]

Systemic corticosteroids should only be used for acute, severe flares of AD and are not recommended for long-term maintenance therapy. The indications for the use of systemic immunosuppressive therapy in AD are: 1) severe or extensive AD refractory to conventional therapy with frequent relapses; 2) severe impairment of the patient's quality of life; 3) steroid-dependent patients with 3 or more courses of systemic corticosteroids in the past 12 months; and 4) as a steroid-sparing option in patients with complications

from prolonged topical or systemic corticosteroid use.

Criteria for severe AD include: 1) extensive body surface area involvement (>20%); 2) objective SCORing Atopic Dermatitis (SCORAD) >40 and total SCORAD >50;[42] and 3) poor quality of life – Dermatology Life Quality Index score >21.[43]

Based on recent systematic reviews of the efficacy and safety of systemic treatments for moderate-to-severe AD, cyclosporine, azathioprine and methotrexate have been recommended as first-, second- and third-line treatment options.[37,40,41,44] Table 5 summarises their key indications, dose, baseline investigations, monitoring, and side effects. These drugs should be given only by doctors with experience in their use and after careful discussion with the patient regarding the off label indication, risks, benefits, costs, monitoring requirements, expected duration of therapy, and outcomes.

Management of Eczema in Pregnancy

Topical Therapy during Pregnancy

Moisturisers

These are safe to use during pregnancy.

Corticosteroids

Large population-based studies and a Cochrane review have not shown an increased risk of congenital malformations, including oral cleft palate, with TCS.[45] Fetal growth restriction has been reported with the use of potent TCS during the third trimester. Pregnant women are advised to apply mild-to-moderate corticosteroids for short durations.[46] The workgroup members agree that intermittent use of TCS is safe for pregnant women.

Calcineurin Inhibitors

Topical tacrolimus and pimecrolimus have not been associated with congenital malformations. They are poorly absorbed systemically as their large molecular size prevents penetration.

Systemic Therapy during Pregnancy

Antihistamines

First- and second-generation oral antihistamines like chlorpheniramine, loratadine and cetirizine are safe options in pregnancy to relieve itch.

Corticosteroids

These appear to be safe when used in moderate doses and for short durations. Potential complications of high doses of systemic corticosteroids during pregnancy include premature delivery, premature membrane rupture, intrauterine growth retardation, maternal gestational diabetes, hypertension and eclampsia. It is recommended to limit prolonged use of oral prednisone to 7.5 mg/day and the avoidance of >20 mg/day.[45] The workgroup members agree that the use of oral corticosteroids not exceeding 2 weeks is usually safe for pregnant women. Some studies have shown an association between orofacial clefts and corticosteroid use in pregnancy, but a recent publication shows no such association.[47]

Phototherapy during Pregnancy

Ultraviolet B light phototherapy is a safe option in pregnancy. Phototherapy may worsen melasma, so facial shielding is advisable.[45] Please refer to Table 6 for a summary of eczema treatments in pregnancy.[48]

Food Allergy and Diet Intervention

The role of food allergy in AD is controversial. AD in older children and adults is unlikely to be worsened by food allergy. Consequently, the role of food allergy testing and exclusion diets in this group of patients is minimal.

In infants and young children (<3 years) with extensive, recalcitrant AD, food allergy may play a role in the exacerbation and persistence of symptoms, especially if there are associated gastrointestinal symptoms (e.g. diarrhoea, vomiting) and failure to thrive.[49] Common food allergies in this group of patients include cow's milk, egg, wheat and soy. Dietary intervention in these patients with proven food allergies can decrease disease severity and improve growth. These patients should be evaluated and managed in conjunction with a paediatric dermatologist and allergist.

The majority of food allergies can be diagnosed with thorough history taking. If in doubt, skin prick testing and measurement of specific IgE levels can be used to aid in the diagnosis. The sensitivity and specificity of these tests vary according to the food type, age of patient and testing platform.[50] Results of these tests must be interpreted within the context of the clinical history of the patient. Negative tests have a high negative predictive value. However, positive tests should be verified by controlled food challenges or a controlled avoidance diet. Positive skin prick or specific IgE tests should be repeated yearly as many children outgrow their food allergies. Exclusion of foods during pregnancy and breastfeeding has not proven to be beneficial in the prevention of AD in infants.[51] The evidence for the use of prebiotics and probiotics in the prevention and treatment of AD is poor.[52]

Table 5. Summary of the Systemic Agents Used in Atopic Dermatitis

Drug	Key Considerations	Dosing	Specific Baseline Investigations	Monitoring	Side Effects
Systemic corticosteroids e.g. prednisolone	Reserved only for acute, severe flares or as a temporary bridging measure while transitioning to other non-steroidal agents or phototherapy. Should not be used as continuous or maintenance therapy for control of AD. Repeated "short" courses of corticosteroids should be avoided. Best avoided in children and in severely infected AD.	Short tapering dose of oral prednisolone over 1 to 2 weeks. Start at lowest effective dose (0.3 – 0.5 mg/kg/day). Oral route is preferred.	For short courses, no baseline investigations are recommended unless there are risk factors, e.g., hepatitis B infection.	None necessary for short courses. Clear documentation to ensure that repeated short courses are not given, especially in patients who are seen by various medical practitioners.	For short courses: hypertension, hyperglycaemia, gastritis, emotional or psychiatric problems, acute flare of hepatitis B, acne, rosacea, folliculitis. For patients who have received multiple courses or long-term corticosteroids: All above plus Cushingoid features, weight gain, decreased bone density, adrenal suppression, skin atrophy, striae, myopathy, osteonecrosis, glaucoma, cataracts, growth retardation, decreased response to live vaccinations. Intramuscular route may cause localised lipoatrophy or skin atrophy.
Cyclosporine	Fast acting. Useful for acute control of severe disease, but rapid relapse upon discontinuation. Costly. Risk of cumulative nephrotoxicity and hypertension over time. Key contraindications: • Uncontrolled hypertension. • Uncontrolled infection.	Recommended starting dose: 2 – 3 mg/kg/day. Recommended maximum dose: 5 mg/kg/day. Reduce dose by 25% to 50%: • If sustained raised blood pressure reading. • Serum creatinine increased >30% to 50% above baseline • Increased liver enzymes above 2 times upper limit.	Blood pressure. Full blood count. Liver function test. Renal function tests, including electrolytes. Urinalysis. Consider : Fasting lipid profile. Serum magnesium. Serum uric acid. Viral hepatitis serology.	Initial frequency – every 2 weeks for blood pressure, renal function for first 2 months, then at least every 2 to 3 months.	Renal impairment. Hypertension. Headache, tremor, paresthesia. Hypertrichosis. Gingival hyperplasia. Nausea, vomiting, diarrhoea. Flu-like symptoms. Myalgias, lethargy. Hypertriglyceridaemia. Hypomagnesaemia. Hyperkalemia. Hyperbilirubinaemia. Increased risk of infection. Risk of malignancies.

AD: Atopic dermatitis

Table 5. Summary of the Systemic Agents Used in Atopic Dermatitis (Con't)

Drug	Key Considerations	Dosing	Specific Baseline Investigations	Monitoring	Side Effects
Azathioprine	Slow onset of action, usually after 6 to 8 weeks with gradual increase in dose.	Recommended starting dose: 0.75 – 1 mg/kg daily. Recommended maximum dose: 2.5 – 3 mg/kg/day.	Full blood count. Liver function tests. Renal function tests. Thiopurine methyltransferase (TPMT) testing. Viral hepatitis serology.	Full blood count and liver function tests every 2 weeks for 2 months or after dose increase, then monthly for 4 months. When stable, tests every 2 to 3 months.	Bone-marrow suppression. Hepatitis. Increased risk of infections. Gastrointestinal upset. Hypersensitivity syndrome. Risk of malignancies and multifocal leukoencephalopathy.
Methotrexate	Slow onset of action, usually after 6 to 8 weeks with gradual increase in dose. Considered least immunosuppressive among the 3 agents. May have comparable efficacy to azathioprine.	Adults: 7.5 – 25 mg/week. Paediatric: 0.2 – 0.7 mg/kg/week. Subcutaneous route can be considered if oral route is ineffective or severe nausea. To give folic acid supplementation.	Full blood count. Liver function tests. Renal function tests. Viral hepatitis serology.	Full blood count and liver function tests every 2 weeks for 1 month, and after each dose increase. When stable, tests every 2 to 3 months.	Elevated liver enzymes. Liver cirrhosis. Myelotoxicity. Interstitial pneumonitis. Pulmonary fibrosis. Ulcerative stomatitis. Gastrointestinal upset. Malaise, fatigue. Chills and fever. Risk of infection. Risk of malignancies.

AD: Atopic dermatitis

Table 6. Eczema Treatments in Pregnancy

Safe
Moisturisers
Mild-to-moderate topical corticosteroids
Ultraviolet B phototherapy
Relatively safe
Potent topical corticosteroids, in small quantities
Topical calcineurin inhibitors, in small quantities
Oral corticosteroid, low dose, short duration
Oral cyclosporine, low dose, short duration
Avoid
Azathioprine
Mycophenolate mofetil
PUVA phototherapy
Contraindicated
Methotrexate

PUVA: Psoralen and UVA light therapy
Reproduced from 'Weatherhead S, Robson SC, Reynolds NJ. Eczema in pregnancy. BMJ 2007;335:152-4' with permission from BMJ Publishing Group Ltd.

Patient Education

Therapeutic patient education (TPE) has been shown to empower patients. As topical treatment regimens can be complex, and patients and their families are responsible for applying them daily to their skin,[53] the use of TPE has been shown to improve compliance, disease control, and quality of life.[54]

Therapeutic patient education can be carried out by doctors or nurses and can be conducted either through individualised one-to-one sessions or in group sessions.[53] Individualised sessions include treatment counselling, patient information leaflets and action plans (Appendix 1). Group sessions can be organised as lectures, workshops, camps or through support groups. During these sessions, important information to be conveyed include treatment strategies, avoidance of triggers, use of moisturisers, topical medications and prognosis. The doctor-patient relationship can be further developed during these counselling sessions.

Conclusion

AD is a common, chronic condition with a negative impact on quality of life. Good outcomes can be achieved with an individualised therapeutic approach combined with adequate patient and parental education. Management success depends on a partnership between the patient, family members and the health care team.

Disclaimer

These guidelines have been developed by the Dermatological Society of Singapore and the authors according to the best available evidence at the time of preparation. These guidelines are designed to provide information and to assist in the management of patients with atopic dermatitis. Adherence to these guidelines may not ensure successful outcomes in every case and doctors should use their own clinical judgment in the management of their individual patients. The results of future studies may require revisions to these guidelines.

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Appendix 1
Eczema Action Plan

Patient's Identification Label

Daily Measures:

- Avoid irritants (e.g., grass, sand; pets, carpets, stuffed toys; heat, excessive sweating)
- Shower or bathe 1 – 2 times daily with lukewarm / cool water for 5 – 10 min
- Mild soap or soap substitute: ……
- Anti-bacterial soap / bath: ……times a week.
- Pat dry
- Moisturise with: ……, …… times daily
- Shampoo scalp with: ……, …… times daily

When your skin becomes red and itchy, apply:

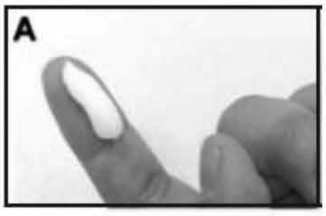
- Eyelids: ……, …… times daily
- Face: ……, …… times daily
- Limbs / trunk: ……, …… times daily
- Thick areas (limbs/trunk): ……, …… times daily
- Scalp: ……, …… times daily

Oral Medications:

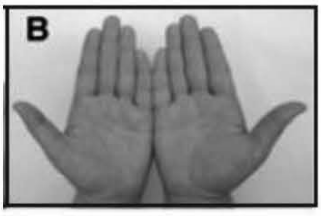
- Antibiotics: ……, …… times daily for ……days/weeks
- For itch: ……, …… times in the day
  …… at bedtime.

How much steroid cream / ointment should you use?

A: One fingertip unit is the amount of cream / ointment from the tip of an adult index finger to the first crease of that finger.



B: This amount is about 0.5 grams and covers an area equal to two adult hands.



Other Remarks: This may be modified to suit the needs of the patient.

……

……

If You Need To See Your Doctor Earlier:

Call the clinic to make an appointment.

Doctor: …… Date: …… / …… /……

Original Article

Anxiety and Depression in Patients with Atopic Dermatitis in a Southeast Asian Tertiary Dermatological Centre

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Abstract

Introduction: This study aimed to assess the frequency of anxiety and depression in a cohort of adult patients with atopic dermatitis (AD) in a tertiary dermatological centre, using the Hospital Anxiety and Depression Scale (HADS). We looked for any correlation between anxiety and depression with skin disease severity. Materials and Methods: Patients with AD were recruited from the National Skin Centre, Singapore, from 2008 to 2009 for a prospective cross-sectional study. The scoring atopic dermatitis (SCORAD) grade was determined and the HADS was administered via interviews. Results: A total of 100 patients (78 males, 22 females) were enrolled (92% Chinese, 4% Malays and 4% Indians). Their average age was 25.7 years. Sixty-five percent used topical steroids, 14% had previously taken oral prednisolone for the control of disease flares, and 20% were on concurrent systemic therapy. The mean SCORAD was 55.0, with 99% of patients having moderate or severe AD. The mean HADS anxiety score was 7.2 and the mean depression score was 5.0. The level of anxiety correlated well with that of depression (Spearman's rank correlation coefficient, $\rho = 0.59$, $P < 0.05$); 18% were considered as cases of anxiety and 5% as cases of depression. These patients also had higher SCORAD values compared to other patients with lower scores for anxiety or depression ($P < 0.05$). Linear regression demonstrated a statistically significant positive relationship between anxiety and depression scores, and SCORAD scores. Conclusion: Our study identified, by means of the HADS, the frequency of anxiety and depression amongst a cohort of Singaporean patients with AD. More severe skin disease correlated to greater psychological burden. The HADS is a useful screening tool that can constitute part of the overall holistic management of patients with AD so as to improve patient care.

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Key words: Eczema, HADS, Mood disorders, SCORAD

Introduction

Atopic dermatitis (AD) is a common skin disease that negatively impacts the physical and mental health of patients, particularly when the skin condition is more severe.[1] The psychological burden of AD may stem from sleep deprivation secondary to nocturnal pruritus, resulting in poor daytime concentration and petulant behaviour.[2] Being at the receiving end of bullying may also cause social embarrassment.[2] Due to the disease chronicity, the treatment journey often places substantial financial and time burden on patients.[3] This may strain interpersonal relationships as the lifestyle adjustments that AD patients make inadvertently affect close family members.[4]

Yaghmaie et al reviewed data from the 2007 National Survey of Children Health in the United States and found significantly higher odds of suffering from various mental health disorders in children with AD, with the lifetime prevalence of anxiety in those children reaching 7.25% and the corresponding number for depression reaching 6.52%.[5] Furthermore, the severity of skin disease alters the strength of the association.[5] The Hordaland Health Studies conducted in Norway in 1992 and 1997 showed that 12.9% of their cohort with AD had anxiety and 4.2% had depression as measured by the HADS.[6] A multicentre cross-sectional study conducted from 2011 to 2013 by Dalgard et al involving 4994 individuals in 13 European countries

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found that anxiety was present in 17.2% of patients with AD (compared to 11.1% in controls) and that depression was present in 10.1% of patients (compared to 4.3% in controls).[7] A South Korean group that studied conscripted males with AD in a military setting showed a prevalence of 9.8% with anxiety and 10.4% with depression.[8] Local data on psychiatric comorbidity in patients with AD is, however, lacking, and this bears important relevance to the subsequent delivery of clinical services.

The purpose of this study was to examine the relationship between psychiatric comorbidities (namely anxiety and depression) with the severity of AD in patients in Singapore. We hypothesised that anxiety and depression were more frequent in patients with more severe skin disease.

Materials and Methods

This prospective cross-sectional study was conducted from August 2008 to January 2009 at the National Skin Centre, Singapore. A total of 100 patients with AD between the ages of 13 to 60 years who visited the outpatient clinics within the study period were recruited. The Hanifin and Rajka criteria[9] for AD was used to ensure diagnostic consistency. Informed consent was obtained and the Institutional Review Board granted ethics approval. We excluded patients who were unable to understand the questionnaire sufficiently.

Assessment Tools

SCORing Atopic Dermatitis (SCORAD)

The SCORAD is a widely used clinical tool for quantifying the severity of AD in research and clinical practice.[10] It measures the extent, intensity and level of pruritus, and insomnia related to AD. Patients' SCORAD were determined objectively through physical examination, and also subjectively, including symptoms of itch and sleep loss. Scores were categorised into mild (<20), moderate (20 to 50) and severe (>50) grades.

Hospital Anxiety and Depression Scale (HADS)

The HADS was used to screen for anxiety and/or depression in our patients. It has been validated against structured psychiatric interviews in patients with dermatological diseases, and has good reliability and validity coefficients.[11] It comprises 2 seven-item subscales on the symptoms of anxiety and depression.[12] Each item has a 4-response category range, from 0 representing the absence of symptoms to 3 representing maximum symptomatology. The scale ranges between 0 and 21; a score of <8 is considered as no anxiety or depressive symptoms, 8 to 10 is considered as borderline anxiety or depressive symptoms and >10 is considered as prominent anxiety or depressive symptoms.

Patients' SCORAD were determined by clinicians involved in the study whereas HADS were assessed by research administrators. Neither group was aware of the findings of the other.

Statistical Analysis

One-way analysis of variance was used to compare means of 3 or more groups. Linear regression was used for normally distributed continuous outcomes in the multivariate analyses. A P value <0.05 was deemed significant.

Results

Females were fewer in numbers compared to males, with 78 males and 22 females recruited (Table 1). Their mean age was 25.7 years (standard deviation [SD] 10.1; range, 14 to 58 years). Of the patients, 92% were Chinese, 4% were Malays and 4% were Indians. A total of 15% of the study cohort had concomitant atopic conditions of asthma and/or allergic rhinitis. All had been prescribed topical steroids for treatment and 24% had previously been prescribed oral prednisolone for the treatment of severe flares. Twenty percent were on concurrent systemic immunosuppressants which included cyclosporine (10%), azathioprine (8%) and methotrexate (2%).

The mean SCORAD of the study cohort was 55.0 (SD 16.2; range, 15 to 96). One patient was scored with mild AD, 39 patients with moderate AD, and 60 patients with severe AD.

Based on the HADS, the mean score for anxiety in the study cohort was 7.2 (SD 3.7; range, 0 to 16) and the mean score for depression was 5.0 (SD 3.4; range, 0 to 14). Cronbach's alphas for the 7 anxiety items and 7 depression items were 0.78 and 0.73, respectively. The level of anxiety correlated well with the level of depression (Spearman's rank correlation coefficient, $\rho = 0.59$; $P < 0.05$); thus, a patient who scored higher for anxiety was likely to score higher for depression. Using the SCORAD score as dependent variable, linear regression established the following predictions from depression and anxiety scores. First, anxiety score could statistically significantly predict the SCORAD score ($F [1, 98] = 4.4.54$, $P = 0.037$) and anxiety score accounted for 4.3% of the explained variability in the SCORAD score. Second, depression score could statistically significantly predict the SCORAD score, ($F [1, 98] = 7.110$, $P = 0.0009$) and depression score accounted for 6.8% of the explained variability in the SCORAD score. The regression equation was: SCORAD score = 48.688 + 1.257 x (depression score) (Fig. 1). The regression equation was: SCORAD score = 48.406 + 0.916 x (anxiety score). In contrast, age could not predict the SCORAD score ($F [1, 98] = 1.159$, $P = 0.284$).

Table 1. Demographic and Clinical Data of the Study Cohort with Corresponding Mean SCORAD and HADS Scores

	Mean SCORAD	Mean HADS Anxiety Score (SD)	*P* Value	Mean HADS Depression Score (SD)	*P* Value
Gender					
Female (n = 22)	51.5	6.9 (4.0)	0.62	4.8 (4.0)	0.74
Male (n = 78)	56.0	7.3 (3.6)		5.1 (3.2)	
Ethnicity					
Chinese (n = 92)	55.2	7.0 (3.7)		5.0 (3.3)	
Malay (n = 4)	50.2	11.3 (2.8)	0.16	8.5 (4.2)	0.08
Indian (n = 3)	53.4	8.0 (3.5)		2.7 (2.9)	
Others (n = 1)	66.0	7.0 (-)		2.0 (-)	
Age of patients					
11 – 20 (n = 42)	53.7	7.5 (3.8)		4.5 (3.4)	
21 – 30 (n = 36)	55.5	7.3 (3.5)	0.98	5.4 (3.5)	0.78
31 – 40 (n = 12)	57.0	7.0 (4.3)		5.4 (3.6)	
41 – 50 (n = 4)	38.6	7.5 (2.5)		4.5 (1.0)	
51 – 60 (n = 6)	67.9	7.0 (4.0)		5.7 (2.9)	
Age at onset*					
<2 years (n = 23)	60.0	8.3 (4.4)		5.2 (3.6)	
2 – 4 years (n = 12)	57.8	5.8 (3.3)	0.15	3.3 (2.7)	0.13
>4 years (n = 60)	53.8	7.3 (3.4)		5.4 (3.4)	
Unknown (n = 5)	39.8	4.4 (2.5)		3.6 (1.3)	
Hospitalisations past month					
Yes (n = 4)	65.6	10.0 (3.4)	0.12	6.5 (0.6)	0.37
No (n = 96)	54.6	7.1 (3.7)		5.0 (3.4)	
Other medical problems					
Nil (n = 82)	53.8	7.2 (3.7)		4.9 (3.2)	
Asthma, rhinitis (n = 14)	60.9	7.4 (3.9)	0.97	5.5 (4.4)	0.84
Hypertension, diabetes, hyperlipidaemia, heart disease (n = 4)	59.3	7.0 (2.2)		5.3 (2.5)	

HADS: Hospital Anxiety and Depression Scale; SCORAD: Scoring atopic dermatitis

*Cases without known age of onset were excluded from statistical analysis.

Differences in gender, ethnicity, age, age of onset, history of hospitalisations or other comorbidities did not significantly impact HADS scores (Table 1).

Discussion

Based on the HADS, 18% of our patients had anxiety symptoms and 5% had depressive symptoms. These figures are comparable to those in international studies. Four percent of our patients scored positively for both anxiety and depression, and they may be impacted more emotionally as having concurrent anxiety and depression has been found to contribute to poorer mental health status compared with being afflicted with either condition alone.[13] A positive correlation was found between our patients' HADS anxiety and depression scores with their SCORAD. The coexistence of anxiety, depression and AD suggests that genetic or environmental risk factors were present. Hypothalamic-pituitary dysregulation is hypothesised to contribute to the association between psychiatric symptoms and the immune responses in AD.[14] Hyporesponsiveness of the axis, induced by chronic stress, leads to lower cortisol secretion. This upregulates the secretion of inflammatory cytokines that are usually counter-regulated by cortisol. In particular, psychiatric comorbidity affects interferon-gamma and interleukin-4 more in patients with AD.[15] Additionally, higher levels of central corticotrophin-releasing factor in patients with depression may reduce the itch threshold, leading to chronicity of AD and psychological burden, perpetuating the itch-scratch cycle.[16]

While broad screening questions such as "Are you depressed?" and "Do you worry a lot?" have an acceptable

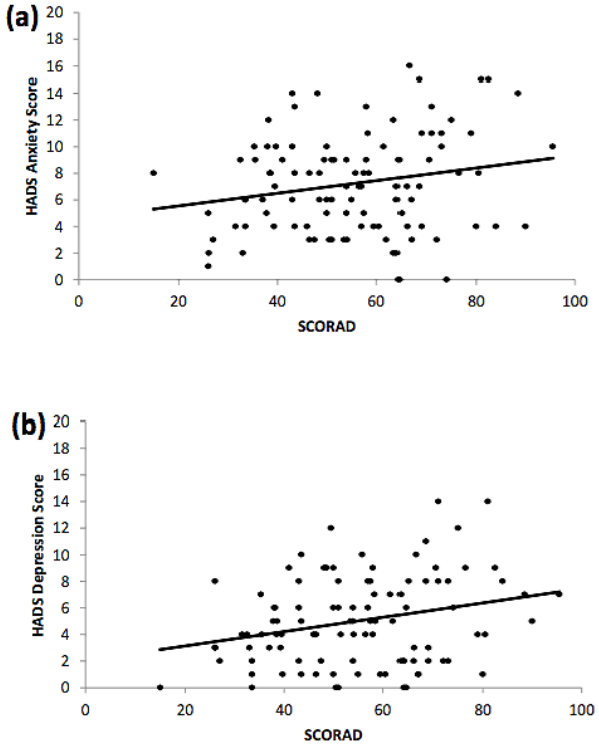

Fig. 1. Linear regression between subjects' SCORAD values with their corresponding a) anxiety and b) depression scores on the HADS. The relationship in both cases was positive but weak (Spearman's rank correlation coefficient, $\rho = 0.18$, $P = 0.08$ for SCORAD vs anxiety and $\rho = 0.21$, $P = 0.03$ for SCORAD vs depression).

sensitivity and specificity in detecting psychiatric comorbidity in AD patients,[17] beyond the routine quality of life (QOL) questionnaire, patients with more severe AD should be further evaluated for the presence of anxiety and depressive symptoms with the HADS. Early psychiatric intervention addressing the psychosocial effects of AD within a multidisciplinary team that involves a dermatologist, psychiatrist and psychologist will improve adherence to treatment and QOL.[18]

An important and critical aspect of holistic management is patient empowerment. A trusting doctor-patient relationship has to be established in order to allow the patient to understand their skin condition and learn how to proactively participate in management.[19] "Eczema schools" have been set up in Germany over the last decade, with comprehensive programmes designed to educate patients on the causes, triggers, allergens, proper use of topical medications and their side effects, adequate coping strategies for stress, and includes patient participation in their choice of medication.[20] Another useful therapeutic intervention is psychotherapy, as Linnet and Jemec have found that AD patients with a higher anxiety level are more likely to improve their psychological and dermatological condition after psychotherapy.[21] Since as many as 18% of our AD patients suffer from anxiety symptoms, psychotherapy interventions such as individual cognitive behaviour therapy and group therapy may improve adherence to AD treatment and overall response to treatment.[22] Such involvement in their own care have improved patients' health-related QOL,[19] alleviating overall psychological burden. Locally, these interventions have yet to be formally structured and delivered, but when done so, are also likely to improve patients' QOL.

Limitations

There are several limitations to the study. As this involves an interviewer-administered questionnaire, we cannot exclude the possibility that response may be influenced by the expectations of the interviewer (Rosenthal effect), although we sought to mitigate this by reminding the administrators to adhere to standardised questions of the HADS. The majority of our study cohort was Chinese, and our experience in the dermatology clinics seems to show fewer affected Indians and Malays. Of course, this parallels the ethnic profile of the general Singapore population with the Chinese being the majority. Males are more affected by AD than females, with the possibility that females may have adhered better to treatment. In clinical practice, less older females may have AD (GYC, personal communication). In addition, almost all enrolled had SCORAD ≥20 (i.e. moderate or severe AD); hence we cannot determine the frequencies of anxiety and depression amongst those with mild disease. Lastly, future studies can focus on mild AD in women, or involve a larger cohort of patients, before and after intervention in management have been developed.

Conclusion

Based on the HADS, there is a significant presence of anxiety and depression in chronic AD patients with moderate to severe disease locally. The HADS is a useful screening tool to detect these conditions and may be considered in routine clinical practice. Following the understanding of the emotional impact on AD, greater emphasis should be placed on building a good doctor-patient relationship, patient education and stress relief as part of holistic management to improve overall patient care.

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Original Article

Screening for Drinking Problems in the Elderly in Singapore Using the CAGE Questionnaire

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Abstract

Introduction: Given that past research on drinking problems has focused primarily on younger samples, the present study sought to examine the prevalence and correlates of alcohol use among the elderly in Singapore. Materials and Methods: Data were extracted from the Well-being of the Singapore Elderly (WiSE) study, a cross-sectional, epidemiological survey conducted among a nationally representative sample of Singapore residents (n = 2565) aged 60 years and above. Variables assessed include drinking problems, depression and anxiety symptoms, obesity, smoking status, chronic physical disorders and disability. Results: The weighted prevalence of drinking problems (CAGE score ≥2) in our sample was 4.2%. Male sex, Indian ethnicity, and being divorced or separated were associated with a significantly higher likelihood of drinking problems. Participants with drinking problems were also more likely to have subthreshold depression. There were no significant differences in disability among those with drinking problems, those without drinking problems and non-drinkers, after adjusting for demographic variables. Conclusion: Our findings contribute to the body of research that indicates an association between drinking problems and depressive symptoms among the elderly. Thus, screening for depressive symptoms in the elderly with drinking problems may be useful in identifying such comorbidities in order to aid treatment planning.

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Key words: Alcohol consumption, Epidemiology

Introduction

Alcohol use disorders (AUDs) can be defined as a maladaptive pattern of alcohol use that causes clinically significant impairment or distress.[1] Studies on alcohol consumption have focused mainly on the young and middle-aged, but less on older adults. However, given the rise in prevalence of alcohol problems among older adults aged 65 and over, and evidence indicating that this trend will continue,[2] it is important to investigate alcohol use in the elderly as well. Caputo et al[3] reported that approximately 50% of adults over 65 years of age and 25% of those aged over 85 regularly consumed alcohol. These figures are expected to rise dramatically[4] due to increasing life expectancy, which allows individuals to live and work longer, thus increasing their access to disposable income.[5] Moreover, the increasingly permissive attitude towards alcohol use[5-7] and its ease of availability in society[4,8] suggest that alcohol use and abuse among the elderly will become a growing area of concern.[3] Recent prevalence estimates of problematic alcohol use, which includes heavy drinking (defined as drinking 5 or more drinks on 1 occasion on each of 5 or more days in the past 30 days) and binge drinking (defined as drinking 5 or more alcoholic drinks on 1 occasion on at least 1 day in the past 30 days),[9,10] among older adults have been found to range between 1% and 15%.[11,12]

Excessive alcohol use has been established as a major contributor of disability and mortality across all age groups.[13] According to the World Health Organization (WHO) global status report on alcohol and health, alcohol consumption accounted for 5.9% of all deaths in 2012

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and 5.1% of the global burden of disease and injury.[14] The elderly may be more vulnerable to the effects of excessive alcohol use due to their compromised ability to metabolise alcohol, exacerbating the associated health risk at any given level of use.[8,15-17] Furthermore, complications due to co-existing disabilities[16] and the similarity between symptoms of excessive alcohol use and those of normal ageing, such as memory difficulties,[18] pose unique problems in identifying and treating this condition among older adults. Epidemiological studies in Singapore, for instance, have found alcohol use problems, including heavy drinking and AUDs, to be associated with other mental and physical conditions (e.g. major depressive disorder, chronic pain) as well as decreased quality of life.[19,20]

Several demographic variables have been implicated as risk factors for drinking problems in the elderly. For example, males, younger age, being divorced, separated, or single, higher education, and higher income have all been associated with increased odds of unhealthy drinking.[5, 11,15,17,18,21]

There also appears to be an association between depression and excessive alcohol use among older adults.[22] Almost 20% of individuals aged 65 and over with a diagnosis of depression have a co-occurring AUD.[3] In addition, Kirchner et al[23] found that heavy drinking alone and heavy drinking combined with binge drinking were linked to depressive symptoms among individuals aged 65 to 103 years in a primary care setting. The tendency to use alcohol as a form of self-medication[5, 17] appears to largely account for the relationship between these 2 variables. On the other hand, the presence of chronic diseases has been associated with alcohol abstention,[24] likely due to the risk of potential drug-alcohol interactions.[16,24]

A review on alcohol use among the elderly by Reid et al[25] yielded mixed evidence on the relationship between alcohol use and disability. For instance, the percentage of studies demonstrating harm, no association, or benefit of alcohol use with respect to functional disability was 38%, 46% and 16%, respectively. Some evidence even indicated that moderate alcohol use has a protective effect against age-related functional decline.[26,27]

Previous research on alcohol use in Singapore used data from the Singapore Mental Health Survey (SMHS), a national survey of mental disorders conducted among residents aged 18 years and above.[19,20,28] As such, alcohol use among older adults was not examined in-depth in these studies. Yet, the greater sensitivity to alcohol, increased health problems and increased use of medication that may react negatively with alcohol among the elderly[10] meant that results gleaned from adult studies may not replicate in an elderly sample. Furthermore, past studies have found some evidence for ethnic and cultural differences in alcohol use.[29] In a review examining drinking patterns among the different ethnicities in the United Kingdom (UK), most ethnic minority groups (i.e. Black, Caribbean, Indian, Pakistani, Bangladeshi and Chinese) were found to have lower levels of drinking and higher rates of abstinence compared to individuals from White backgrounds.[30] Given the potentially high-risk outcomes associated with alcohol use among older adults, lack of clarity of evidence pertaining to disability and alcohol use, ethnic differences in drinking patterns, and scant cross-cultural research, this current study examines the prevalence and correlates of alcohol use among elderly residents in Singapore. By identifying factors associated with drinking problems among the elderly in Singapore, our findings might have implications for the future planning of public health campaigns and policies that aim to prevent excessive alcohol use in at-risk individuals as well as curb drinking problems in vulnerable populations.

Materials and Methods

Setting

Data were extracted from the Well-being of the Singapore Elderly (WiSE) study, a cross-sectional epidemiological survey conducted on a nationally representative sample of Singapore residents aged 60 years and above. Singapore is a multiethnic country in Southeast Asia with a population of 5 million, of which, 74.2% are Chinese, 13.3% are Malay, 9.1% are Indian and 3.3% belong to other ethnic groups.[31] The 4 official languages in Singapore are English, Mandarin, Malay and Tamil, though a small proportion of the population also speak other languages and dialects such as Hokkien, Cantonese and Teochew.

Sample

Participants were randomly selected from a national database of Singapore residents and disproportionate stratified sampling was used to ensure the inclusion of equivalent proportions of the 3 main ethnic groups in Singapore (Chinese, Malay and Indian). Individuals residing in day care centres, or nursing homes at the time of the study were included in the sample, though residents who were living outside the country or were unable to be located due to incomplete or incorrect addresses were excluded. The study was approved by the relevant ethics committees (National Healthcare Group, Domain Specific Review Board and the SingHealth Centralised Institutional Review Board). Participants or their legally acceptable representatives (if participants were unable to provide written informed consent) provided written informed consent before study participation.

Data Collection

As part of the WiSE study, trained lay interviewers conducted face-to-face household interviews with Singapore residents who were at least 60 years of age between October 2012 and December 2013. Each interview lasted 2 to 3 hours, and was conducted in English, Mandarin, Malay, Tamil, or any of the 3 major Chinese dialects in Singapore (i.e. Hokkien, Cantonese or Teochew). More details on the WiSE methodology can be found in a separate paper.[32]

Measures

Demographic Information

A structured interview was used to obtain participants' demographic information, including age, sex, ethnicity, marital status, level of education, and employment status.

Alcohol Use

The CAGE questionnaire[33] is a 4-item "yes/no" screening tool used to assess lifetime self-reported problems related to alcohol use in the present sample. The 4 items were prefaced by a screening question, "Was there ever a period in your life when you drank at least 12 drinks in a year?" (a drink was defined as "a glass of wine, a can/bottle of beer, or a shot/jigger of liquor either alone or in a mixed drink"). Participants who indicated they had never drunk alcoholic drinks or drank less than 12 drinks per year were directed to skip the next 4 items. Those who answered "yes" to the screening question were asked about 4 aspects of their drinking habits: 1) feeling that they should cut down on their drinking; 2) being annoyed about criticism of their drinking; 3) feeling bad or guilty about their drinking; and 4) having a drink first thing in the morning to steady their nerves or to get rid of a hangover (eye opener). Consistent with prior studies,[34-37] lifetime drinking problems were defined as a CAGE score of 2 or greater (i.e. endorsing at least 2 of the 4 aspects of the drinking problems listed above). The questionnaire has demonstrated high test-retest reliability and adequate convergent validity,[38] and has been previously used in samples of older adults.[36,37]

Depression and Anxiety

Symptoms of depression and anxiety were evaluated using the Geriatric Mental State (GMS) examination and its associated diagnostic algorithm, the Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT).[39,40] The GMS is a structured mental health assessment tool designed for use in older samples that has been used in numerous international studies and has shown robust reliability and validity.[39,40] It has also been validated for use in the current sample in a previous paper.[32] The interview focuses on psychiatric symptoms within the past 1 month. The GMS-AGECAT was used in the present study to determine the severity of depression and anxiety. Each syndrome was given a diagnostic confidence level, ranging from 0 (no symptoms) to 5 (very severely affected); level 3 and greater denoted case-level severity, whereas levels 1 and 2 represented subthreshold-level severity. Given that prior research has indicated that depression occurs along a continuum, and that depression and subthreshold depression have similar correlates (e.g. impairment in physical functioning, disability days),[41,42] we combined the latter 2 categories and produced 2 subgroups—"no depression" and "at least subthreshold depression."

Obesity

Obesity was determined by using participants' body mass index (BMI) (kg/m^2) calculated from their height and weight, which were measured using a tape measure attached to the wall and a digital standing scale, respectively. The cutoff score used was based on WHO guidelines, which define obesity as BMI greater than or equal to 30.[43]

Smoking

Lifetime smoking status was determined by those participants who answered "yes" to the question: "Has there ever been a period when you smoked cigarettes, cigars, a pipe, chewing tobacco, beedi (a type of Indian cigarette), or snuff nearly every day?" Participants who gave a negative response were considered as "non-smokers."

Chronic Physical Disorders

Chronic physical conditions were evaluated using a checklist. Participants were asked if they had ever experienced or had been told by a doctor that they had any of the following conditions: 1) hypertension; 2) heart trouble (including heart attack, angina, heart failure, valve disease, and other related conditions); 3) stroke; 4) transient ischaemic attacks (TIAs); and 5) diabetes.

Disability

Disability was assessed using the World Mental Health (WMH) Survey version of the WHO Disability Assessment Schedule II (WHODAS II).[44] The modified WHODAS II evaluates 5 domains of functioning: understanding and communicating, self-care, getting around, getting along with others, and life activities. Each of the first 4 domains was prefaced by a filter question, followed by specific items that yielded severity ratings as well as a question on the number of days in the last month that the respondent had experienced an impairment in functioning. The scale has demonstrated acceptable levels of internal consistency and validity.[44]

Table 1. Demographic Profile of Sample

	Overall Sample (n = 2565)			Drinking Problems (CAGE Score ≥2) (n = 101)			Drinking Problems (CAGE Score ≥1) (n = 218)		
	Frequency	Unweighted (%)	Weighted (%)	Frequency	(%)*	Row (%)†	Frequency	(%)*	Row (%)†
Age group									
60 – 74	1494	58.25	75.01	77	3.50	4.67	155	8.34	11.12
75 – 84	669	26.08	19.46	17	0.59	3.03	47	1.58	8.11
85+	402	15.67	5.53	7	0.07	1.25	16	0.21	3.85
Sex									
Female	1448	56.45	55.91	6	0.45	0.81	12	1.01	1.80
Male	1117	43.55	44.09	95	3.71	8.41	206	9.13	20.70
Ethnicity									
Chinese	1012	39.45	83.30	37	3.39	4.07	96	8.71	10.45
Malay	745	29.04	9.28	24	0.31	3.30	41	0.54	5.86
Indian	772	30.10	5.98	38	0.39	6.44	77	0.73	12.29
Others	36	1.40	1.44	2	0.08	5.76	4	0.15	10.13
Marital status									
Married/cohabiting	1484	57.90	64.01	73	2.88	4.50	158	7.11	11.11
Never married	136	5.31	7.95	7	0.41	5.11	17	1.27	15.96
Widowed	836	32.62	22.51	10	0.35	1.56	27	0.90	3.98
Divorced/separated	107	4.17	5.53	11	0.53	9.61	16	0.87	15.76
Education									
None	511	20.04	16.45	6	0.36	2.17	16	0.78	4.73
Some, but did not complete primary	620	24.31	23.94	22	0.99	4.16	53	2.95	12.34
Completed primary	640	25.10	24.83	32	1.26	5.09	67	2.94	11.85
Completed secondary	517	20.27	22.37	26	1.01	4.52	51	2.39	10.67
Completed tertiary	262	10.27	12.41	15	0.55	4.40	30	1.07	8.63
Employment status									
Paid work (part-time and full-time)	688	27.15	33.88	54	1.86	5.49	102	4.54	13.41
Unemployed	32	1.26	1.54	3	0.09	5.56	7	0.41	26.70
Homemaker	808	31.89	26.26	4	0.34	1.29	7	0.67	2.56
Retired	1006	39.70	38.32	39	1.81	4.73	100	4.40	11.49

*Using weighted data.

†Calculated within each subgroup. For example, 4.67% of participants aged between 60 and 74 years reported drinking problems.

Statistical Analysis

To ensure that the survey findings were representative of the Singapore elderly population, the data were weighted and analysed using survey data analysis procedures implemented in SAS version 9.3. The purpose of weighting the WiSE data was to compensate for oversampling, non-coverage, non-response and post-stratification, thereby making the weighted data representative of the population of inference as closely as possible.[45] Means and standard deviations (SD) were calculated for continuous variables, whereas frequencies and percentages were calculated for categorical variables. Multiple logistic regression analysis was performed to examine the demographic correlates of drinking problems as well as how drinking problems is linked to other health conditions with adjustment for demographic variables (age, sex, ethnicity, marital status, level of education and employment status). To investigate the relationship between alcohol use and disability, we regressed alcohol consumption patterns on disability, controlling for the same demographic variables. For analyses on disability, participants were divided into 3 groups based on their consumption patterns: 1) has never drunk at least 12 drinks in a year ("non-drinkers"); 2) has drunk at least 12 drinks in a year before but no lifetime drinking problems ("those without drinking problems"); and 3) has drunk at least 12 drinks in a year before with lifetime drinking problems ("those with drinking problems"). Standard errors (SE) and significance tests for survey data analysis procedures were estimated using the Taylor series' linearisation method to adjust for the weighting. Multivariate significance was evaluated using Wald X^2 tests based on design corrected coefficient variance-covariance matrices. Statistical significance was set at the conventional level of $P < 0.05$, using two-sided tests.

Results

Sample Description

A total of 2565 participants were recruited for the present study. The mean age of the sample was 72.7 years (range, 60 to 105 years). The majority of the sample was female (56.5%), Chinese (39.5%), married/cohabiting (57.9%), and retired (39.7%). About a quarter of the sample completed primary education (Table 1). The study response rate was 66%. Relative to responders, non-responders were less likely to be in the older age group (85+ years old vs 60 to 74 years old; OR: 0.7; 95% CI, 0.6, 0.8) and more likely to be of Malay (OR: 2.9; 95% CI, 2.4, 3.4) or Indian ethnicity (OR: 2.3; 95% CI, 2.0, 2.7).

Prevalence

Based on a CAGE cutoff score of 2, 4.2% of our overall sample reported drinking problems. The unweighted prevalence was 3.9%. The prevalence of drinking problems in the subgroup of participants who had ever drunk at least 12 drinks in a year was 18.5%. Table 1 provides a breakdown of the prevalence estimates of drinking problems by demographic variables.

Demographic Correlates

Being male (OR: 26.9; 95% CI, 4.5, 160.8), Indian (OR: 1.8; 95% CI, 1.1, 3.0), or divorced/separated (OR: 2.9; 95% CI, 1.1, 7.6) was significantly associated with drinking problems (Table 2). Specifically, men were more likely than women, Indians were more likely than Chinese, and divorced/separated participants were more likely than married participants to report drinking problems.

Drinking Problems and Other Conditions

In subsequent logistic regression analyses, we examined the relationship between drinking problems and other conditions (e.g. depression, anxiety, obesity, and hypertension), adjusting for age, sex, ethnicity, marital status, level of education, and employment status. Participants with drinking problems were more likely to have at least subthreshold depression within the past 1 month than participants without drinking problems (OR: 2.7; 95% CI, 1.3, 5.4). However, drinking problems was not significantly associated with general anxiety within the past month, obesity, smoking, hypertension, stroke, transient ischaemic attacks (TIAs), heart problems, or diabetes (Table 3).

Alcohol Use and Disability

Those with drinking problems (mean: 9.6, SE: 2.7) reported significantly greater disability than those without drinking problems (mean: 6.2, SE: 0.9, $P < 0.001$), though there was no significant difference in disability between those with drinking problems and non-drinkers (mean: 12.1, SE: 0.5, $P > 0.05$). The difference in disability between those with drinking problems and those without drinking problems was no longer significant after controlling for age, sex, ethnicity, marital status, level of education, and employment status.

Comparison of CAGE Scores

Given the low prevalence of drinking problems in our study population, the decision was made to conduct additional analysis to examine the prevalence and correlates of drinking problems using a lower cutoff score (CAGE score ≥ 1).[46] In using a CAGE cutoff score of 1 or greater, the prevalence of drinking problems in our sample was

Table 2. Demographic Predictors of Drinking Problems

	CAGE Score ≥2 (95% CI)				CAGE Score ≥1 (95% CI)			
	Odds Ratio	**Lower Limit**	**Upper Limit**	***P* Value**	**Odds Ratio**	**Lower Limit**	**Upper Limit**	***P* Value**
Age group								
60 – 74*								
75 – 84	0.61	0.26	1.45	0.26	0.66	0.40	1.10	0.11
85+	0.31	0.08	1.27	0.10	0.32	0.13	0.74	0.01
Sex								
Female*								
Male	26.87	4.49	160.77	<0.001	26.07	8.24	82.42	<0.0001
Ethnicity								
Chinese*								
Malay	0.78	0.43	1.40	0.40	0.47	0.31	0.73	0.001
Indian	1.79	1.06	3.00	0.03	1.33	0.92	1.91	0.13
Others	1.43	0.34	6.07	0.63	0.99	0.31	3.16	0.99
Marital status								
Married/cohabiting*								
Never married	1.56	0.54	4.48	0.41	1.80	0.88	3.69	0.11
Widowed	1.02	0.29	3.58	0.98	1.00	0.49	2.05	1.00
Divorced/separated	2.92	1.11	7.63	0.03	1.79	0.73	4.41	0.21
Education								
None*								
Some, but did not complete primary	0.72	0.21	2.49	0.61	1.04	0.46	2.36	0.93
Completed primary	0.76	0.20	2.85	0.68	0.79	0.32	1.92	0.60
Completed secondary	0.66	0.16	2.71	0.57	0.67	0.26	1.72	0.40
Completed tertiary	0.44	0.10	1.95	0.28	0.39	0.14	1.08	0.07
Employment status								
Paid work (part-time and full-time)*								
Unemployed	0.74	0.12	4.69	0.74	1.98	0.60	6.60	0.26
Homemaker	4.27	0.43	42.66	0.22	2.78	0.64	12.09	0.17
Retired	1.25	0.64	2.42	0.52	1.14	0.71	1.83	0.58

CI: Confidence interval
*Referent group.

found to be 10.1% (unweighted prevalence: 8.5%). Similar to using a CAGE cutoff score of 2 or greater, the use of a lower cutoff score found men (OR: 26.1, 95% CI, 8.2, 82.4) to be significantly more likely than women to have drinking problems. Malay ethnicity and those aged 85 years and above emerged as significant correlates of drinking problems, with Malays being less likely than Chinese (OR: 0.5; 95% CI, 0.3, 0.7) and those aged 85 years and above (OR: 0.3; 95% CI, 0.1, 0.7) being less likely than those aged 60 to 74 years to report drinking problems.

Discussion

The use of CAGE cutoff score of 2 or greater yielded a prevalence estimate of 4.2% in our sample for lifetime drinking problems. This estimate, though higher than the rate of AUDs (1.6%) among individuals over 65 years old in Singapore,[47] was comparable to past studies such as León-Muñoz et al,[37] and Hoeck and Van Hal[35] which found 3.1% of their Spanish sample aged 60 years and above to have alcohol use problems, and 4.7% of elderly Belgian adults aged 65 years and above to have drinking problems, respectively.

However, in view of increasing evidence indicating a rising trend in the prevalence of alcohol problems among older adults aged 65 years and over[2,3] and the relatively low estimate of drinking problems in the current sample,

Table 3.Drinking Problems as a Predictor of Other Conditions*

Outcome Variable	95% CI			*P* Value
	Odds Ratio	Lower Limit	Upper Limit	
Depression	2.66	1.31	5.39	0.01
Anxiety	1.79	0.83	3.82	0.14
Obesity	1.73	0.66	4.54	0.26
Smoking	1.95	0.97	3.91	0.06
Hypertension	1.79	0.78	4.12	0.17
Heart trouble†	0.99	0.47	2.11	0.98
Stroke	2.04	0.78	5.38	0.15
TIAs	1.98	0.43	9.23	0.38
Diabetes	1.17	0.60	2.28	0.64

CI: Confidence interval; TIA: Transient ischaemic attack
*Findings were adjusted for age, sex, ethnicity, marital status, level of education and employment status.
†Heart trouble includes heart attack, angina, heart failure, valve disease and other related conditions.

supplementary analysis was conducted using a lower CAGE cutoff score of 1 or greater given some evidence for increased sensitivity and specificity among the elderly population using a lower cutoff score.[46] In using a CAGE cutoff score of 1 or greater, 10.1% of the sample was found to report lifetime drinking problems. While this figure was still slightly lower than the frequency of lifetime heavy drinking (15.9%) among adult Singapore residents aged between 18 and 65 years,[47] it fell within the range of drinking problems prevalence estimates in Western samples,[2,3] suggesting some similarity across cultures with respect to the frequency of drinking problems among older adults.

The lack of significant variation between our sample and Western samples could be due to accelerated Westernisation as well as economic factors that have increased the availability of alcoholic beverages in Singapore, similar to the changes that occurred in China within the past few decades, which ultimately served to increase alcohol consumption in China.[48] Regardless of the reason, the relatively common occurrence of drinking problems in our sample, increased susceptibility to the negative effects of excessive alcohol use among elderly, and the low rate of treatment-seeking among those with drinking problems in Singapore[20] indicate the need for greater awareness of excessive alcohol consumption among policymakers who can work towards improving public health outcomes for the elderly in Singapore.

Evidence from studies conducted across cultures, including Singapore, corroborate our finding of increased risk of alcohol-related problems in men relative to women.[11,18,20,28,49] One factor contributing to the increased risk of drinking problems in males could be the greater acceptability of alcohol consumption among men compared to women among Chinese,[48] who comprise the majority of Singapore residents. The combination of a general increased risk of alcohol consumption and a more permissive social context for drinking in Singapore among men might explain why they were 27 more times as likely to report drinking problems as women.

The other risk factors identified in the present study (i.e. Indian ethnicity, being divorced/separated) were somewhat consistent with those reported in previous studies on alcohol use among adults aged 18 to 65 years in Singapore.[19,20,28] Abdin et al[28] found that, relative to Chinese, Indians were more likely to report regular alcohol use and transition from regular alcohol use to alcohol abuse and alcohol dependence. Subramaniam et al[20] found that Indians were more likely than Chinese to have lifetime alcohol dependence and that divorced/separated individuals were more likely than single individuals to have any AUD within the past 12 months. In addition, Lim et al[19] found that being divorced/separated increased the risk of lifetime heavy drinking relative to being single, though the study did not find a significant association between Indian ethnicity and heavy drinking.

It is unclear why divorce/separation may be specifically linked to drinking problems in Singapore. However, given that stressful events have been postulated as a moderator of alcohol use over time,[50] it is possible that the stress associated with separation from one's spouse interacts with other factors to predict greater alcohol consumption. Furthermore, the finding that Indians are more likely to develop AUDs from regular use might explain why Indian ethnicity increases the risk of drinking problems and alcohol dependence, but not heavy drinking. Such a phenomenon could, in turn, be explained by differences in cultural and/or religious attitudes governing alcohol consumption as well as in biological processes responsible for metabolising alcohol. However, given mixed evidence on the relationship between Indian ethnicity and drinking problems, further research is needed to better interpret current findings. Nonetheless, the demographic variables that have been consistently identified as risk factors for drinking problems in Singapore—male sex and being divorced/separated—provide guidance for the development of public health policies aimed to curb such problems across age groups.

Drinking problems also predicted depressive symptoms within the past 1 month, corroborating findings from previous studies.[22] In particular, using the same measure of alcohol use problems (i.e. CAGE), Bell et al[34] found that drinking problems doubled the likelihood of having depressive symptoms within the past week. Likewise, a longitudinal study by Gilman and Abraham[51] reported that alcohol dependence and major depression (including subthreshold depressive symptoms) were strong risk factors for the development of the other disorder at 1-year

follow-up. Our findings contribute to the body of evidence that indicate a relationship between drinking problems and depressive symptoms. Taken together, they suggest that screening for depressive symptoms among elderly with drinking problems and vice versa may be useful in identifying comorbidities, which can facilitate treatment planning. Furthermore, given that studies have shown that both case-level and subthreshold depression are associated with substantial impairment in functioning,[41,52,53] screening and treatment of depression among elderly with drinking problems could result in a better prognosis.

Evidence on the association between alcohol use and disability is mixed.[25] Congruent with present findings, drinking problems were not found to be associated with disability in some Western samples of older adults.[36] In addition, Lim et al[19] reported no significant difference in the quality of life between heavy drinkers without AUD and non-heavy drinkers in Singapore. One reason for the lack of significant association in our sample could be that we did not account for the role of potential moderators of the relationship between drinking problems and disability. For example, Cheng and McBride[54] found that the relationship between alcohol dependence and physical disability depended on the presence of antecedent mental disorders, whereas Karlamangla et al[55] found that the effect of alcohol consumption on disability was contingent on the pre-existing health status among older adults. Clearly, investigating the complex relationship between drinking problems and disability requires consideration of the moderating effects of other factors, so as not to obscure any potential significant links between the 2 variables.

Limitations

The CAGE questionnaire has been widely used as a screening instrument for alcohol use problems,[56] rather than as a comprehensive measure of alcohol consumption. Thus, analyses were based on a rudimentary classification of alcohol consumption patterns, which means that conclusions that can be drawn from the current data are limited in scope. Furthermore, the CAGE evaluates the presence of lifetime drinking problems, rather than current drinking problems. Hence, individuals who had quit drinking years before their participation in the study (ex-problem drinkers) would have been classified as those with drinking problems in our sample, even if they were no longer experiencing active symptoms of drinking problems. This presents a problem in examining the relationship between drinking problems and other variables as 1) individuals who do not have current symptoms of drinking problems are different from those with current symptoms of drinking problems, and 2) lifetime drinking problems provides a protracted timeline during which multiple events could occur without overlapping. For example, individuals who quit drinking many years ago and are only currently experiencing minimal residual symptoms of drinking problems (if any) might have developed depressive symptoms within the past 1 month, fulfilling both our criteria for drinking problems and depressive symptoms. Yet, it would be unlikely that the 2 events are linked. In addition, examining the relationship between lifetime drinking problems and 1-month disability might partially explain the lack of a significant relationship between drinking problems and disability. Using concordant timelines (e.g. 12-month prevalence and 1-month impairment) would better illustrate the impact of alcohol consumption on disability.

Moreover, because the CAGE assessed self-reported drinking problems, heavy drinkers who did not feel that they had any problem with their drinking habits would have been classified as those without drinking problems. As a result, "those without drinking problems" could have had more severe current alcohol use problems than "those with drinking problems" in our sample.

The interview-based format of survey administration also presents the possibility of underreporting of drinking problems, particularly if alcohol use has negative social or cultural connotations for the individual. For instance, Muslim participants might have underreported their alcohol consumption, which is expressly forbidden in the Quran, the primary religious text of Islam. Thus, future studies aiming to elucidate drinking problems among the elderly may benefit from using more comprehensive measures that incorporate information from other sources (e.g. family members, clinicians).

The cross-sectional nature of the study does not allow for the establishment of temporal relationships. As such, we are unable to determine the direction of the association between drinking problems and depressive symptoms, as well as the ways in which these symptoms might interact over time. Prospective research on this relationship to identify the developmental progression of alcohol use and depression may have significant implications for prevention and intervention efforts. The design of the study introduces the possibility of survivor bias as those with more impaired drinking problems may have died before the age of 60, leaving a relatively well functioning group of those with drinking problems in our sample. Finally, although the current study briefly explored the prevalence and demographic correlates of drinking problems using a lower cutoff score, an in-depth analysis was not carried out. Future studies can examine the use of a lower CAGE cutoff score, given that past studies have shown some evidence of increased sensitivity and specificity when using a lower cutoff.

Conclusion

In the present study, we examined alcohol consumption among the elderly in Singapore and found that male sex, Indian ethnicity and being divorced or separated were significantly associated with drinking problems. Individuals with drinking problems were also more likely to have subthreshold depression within the past month. However, lifetime drinking problems were not significantly linked to disability. Our findings are consistent with previous studies on alcohol use in Singapore adults and add to the body of research that indicate a link between drinking problems and depressive symptoms among the elderly. This study suggests a need for public health campaigns and policies to raise the awareness and address alcohol use problems among the elderly, as well as to support the screening and treatment of depressive symptoms in the elderly with drinking problems.

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Commentary

Understanding How Postnatal Depression Screening and Early Intervention Works in the Real World – A Singaporean Perspective

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Abstract

Postnatal depression is a major public health problem with clearly established adverse effects in child outcomes. This study examines the 4-year outcomes of a screening and early intervention programme, in relation to improvement in symptoms, functioning and health quality of life. Women were prospectively recruited up to 6 months postdelivery, using the Edinburgh Postnatal Depression Scale (EPDS) as a screening tool. High-scorers (EPDS >13), were offered psychiatric consultation, and those with borderline scores (EPDS 10-12) were provided counselling, and offered follow-up phone counselling by the assigned case manager. Outcome measures were obtained at baseline, and at 6 months or discharge if earlier, for levels of symptoms, functioning, and health quality of life. From 2008 to 2012, 5245 women were screened, with 307 (5.9%) women with EPDS >13 receiving intervention. Of these, 70.0% had depression, 4.6% anxiety and 3.4% psychosis. In the depression subgroup, the net change was improvement of 93.4% EPDS symptom scores, 92.2% Global Assessment of Functioning (GAF) scores, and 88.3% visual analogue scale (EQ VAS) health quality of life scores. Outcome scores across diagnostic categories demonstrated median changes of 10 points on EPDS, 20 points on GAF, and 25 points on EQ VAS, reflecting 73.9%, 36.4% and 41.7% change from baseline scores. Women with psychosis showed the biggest (80.0%) relative change in GAF functioning scores from baseline to discharge but had the lowest median change in EPDS symptom scores. A screening and intervention programme rightly-sited within an obstetric setting can improve clinical outcomes because of early detection and intervention.

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Key words: Early detection, Maternal mental health, Postpartum mood

Introduction

Postpartum depression is a major public health problem; left untreated, it can lead to increased morbidity in the mother, the infant and the family system.[1,2] These include negative effects on maternal-infant attachment, as depressed women have been found to have poorer responsiveness to infant cues and more negative, hostile or disengaged parenting behaviours. This then affects child development, as there is associated lower cognitive functioning and adverse emotional development in the children.[3,4] Children of chronically depressed mothers are also at a higher risk of stunted growth and behavioural problems.[5,6]

The estimated prevalence of postpartum depression in the United States (US), United Kingdom (UK) and Australia ranges from 7% to 20%. In Singapore, the prevalence of peripartum depression is about 12% for antepartum depression, and about 7% for postpartum depression.[7] Peripartum depressive symptomatology is seen in about 1 in 5 pregnant women, although not all cases amount to major depression.[8] In the US and Australia, maternal health services and well established programmes target this population, whilst Singapore developed its first postpartum depression early intervention programme only in 2008.[9] The programme is funded by the health ministry and was

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developed at the KK Women's and Children's Hospital (KKH), which handles some 12,000 deliveries annually (representing about a third of Singapore's national births). This paper looks at the 4-year outcomes of the programme, and studies the effectiveness of early intervention in relation to improvement in symptoms, functioning and health quality of life.

Materials and Methods

This prospective cohort study of postpartum women was conducted at KKH between 2008 to 2012. The study had approval from the KKH Institutional Review Board, and the clinical programme was funded by the Ministry of Health. We recruited subjects 2 to 26 weeks postdelivery from 2 obstetric outpatient clinics. The subjects were screened by trained perinatal mental health case managers with the well validated self-report Edinburgh Postnatal Depression Scale (EPDS),[10] following which the high-scorers were offered psychiatric intervention based on a case management model. We used a threshold of 13 to identify women likely to suffer from major depression, as previously validated with good psychometric properties in Singaporean women (area under the curve [AUC] 94.4%),[11] similar to that determined by the Edinburgh and Cambridge researchers in a community sample.[12] Outcome measures of symptoms (EPDS), functioning (Global Assessment of Functioning [GAF])[13] and health quality of life (EQ-5D, VAS)[14] were taken at baseline and again at 6 months or the last visit, if earlier.

Intervention Programme

Early intervention included full psychiatric assessment, supportive counselling, psychoeducation, and problem-solving focussed counselling incorporating principles of interpersonal and cognitive behavioural therapy. Components of the supportive counselling incorporate care for the mother and her partner.

Antidepressant medication for cases was recommended for those with depression of moderate severity, taking into consideration breastfeeding preferences. A case management model was used, providing integrated, individualised and continuous care from screening through to intervention.[15] Patients were encouraged to join the support group, as postpartum depression peer support is beneficial.[16] For women with more entrenched psychological difficulties, psychotherapy was provided. Women with mother-infant bonding difficulties were provided therapy, whilst those with social problems, for example, marital conflicts, were referred to the social worker or community resources.

Data Analysis

To evaluate the programme in the treatment cohort, we calculated the change scores (discharge-baseline) in EPDS, GAF and EQ-VAS and summarised the distribution of change scores using the mean and standard deviation. In the absence of a well defined control group (eg. women eligible for treatment who opted out of the programme), we prespecified treatment targets as criteria for programme effectiveness for each of the following outcomes: 1) a mean absolute reduction of 4 points in the EPDS baseline score[17] or a 4-point absolute reduction achieved for at least 50% of the treatment cohort, 2) a mean increase of 10 points in GAF or a 10-point increase in GAF for at least 50% of the treatment cohort.[18]

The rationale for the above targets is as follows: the reliable change index for the EPDS was determined to be 4 points. This is the difference between 2 scores needed for a clinician to be 95% confident that it reflects a real change in the individual's mood, and is not likely to be due to measurement error.

Improvement in GAF ratings were computed by subtracting baseline from discharge ratings. Difference in scores were considered improved if discharge ratings were 10 or more points higher than baseline scores, and not improved if otherwise. The 10-point difference criterion was used because the GAF uses 10-point ranges to define impairment severity levels, so that a 10-point change represents a change in level of impairment based on the clinician's assessment. We also examined median absolute change and percentage improvement in all outcome measures.

Results

During the study period, 5245 women were screened. The mean age was 30.38 (SD 4.80) years and they were screened at the mean of 4.91 (SD 2.65) weeks postpartum. The mean EPDS score was 4.58 (SD 4.31). A total of 307 (5.9%) women with EPDS >13 entered the intervention arm. Table 1 shows the demographic characteristics of these women.

Primary Diagnosis for Those Entering Intervention

Using DSM IV criteria, a little over half of the 307 women were diagnosed to have postpartum depression. Of these, 40.7% were diagnosed to have major depression, postpartum onset and 12.4% were diagnosed to have minor depression, postpartum onset. We observed that 16.4% suffered from major depression in pregnancy that continued to the postpartum period. About an eighth (11.8%) of the subjects were diagnosed to have adjustment disorder and 3.4% had puerperal psychosis (Table 2).

Table 1. Descriptives of Women that Entered Clinical Intervention

	n = 307	%
Maternal age (years)		
19 – 24	22	12.4
25 – 34	110	62.1
35 – 40	38	21.5
>41	7	4
Marital status		
Married	168	94.9
Separated	2	1.1
Divorced	1	0.6
Cohabitating	3	1.7
Single	3	1.7
Race		
Chinese	111	62.7
Malay	32	18.1
Indian	23	13.0
Others	11	6.2
Nationality		
Singaporeans	134	75.7
Permanent residents	31	17.5
Foreigners	12	6.8
Educational qualifications		
Primary	7	4
Vocational	13	7.3
Secondary	40	22.6
Tertiary (diploma & degree)	116	65.5
Occupation		
Home maker	72	40.7
Professional	39	22
Administrative/executive	37	20.9
Service line	19	10.7
Housing		
Public	159	89.8
Private	18	10.2
Income (monthly)		
<$3000	46	25.9
$3001 – $6000	51	28.9
>$6001	43	24.9
Unplanned pregnancy	93	52.5
Planned pregnancy	84	47.5

Table 2. Primary Diagnosis

Primary Diagnosis	Frequency	%
Depression		
Major depression		
Antepartum onset – now postpartum	49	16.0
Postpartum onset	137	44.8
Minor depression		
Antepartum onset – now postpartum	4	1.3
Postpartum onset	38	12.4
Postnatal anxiety	14	4.6
Obsessive compulsive disorder (postpartum onset)	2	0.7
Adjustment disorder		
Postpartum onset with depression	25	8.2
Postpartum onset with anxiety	8	2.6
Puerperal psychosis	10	3.3
Pre-existing illness (eg. dysthymia)	4	1.3
Others (eg. acute grief, borderline IQ, acute stress, insomnia)	13	4.2
No mental illness	2	0.7
Total	306	100

IQ: Intelligence quotient

The majority (83.4%) had only 1 primary diagnosis. Among the remaining 16.6% with a secondary diagnosis, anxiety disorder (4.2%) was the most prevalent comorbid condition. When classified according to clinical symptoms, the majority (83.2%) had depressive symptoms, 8.3% had anxiety symptoms and only 3.3% had psychotic symptoms.

The common associated problems cited were marital conflicts (41.8%), lack of social support (33.9%), conflicts with in-laws (27.7%), financial problems (15.3%) and work-related stress (9.6%).

Baseline Scores (EPDS, GAF and EQ VAS) amongst Diagnostic Groups

The diagnostic groups did not vary significantly in baseline scores of EPDS, GAF and EQ VAS (Table 3). However, the range of baseline GAF scores was widest in women with puerperal psychosis.

Clinical Outcomes of Intervention

Most of the patients in the intervention group were seen for at least 2 visits. However, 26 (10.3%) of those in the depression group were seen only once. There were some patients in the depression and anxiety subgroups that required ongoing evaluation and treatment. A minority (15.4%) of the patients in the anxiety subgroup were still receiving intervention beyond 6 months.

In the depression subgroup, the net change of EPDS symptom scores was an improvement in 93.4%. Similarly, net improvement of GAF functioning scores was 92.2%, and of EQ VAS health quality of life scores was 88.3%.

Table 3. EPDS, GAF and EQ VAS Scores at Baselines According to Diagnostic Subgroups

	Baseline Summary								
	EPDS			GAF			EQ VAS		
	Mean	SD	n	Mean	SD	n	Mean	SD	n
Depression	18.23	5.350	252	58.74	8.158	251	52.53	19.279	251
Anxiety	16.92	5.782	26	59.54	7.664	26	54.62	19.946	26
Puerperal psychosis	16.00	10.198	10	53.11	15.560	9	50.00	38.079	9
Others	15.87	6.034	15	65.40	11.463	15	49.67	22.238	15
Total	17.93	5.643	303	58.97	8.724	301	52.49	20.140	301

EPDS: Edinburgh Postnatal Depression Scale; EQ VAS: Visual analogue scale; GAF: Global Assessment of Functioning
Note: The diagnostic groups (Dep, Anx, PP, Others) did not statistically significantly differ in their baseline distributions for EPDS (KW = 3.21, df = 3, P = 0.359), GAF (KW = 7.71, df = 3, P = 0.052) and EQ VAS (KW = 1.15, df = 3, P = 0.765).

The respective net changes in the anxiety subgroup were improvements in EPDS and GAF in all patients, and an improvement of 71.4% in EQ VAS. In the psychosis subgroup, the net improvement in EPDS scores was 60.0%, with GAF 100.0% and EQ VAS 77.8%. Whilst the median (absolute) change in scores for the EPDS, GAF and EQ VAS across the different diagnostic groups were not dissimilar, the patients with psychosis showed the biggest absolute (40%) and relative (80.0%) change in the GAF functioning scores from baseline to discharge (Fig. 1).

When the diagnostic groups were compared based on the outcome EPDS scores, there was no statistical significance between groups in the proportion of women experiencing improvement, no change or worsening "depressive" symptoms assessed by EPDS scores. Outcome scores across diagnostic categories demonstrated a median change of 10 points on the EPDS, 20 points on the GAF, and 25 points on the EQ VAS, reflecting 73.9%, 36.4% and 41.7% change from baseline scores.

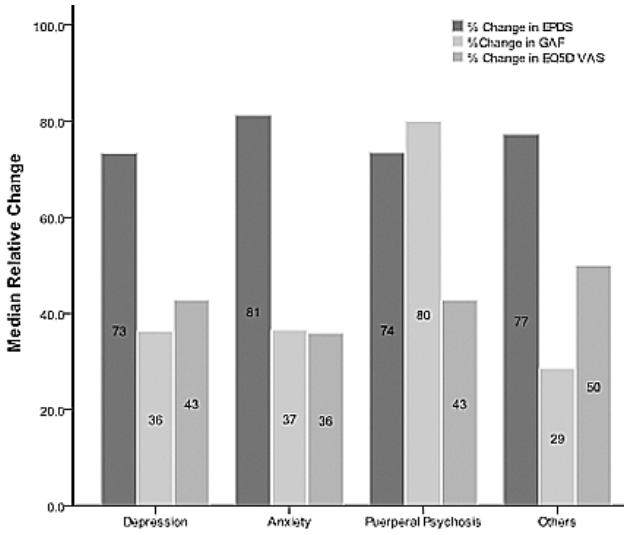

Fig. 1. Graph showing median relative improvement in outcome measures across diagnostic groups.

Discussion

Of the 5245 women, 307 (5.9%) screened positive and received clinical intervention. This is in keeping with the worldwide prevalence rate of peripartum disorders[19] and the local rate reported in published studies.[7,8]

Most studies on postpartum women focus on the primary diagnosis of major depression. However, our study showed that 16.6% have a secondary diagnosis of which anxiety is the most common comorbid disorder. Interestingly, women with anxiety as the primary disorder required a longer duration of intervention as compared to women with depression as the primary disorder. Hence, it is important to recognise comorbid postpartum anxiety and treat accordingly.

The clinical outcomes showed that intervention was beneficial as all 3 subgroups reported improvement in their overall EPDS, GAF and EQ VAS scores on discharge. The patients in the psychosis subgroup showed the biggest relative change in GAF functioning and EQ5D health quality of life scores, which emphasises the importance of treatment in this subgroup, whilst they had comparable relative change in EPDS symptom scores with the other diagnostic groups. The 13-point median change in the EPDS suggests that this programme is effective, based on Matthey et al's proposed Reliable Change Index of 4 points for the EPDS.[17] Similarly, the 20-point median change on the GAF suggests the effectiveness of the programme, as each symptom or functional level is represented by a 10-point difference.

The main limitation of this study is that it is not a

randomised study, but an observational one. The groups are thus not directly comparable and the results cannot be generalised. The measures were also not taken at fixed time-points, as the patient visits were determined based on individual needs. The research team was also not blinded as to the diagnostic types used, as the clinical team doubled up as the research team for continuity of care. The EPDS was also used as both an entry and outcome measure when a preferred methodology would include an alternative symptom rating outcome measure. The GAF has also been shown to have limitations in assessing health outcomes, due to a lack of research-based development and limited empirical testing.[20] Similarly, little is understood about the psychometric properties of the EuroQol measure, and future studies are needed in the postpartum population. We were also not able to examine aspects of effectiveness such as programme uptake, aspects of delivery (staff, competence), resource utilisation and patient outcomes.

Nonetheless, we believe this study adds valuable understanding about intervention on the whole range of postpartum mental disorders in the real world setting, and provides an audit of a postpartum depression screening programme with the widely used EPDS.

Conclusion

Postpartum psychiatric disorders are a public health concern. A screening programme rightly-sited within an obstetric setting can improve clinical outcomes because of early detection and intervention.

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Stress and Burnout among Physicians: Prevalence and Risk Factors in a Singaporean Internal Medicine Programme

Dear Editor,

Stress is a feeling of strain and pressure while burnout is a multidimensional syndrome comprising emotional exhaustion, depersonalisation (establishment of distant and cynical relationships) and a diminished sense of personal accomplishment.[1] Psychological stress and burnout harm physician health and work performance, and can lead to poorer patient care.[2] Relatively little data are available from Asian academic medical centres. We thus investigated the prevalence and risk factors of stress and burnout among physicians in our institution's internal medicine programme.

Materials and Methods

We performed a cross-sectional survey of attendings and trainees across 2 training sites: a 1081-bed sponsoring institution (SI), and a 400-bed participating site (PS). We assigned the physician to either the SI or PS depending on their place of practice in the previous month. We conducted the survey via SurveyMonkey® (www.surveymonkey.com) between June 2013 and October 2013. The survey was voluntary and consent was implied if physicians responded. Our institutional ethics board approved the study (F/2013/00770).

All measures reflected respondent experiences over the preceding month, except for the Patient Health Questionnaire (PHQ) which reflected experiences over 2 weeks. Our main outcome measures were assessed using the following psychometric instruments: Cohen Perceived Stress Scale (PSS; 4-question version, total score range 0-16)[3] and the Copenhagen Burnout Inventory (CBI).[4] To obtain the prevalence of stress, we dichotomised the PSS total score using prior normative data (high degree of stress if total score was >8).[5] The CBI is a freely available 19-item self-reported measure of burnout, comprising 3 subscales according to its perceived source (personal, work-related and patient-related subscales). High level of burnout was defined based on standard methods of at least 50 of 100 points on any subscale.[4] To assess for the correlation between the CBI and another widely used but proprietary burnout measure, the Maslach Burnout Inventory (MBI), participants completed a validated two-item version of the MBI.[6]

Our survey examined possible risk factors for stress and burnout: age, gender, having a religion, marital status, number of children, hours spent per week on clinical work/research/teaching/exercise, number of overnight calls per week, number of hours slept per night and disrespect. As no previously published scales or objective measures were available, we assessed how much participants felt respected using these 3 questions: "How much do colleagues respect you?", "How much do patients respect you?" and "How much do patients' family members respect you?" Answers to these questions were scored on a scale of 0 (not at all) to 10 (extremely). To facilitate interpretation, scores were dichotomised to high degree of respect if the score was >5, and low degree of respect otherwise.

Univariate comparisons of proportions, means and medians were done using Fisher exact, student-t, and Wilcoxon rank-sum tests, respectively. Internal validity for the PSS and the CBI were computed using Cronbach's alpha. Correlation between the CBI and the two-item MBI was done using Spearman's correlation coefficient. Multivariate backward stepwise regression analyses (P for entry 0.1, P for removal 0.2) were done for PSS score (as a continuous outcome) and burnout (as a dichotomous outcome), adjusting for training site (SI vs PS) to account for possible site differences on stress/burnout. We did not include training stage (trainee vs attending) as a covariate as we expected it to be highly correlated with age, work hours and call frequency.

Results

From 268 physicians (145 trainees, 123 attendings), we received 109 completed questionnaires (response rate 40.7%, median age 34 years old, 46.8% female). The PSS had moderate reliability while the CBI had excellent reliability (Cronbach's alpha 0.71 and 0.96, respectively). Correlations between the CBI total score and MBI items were good: Spearman's rho was 0.779 for the emotional exhaustion item and 0.813 for the depersonalisation item (both P <0.001) (Table 1).

High stress was present in 17.4% (trainees 21.8%, attendings 11.1%, P = 0.201), while burnout was present in 55.1% (trainees 71.8%, attendings 31.1%, P <0.001) (Table 1). Overnight calls and low degree of respect from colleagues were associated with increased PSS, controlled for training site (Table 2). Younger age, shorter exercise

Table 1. Outcome Measures

Outcome Measures	All (n = 109)	Trainees (n = 64)	Attendings (n = 45)	*P* Value
Perceived stress scale[†] (± SD)	6.2 ± 2.8	6.4 ± 2.5	5.9 ± 3.1	0.315
High degree of perceived stress[‡] (%)	19 (17.4)	14 (21.8)	5 (11.1)	0.201
CBI[§] score (± SD)				
Overall (range 0 – 300)	124 ± 57	140 ± 54	102 ± 55	<0.001[*]
Personal (range 0 – 100)	50 ± 23	57 ± 20	39 ± 22	<0.001[*]
Work-related (range 0 – 100)	45 ± 19	50 ± 18	38 ± 18	<0.001[*]
Patient-related (range 0 – 100)	30 ± 21	33 ± 21	38 ± 18	38 ± 18
Burnout as defined by the CBI (%)				
Overall	60 (55.1)	46 (71.8)	14 (31.1)	<0.001[*]
Personal	60 (55.1)	45 (70.3)	12 (26.7)	<0.001[*]
Work-related	60 (55.1)	36 (56.3)	12 (26.7)	0.003[*]
Patient-related	60 (55.1)	19 (26.7)	5 (11.1)	0.033[*]

CBI: Copenhagen Burnout Inventory; PHQ: Patient Health Questionnaire; SD: Standard deviation

[*]*P* <0.05.

[†]Four-item version of the Cohen Perceived Stress Scale, graded on a scale of 0 – 16. Cronbach's scale reliability coefficient alpha = 0.71.

[‡]Using Cohen Perceived Stress Scale, dichotomised to high degree of stress if score was >8, and low degree of stress otherwise. This is in keeping with normative data from Internet users in Spain (Herrero J, Meneses J. Short web-based versions of the perceived stress (PSS) and Center for Epidemiological Studies-Depression (CESD) Scales: a comparison to pencil and paper responses among Internet users. Comput Human Behav 2006;22:830-46).

[§]Cronbach's scale reliability coefficient alpha = 0.96.

Table 2. Risk Factors for Stress as Determined by the Four-Item Cohen Perceived Stress Scale—Univariate Analysis and Multiple Linear Regression[§]

Risk Factor	Coefficient (95% CI)	Univariate *P* Value	Coefficient (95% CI)	Multivariate *P* Value
SI vs PS	1.45 (0.19, 2.70)	0.024[*]	0.57 (-0.66, 1.80)[‡]	0.362
Age (years old)	-0.06 (-0.12, -0.00)	0.040[*]	-	-
Female sex	0.67 (-0.38, 1.73)	0.211	-	-
Has a specific religion	0.67 (-0.79, 2.13)	0.367	-	-
Married	-0.37 (-1.44, 0.69)	0.484	-	-
Number of children	-0.25 (-0.75, 0.25)	0.326	-	-
Work hours per week	0.01 (-0.02, 0.04)	0.450	-	-
Overnight calls per week	1.09 (0.57, 1.62)	<0.001[*]	1.10 (0.59, 1.62)[‡]	<0.001[*]
Hours/week spent on exercise	-0.08 (-0.19, 0.03)	0.143	-0.09 (-0.19, 0.01)[‡]	0.087
Hours/week spent on research	0.00 (-0.09, 0.08)	0.937	-	-
Hours/week spent on teaching	0.01 (-0.11, 0.13)	0.815	-	-
Hours of sleep per day	-0.29 (-0.79, 0.20)	0.246	-	-
High degree of respect from colleagues[†]	-1.54 (-2.80, -0.30)	0.016[*]	-1.25 (-2.42, -0.08)[‡]	0.037[*]
High degree of respect from patients[†]	-1.39 (-2.74, -0.04)	0.043[*]	-	-
High degree of respect from patients' families[†]	-1.50 (-2.77, -0.22)	0.022[*]	-	-

CI: Confidence interval; PS: Participating site; SI: Sponsoring institution

[*]*P* <0.05.

[†]Graded on a Likert scale of 0 – 10, then dichotomised to high degree of respect if score was >5, and low degree of respect otherwise.

[‡]Variance inflation factors between 1.03 – 1.15.

[§]All risk factors were included in backward stepwise multivariable logistic regression (*P* for entry 0.1, *P* for removal 0.2), adjusted for training site (SI vs PS).

duration, and low degree of respect from colleagues were associated with increased burnout, controlled for gender, religion, sleep duration and training site (Table 3).

Discussion

In our programme, stress levels were moderate but the burnout rate was high with significantly more trainees than attendings suffering from burnout. Risk factors included the following: more overnight calls per week and less respect from colleagues were associated with increased stress, while younger age, fewer hours of exercise per week and less respect from colleagues were associated with increased burnout. The high correlation between the CBI and two-item MBI showed that both instruments were measuring the same construct of burnout.

For attending physicians, it appeared that our institution's burnout rates (31.1%) were lower than in the United States (US) (45% to 55%) despite similar work hours (median ~50 hours/week).[2] In comparison, although our psychometric instrument was different, the burnout rate of 31.1% among our attendings was very close to that in Hong Kong public hospital doctors (31.4%), possibly reflecting similar work and cultural milieus in both Asian countries.[7] Our Asian values could have blunted the effect of chronic stress in an academic environment, as prior studies have shown that Chinese work values, comprising collectivism (prioritising group goals over personal interests), endurance (patience and persistence), hard work (thrift and steadiness), and guanxi (relation orientation, respecting social order and protecting others' reputation), contributed to greater overall well-being.[8,9] It is possible that promotion of such values may help reduce stress and burnout in both Asian and non-Asian settings.

Conversely, the burnout rate among our trainees was very high at 71.8%, more than twice that of the attendings, and near the upper limit of that found in a systematic review of burnout during residency training.[10] Trainees could be adversely affected by competition for increasingly limited fellowship and attending positions. For both attendings and trainees, we could show that overnight calls predisposed to increased stress, older age was associated with less burnout, exercise was a protective factor for burnout, and respect was a protective factor for both stress and burnout.[2,11-13]

Our study had several limitations. Firstly, the response rate was only ~40%, but this was comparable to other surveys among US and Hong Kong physicians.[2,7,14] Secondly, we did not control for internal medicine subspecialty as our practice model involved managing both general medical and subspecialty cases, regardless of subspecialty. Thirdly, our cross-sectional survey could only reveal associations and not prove causation.

Table 3. Risk Factors for Overall Burnout as Determined by the Copenhagen Burnout Inventory: Univariate Analysis and Multiple Logistic Regression‡

Risk Factor	Burnout Group (n = 60)	Non-Burnout Group (n = 49)	Univariate *P* Value	Odds Ratio (95% CI)	Multivariate *P* Value
SI vs PS (%)	54 (90.0)	31 (63.3)	0.001*	2.04 (0.57 – 7.33)	0.275
Age in years (SD)	31.9 (6.0)	38.2 (10.2)	<0.001*	0.93 (0.87, 0.99)	0.028*
Female sex (%)	36 (60.0)	15 (30.6)	0.004*	2.49 (0.93, 6.67)	0.071
Has a specific religion (%)	49 (81.7)	43 (87.8)	0.436	0.38 (0.09, 1.61)	0.188
Married (%)	27 (45.0)	31 (63.3)	0.082	-	-
Number of children (IQR)	0 (0 – 2)	0 (0 – 3)	0.007*	-	-
Work hours per week (IQR)	65 (10 – 80)	60 (40 – 80)	0.031*	-	-
Overnight calls per week (IQR)	1 (0 – 2)	0 (0 – 1)	0.003*	-	-
Hours/week spent on exercise (IQR)	1 (0 – 4)	2 (0 – 7)	<0.001*	0.64 (0.45, 0.89)	0.009*
Hours/week spent on research (IQR)	0 (0 – 6)	2 (0 – 10)	<0.001*	-	-
Hours/week spent on teaching (IQR)	2 (0 – 10)	5 (0 – 10)	<0.001*	-	-
Hours of sleep per day (SD)	5.7 (1.2)	6.3 (0.8)	0.007*	0.66 (0.37, 1.16)	0.145
High degree of respect from colleagues† (%)	40 (66.8)	45 (91.8)	0.002*	0.21 (0.06, 0.80)	0.022*
High degree of respect from patients† (%)	43 (71.7)	46 (93.9)	0.003*	-	-
High degree of respect from patients' families† (%)	41 (68.3)	45 (91.8)	0.004*	-	-

CI: Confidence interval; IQR: Interquartile range; PS: Participating site; SD: Standard deviation; SI: Sponsoring institution

*P <0.05.

†Graded on a Likert scale of 0 – 10, then dichotomised to high degree of respect if score was >5, and low degree of respect otherwise.

‡All risk factors were included in backward stepwise multivariable logistic regression (P for entry 0.1, P for removal 0.2), adjusted for training site (SI vs PS).

Conclusion

We hope our results can stimulate academic medical centres to check for and manage the known risk factors of stress and burnout. Since the major source of burnout stemmed from personal burnout, which is a generic measure of physical and psychological fatigue and exhaustion experienced by the person regardless of occupational status, non-work-based approaches would be important. For instance, a 12-week aerobic training programme was shown to reduce overall perceived stress and symptoms of burnout.[12] Given that we found that fewer night calls, greater exercise, and greater respect were associated with less stress/burnout, other solutions might include assigning more physicians to the call roster (thereby decreasing the call frequency per physician), incentivising exercise using monetary and other rewards, promoting a supportive work atmosphere, and conducting team-building activities.[15]

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A Case of Recalcitrant Actinomycosis Unresponsive to Antibiotic Therapy

Dear Editor,

Actinomycosis is a chronic granulomatous disease caused by gram-positive, anaerobic *Actinomyces* bacteria.[1] These commensal microbes can cause opportunistic infection following mucosal breach. Classically, histology shows granulomatous inflammation with abscesses or sinuses containing sulphur granules, bearing clusters of gram-positive, non-acid-fast bacteria with club-shaped ends within dilated infundibulocystic cavities.[2] Treatment involves long-term antibiotics, sometimes with adjunctive surgery.

We introduce an 86-year-old retired bus driver who presented with a 3 x 4 cm discoloured right thigh induration (Fig. 1), stable for more than 30 years without treatment. During the past year, it had occasionally expressed purulent, foul-smelling discharge. He denied prior trauma, soil exposure and insect bites.

Gram stain showed many gram-positive cocci in clusters and few gram-negative bacilli. Cultures yielded methicillin-resistant and sensitive *Staphylococcus aureus* (MRSA and MSSA). An x-ray excluded bony involvement. A skin biopsy was done, showing pseudoepitheliomatous hyperplasia with dilated infundibulocystic cavities containing keratinaceous debris and large clumps of gram-positive bacteria, in association with chronic dermal inflammation (Fig. 1). Together with the clinical presentation, actinomycosis was considered the most appropriate diagnosis.

The patient was given repeat, prolonged courses of amoxicillin-clavulanate, ciprofloxacin and cephalexin. Despite bouts of transient improvement, the lesion continued to enlarge to 11 x 10 cm, 2 years later with visible sulphur granules. Repeat cultures showed MSSA, *Escherichia coli* and *Pseudomonas*. Oral clindamycin and trimethoprim-sulfamethoxazole were given.

Five years after first presentation, the lesion was 40 x 15 cm, from greater trochanter to knee (Fig. 1). Repeat biopsies showed similar histology, but no organisms. Itraconazole was given empirically for occult fungal infection or eumycetoma, without clinical improvement. Cultures again yielded *Actinomyces*, *Enterococcus* and *Pseudomonas*. The patient was restarted on ciprofloxacin, amoxicillin-clavulanate and trimethoprim-sulfamethoxazole.

Actinomycosis is rare and can mimic malignancy and other infections.[3] Moreover, the skin is an unusual site and this patient lacked risk factors, including diabetes and trauma.[4] Co-infection with "companion bacteria" (e.g. *Staphylococci*, *Streptococci*) is common in actinomycosis[5] and may render diagnosis challenging, as isolation of *Actinomyces* is commonly unsuccessful.[1] Less likely differentials include botryomycosis and mycetoma, both also chronic granulomatous infections with sulphur granules. Mycetoma infections are subdivided into eumycetoma, caused by fungal organisms, and actinomycetoma. Actinomycetoma is caused by aerobic, sometimes weakly acid-fast gram-positive filamentous bacteria (e.g. *Nocardia*), in contrast to the *Actinomyces* species implicated in actinomycosis. Another differential is pyoderma vegetans, although histology here showed no suprabasal clefting or acantholysis.

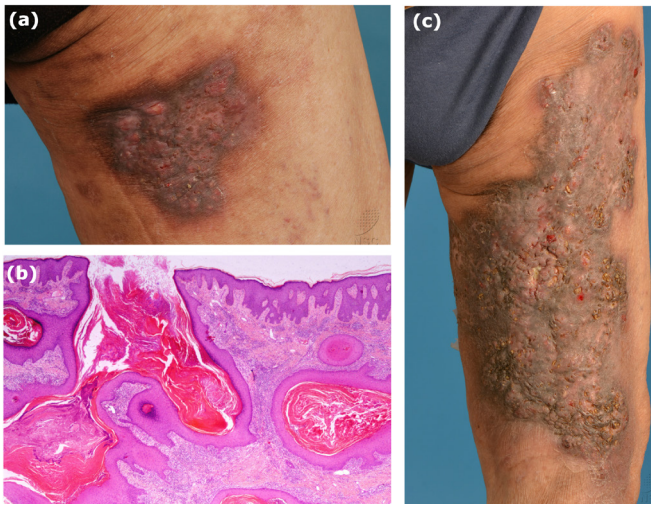

Fig. 1. Slide A shows the patient's first presentation with a 3 x 4 cm hyper pigmented, non-tender induration on the right posterior thigh. In slide B, histology from skin biopsy shows pseudoepitheliomatous hyperplasia with dilated infundibulocystic cavities containing keratinaceous debris, large clumps of gram-positive bacteria and occasional neutrophilic foci. There was a mixed dermal infiltrate of lymphocytes, histiocytes, plasma cells and neutrophils. (Hematoxylin and Eosin stain, magnification x 25). Slide C shows the lesion 5 years later, showing extension with sinus tracts and sulphur granules.

While *Actinomyces* rarely develop penicillin resistance, coverage for co-pathogens is essential.[1] Interestingly, despite multiple prolonged antibiotic courses, this patient's lesion remained progressive. He declined amikacin and spectinomycin, as well as surgical management. Going forward, he will likely require continued long-term antibiotics.

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Persistent Unilateral Conjunctival Inflammation as the First Sign of Granulomatosis with Polyangiitis

Dear Editor,

Granulomatosis with polyangiitis (GPA) or, formerly known as Wegener's granulomatosis, is an autoimmune, small-to-medium sized vessel vasculitic disease that can affect multiple organs, including the eyes.[1] We report an interesting case of atypical persistent unilateral conjunctival inflammation in a patient with previously undiagnosed GPA.

An 83-year-old male presented to the eye casualty with a 4-week history of painful and injected left eye. Previous ocular history included bilateral age-related macular degeneration. Best-corrected visual acuity (BCVA) was 6/60 in the right eye and 6/12 in the left eye. Examination revealed bilateral blepharitis with left conjunctivitis associated with peripheral corneal infiltrates.

The patient was treated for left blepharokeratoconjunctivitis with oral doxycycline, topical steroids and antibiotic drops. The eye improved but there remained a localised persistent, area of fleshy, inflamed conjunctiva superonasally with abnormal-looking vasculatures encroaching onto the cornea after 3 months of treatment (Fig. 1).

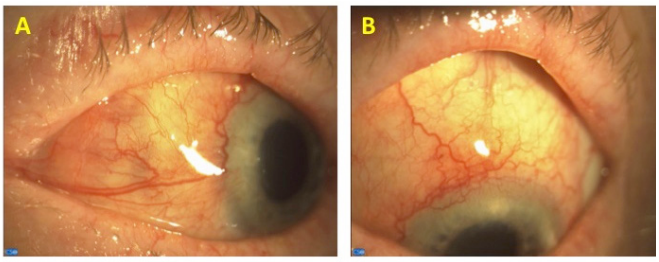

Fig. 1. A and B show patient's persistent conjunctival inflammation superonasally with abnormal-looking vasculatures encroaching onto the cornea of the left eye after 3 months of initial treatment.

A conjunctival biopsy was performed, which revealed chronic inflammatory infiltrates comprising plasma cell, lymphocytes and prominent population of eosinophils in the substantia propria. Such inflammation could be consistent with atopic or rosacea keratoconjunctivitis but an auto-immune/vasculitic screen was recommended as part of the investigation for potential underlying systemic vasculitides affecting the conjunctiva. Vasculitic screen showed low haemoglobin 11.2 g/L (normal: 13-18 g/L), raised erythrocyte sedimentation rate 49 mm/hr (normal: 2-10 mm/hr) and raised antineutrophil cytoplasmic antibodies (ANCA)-proteinase 3 antibodies 25 IU/ml (normal: <2 IU/mL), supporting the diagnosis of GPA. Rheumatoid factor, antinuclear antibodies and ANCA-myeloperoxidase antibodies were negative.

Patient was referred to rheumatology for further assessment, which revealed a recent history of epistaxis and nasal crusting, some extent of Raynaud's disease affecting the fingers and toes, and livedo reticularis affecting the legs and forearms. There was no evidence of pulmonary or kidney involvement. A diagnosis of GPA was made and the patient started on a tapering regime of oral prednisolone and azathioprine. Patient was started on oral prednisolone 40 mg daily for 1 month, then 30 mg daily for 1 month, followed by 5 mg reduction every month thereafter until 10 mg daily. Oral azathioprine was started at 100 mg daily 1 month later after the initial commencement of oral prednisolone.

The conjunctival inflammation improved significantly within a week following the systemic steroids and completely resolved within 2 months. At 2 years follow-up, the patient had come off from oral prednisolone and remained on azathioprine 100 mg daily under the care of rheumatology with no recurrence of ocular inflammation.

Discussion

GPA is a systemic inflammatory condition that is commonly diagnosed at the age of 40 to 55 years old.[2] Ocular manifestations of GPA include episcleritis, scleritis, peripheral ulcerative keratitis, uveitis, retinal vasculitis, and orbital inflammation;[2-4] however, non-specific conjunctivitis manifesting as the isolated finding is rare.[3,4]

Our case highlights the importance of tissue diagnosis and appropriate screening for autoimmune disease in patients with unusual persistent conjunctival inflammation. Collaboration between ophthalmologists and rheumatologists is essential in these cases.

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Painful Rashes on the Palms and Soles

A 72-year-old male of Caucasian descent was referred for consideration of systemic therapy after receiving a diagnosis of hepatocellular carcinoma (HCC). His past medical history was unremarkable with no comorbidities and he was not on any other medications. Computer tomography (CT) scan revealed multifocal HCC, and a biopsy of which confirmed HCC. There was no underlying cirrhosis or features of portal hypertension. His viral hepatitis profile was negative, as were his autoimmune screen. His iron studies, copper levels and thyroid function were all in the normal range. He was well with a performance status of Eastern Cooperative Oncology Group (ECOG) 0. He was started on a trial of sorafenib at a dose of 400 mg twice daily. Nine weeks later, he presented with well demarcated, tender well defined yellowish hyperkeratotic plaques on his plantar surfaces (Fig. 1) and erythematous patches on the palmar surfaces (Fig. 2). It gradually spread to the arms and legs forming pustules and blisters with raw ulcerated surfaces.

What is the most likely diagnosis of his skin condition?

A. Plaque psoriasis
B. Pityriasis rubra pilaris
C. Cutaneous infiltration of malignancy
D. Keratoderma blennorrhagica
E. Palmar-plantar erythrodysesthesia

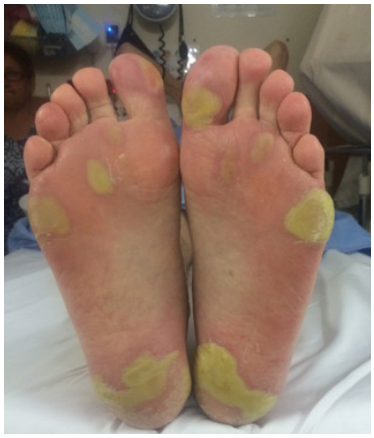

Fig. 1. Symmetrical hyperkeratotic yellow plaques on the plantar surfaces of the soles.

Discussion

Hand-foot syndrome (HFS) or palmar-plantar erythrodysesthesia is an adverse cutaneous reaction seen with multikinase antineoplastic therapy. In our patient, sorafenib which has been approved for use in the treatment of HCC and renal cell carcinomas was the causative drug. Other anticancer drugs commonly implicated in HFS are capecitabine and 5-FU.[1]

Sorafenib is a molecule capable of multilevel kinase inhibition, simultaneously inhibiting molecular components of the Raf-MEK-ERK signalling pathway, abrogating tumour growth and vascular endothelial growth factor receptor (VEGFR-1, VEGFR-2, VEGFR-3,) and platelet-derived growth factor receptor (PDGFR-β). This gives the drug a pro-apoptotic and anti-angiogenic effect.[2] The safety and efficacy of sorafenib in treating HCC was established in the Phase III SHARP Trial (Sorafenib in Advanced Hepatocellular Carcinoma) in patients with advanced disease if they were not eligible for or have had disease progression after surgical or locoregional therapies.[3] In the SHARP Trial, 21% of patients developed HFS and it was severe (grade 3) in 8%. This drug-related adverse event has been previously observed in its use in the treatment of renal cell carcinoma, leading to dose reductions and interruptions in a subgroup of patients.[4]

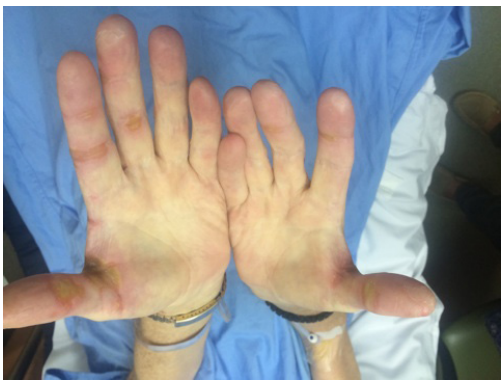

Fig. 2. Palmar erythema were more pronounced on the finger pads.

Answer: E

The diagnosis of HFS is a clinical one based on the temporal relationship with the drug and typical clinical presentation. The pathogenesis remains unclear at present. There are 3 grades used to assess the severity of the lesions. Grade 1 lesions are palmar erythema predominantly on the finger pads and yellow hyperkeratotic plaques with erythematous borders on pressure-bearing areas of the soles.[1] Grade 2 lesions present as palmar erythema with superficial desquamation or tense bullae with mild background erythema.[1] Grade 3 lesions are described as markedly erythematous plaques with discrete, tense bullae.[1] The severity of the lesions tend to be dose-related. In some cases, HFS may have a profound negative impact on the patients' quality of life (QoL). The HFS-14, is a validated tool for the QoL assessment in HFS patients.[5] It can be used by treating physicians to guide them on the appropriate next steps.

HFS side effects have been investigated to correlate to treatment efficacy. In some drugs such as cetuximab and panitumumab in metastatic colorectal cancer, skin rash represents a significant predictor of the efficacy of the drugs.[6,7] The occurrence of skin toxicity represents a predictive factor for survival (HR 0.51; P <0.00001) and progression (HR 0.58; P <0.00001). Similarly, patients who developed moderate or severe rash had an increased chance of response (35 vs 13%; RR 2.23, P <0.00001).[6,7] However, even though it is recognised that skin rash is a common side effect of sorafenib, its ability to serve as a surrogate biomarker for drug efficacy is difficult because the drug has a relatively low objective response rate (ORR) in the order of 2% to 3%.[3]

Two retrospective studies, one conducted in Japan and the other in South Korea, revealed that the occurrence of skin toxicities during sorafenib treatment in HCC is associated with improved overall survival (OS).[8,9] However, a retrospective analysis of skin toxicities during the treatment trial period may have been confounded by an inherent observation bias because patients who are treated for longer periods may be at a greater risk of experiencing toxicities.[8-10] Vincenzi et al[11] examined associations between treatment outcomes and skin toxicities within the first month of treatment. Sixty-five patients who received sorafenib for advanced HCC were enrolled, and early all-grade skin toxicities predicted a significantly improved disease control rate (DCR) and time to progression (TTP) and prolonged OS with borderline significance. The clinical value of an association between skin rash and efficacy remains to be established and further studies need to be done to validate its use as a reliable and predictable biomarker in clinical practice.

Treatment options for HFS vary according to the severity of the lesions. In milder cases, topical therapy consisting of keratolytics, topical steroids and emollients would suffice. In the more severe cases, the causative drug would have to be discontinued as the lesions have the tendency to progress while the patient is on chemotherapy. In our patient, we opted to cease treatment indefinitely. After a 2-week period of cessation of therapy, the rash showed some degree of improvement.

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Large Forehead Nodule with Multiple Facial and Oral Papules

A 25-year-old male presented with an asymptomatic nodule on his forehead. It first appeared 2 years ago and gradually enlarged with time. Physical examination revealed a 13 mm x 15 mm smooth solitary skin-coloured nodule on his forehead (Fig. 1a). He also had several skin-coloured papules on his nose and over his left periocular region (Fig. 1b), oral papillomatosis on his tongue (Fig. 1c) and gums (Fig. 1d) and acral keratosis on bilateral palms (Fig. 1e) and soles. Further examination revealed macrocephaly with an occipital frontal circumference measuring 64 cm and macular pigmentation on glans penis. There were no neurological deficits or cerebellar signs. There were no organomegaly, breast masses, thyroid nodules or palpable lymph nodes. There were also no constitutional or systemic symptoms. Family history was significant for breast cancer in his mother, diagnosed in her 40s. There was no other personal or family history of malignancy. An excision biopsy of the forehead nodule was performed and sent for histopathologic analysis (Fig. 2). A diagnostic punch biopsy of a nose papule was also performed.

What is your diagnosis?

A. Darier disease
B. Cowden syndrome
C. Birt-Hogg-Dubé
D. Brooke-Spiegler syndrome
E. Tuberous sclerosis

Discussion

Cowden syndrome is a rare autosomal dominant disorder first reported in 1963 by Lloyd et al.[1] It is one of the clinical entities in a group of rare syndromes collectively known as phosphatase and tensin homolog (PTEN) harmatoma tumour syndrome (PHTS), characterised by multiple hamartomatous tumours. Mutations in the PTEN gene, a

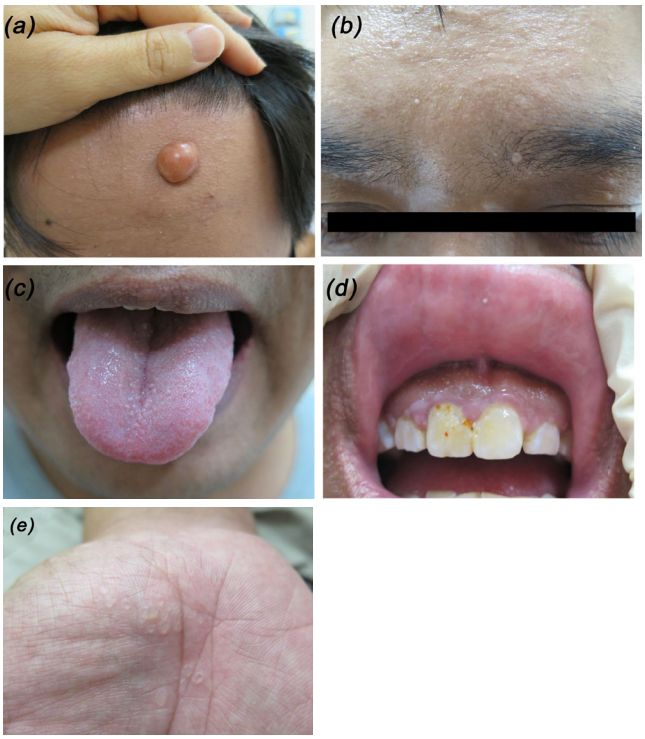

Fig 1. a) Large nodule on forehead; b) facial papillomas; c,d) oral papillomatosis in tongue and gums; e) acral keratoses.

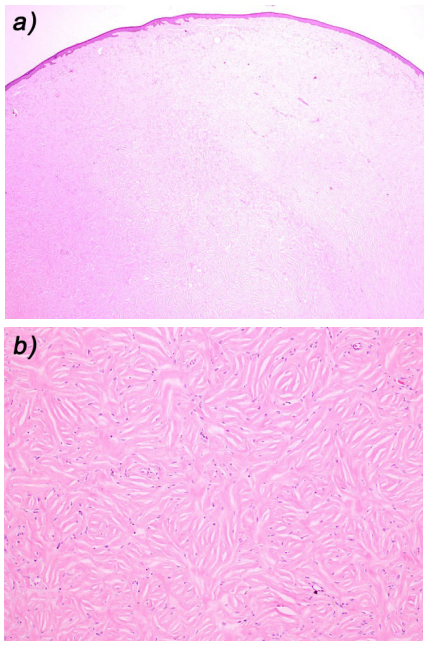

Fig. 2. Excision biopsy of the forehead nodule: a) low power view (x 20 magnification) of a well circumscribed hypocellular nodular fibrous tumour that is composed of collagenous fibres; b) high power view (x 400 magnification) of a prominent storiform growth pattern with elongated clefts between the collagenous bundles, which is characteristic of this tumour.

Answer: B

tumour suppressor gene, results in the dysregulation of the phosphatidylinositol 3-kinase-AKT and mammalian target of rapamycin (mTOR) signalling pathways. This results in dysfunction of cell proliferation, cell cycle progression, and apoptosis, overall contributing to oncogenesis.[2]

The International Cowden Consortium diagnostic criteria proposed by an international group of experts is categorised into pathognomonic criteria, major criteria and minor criteria[3] as presented in Table 1.

Our patient fulfilled operational diagnostic criteria for Cowden syndrome—he had multiple cutaneous facial papules, oral mucosal papillomatosis and multiple palmoplantar acral keratosis bilaterally. In addition, he fulfilled 1 major criteria—macrocephaly (≥97th percentile). He also had macular pigmentation, a feature known to be associated with PTEN mutations. A biopsy of a facial papule (nose) showed a fibrous papule. Although it did not show trichilemmoma, he had fulfilled the other criteria described above. An excision biopsy of the forehead nodule was performed and closed with an advancement flap. Its histopathological examination was consistent with a sclerotic fibroma. Sclerotic fibroma, or storiform collagenoma, is an uncommon cutaneous neoplasm first reported in 1972 by Weary at al.[4] It is characterised histologically by a well circumscribed and non-encapsulated dermal nodule comprising hypocellular sclerotic collagenous bundles with prominent clefts. Although it may occur as a sporadic tumour, there is a known association with Cowden syndrome which further supports the diagnosis in our patient.

As the facial papules were benign and asymptomatic, and the patient was not concerned with his cosmetic appearance, they were left alone. As per screening guidelines advocated by National Comprehensive Cancer Network (NCCN),[3] we completed a full clinical examination with a baseline thyroid ultrasound scan and educated him on the signs and symptoms of cancer. He was also referred to our gastroenterology colleagues for endoscopic evaluation. Last but not least, he was referred to the adult's genetic clinic for counselling and family screening. He underwent genetic testing which showed a deleterious mutation in PTEN gene, confirming the diagnosis of Cowden syndrome.

Table 1. International Cowden Consortium Diagnostic Criteria

Pathognomonic Criteria	**Major Criteria**	**Minor Criteria**
1. Mucocutaneous lesions - facial trichilemmomas - acral keratosis - papillomatous lesions	1. Breast carcinoma	1. Other thyroid lesions (adenoma or multinodular goitre)
2. Lhermitte-Duclos disease (adult)	2. Thyroid carcinoma (especially follicular)	2. Mental retardation (IQ ≤75)
	3. Macrocephaly (occipital frontal circumference ≥ 97th percentile)	3. GI harmatomas
	4. Endometrial carcinoma	4. Lipomas
		5. Fibrocystic disease of the breast
		6. Uterine fibroids
		7. Fibromas
		8. Genitourinary tumours or malformations
Operational Diagnosis		
1. Two or more major criteria		
2. One major and 3 minor criteria		
3. Four minor criteria		
4. Mucocutaneous lesions alone in conjunction with: - ≥6 facial papules (≥3 trichilemmomas) or, - cutaneous facial papules and oral mucosal papillomatosis or, - oral mucosal papillomatosis and acral keratosis or, - ≥6 palmoplantar keratosis.		
For Individuals in a Family in which 1 Relative is Diagnostic for Cowden Syndrome		
• A pathognomonic criterion • Any one major criteria with or without minor criteria • Two minor criteria • History of Bannayan-Riley-Ruvalcaba syndrome (BRRS)		

GI: Gastrointestinal; IQ: Intelligence quotient

Several differential diagnoses were considered during the initial evaluation of this patient. Although Darier disease is associated with acral keratosis, oral and facial papules, our patient lacked the characteristic keratotic crusted reddish-brown papules in the seborrhoeic and intertriginous areas. There were no associated nail changes typical of Darier disease. Patients with tuberous sclerosis typically have facial angiofibromas and gingival fibromas, which may appear similar to facial papules and oral mucosal papillomatosis. However, there was a lack of other supporting cutaneous feature such as ashleaf macules, periungual fibromas and Shagreen patch. Thirdly, Birt-Hogg-Dubé may also present with multiple facial and oral papules. However in this case, although the biopsy of the facial papule did not show trichilemmoma, it did not show fibrofolliculoma or trichodiscomas either, both of which are typical of this condition.

There was no history of any lung problems thus far, suggestive of pulmonary cysts which be found in Birt-Hogg-Dubé. Similarly for Brooke Spiegler (although multiple trichoepitheliomas are seen on the central face), the biopsy was not consistent with this.

Our patient did not have any cylindromas or spiradenomas which are seen in this condition. The nodule on the forehead was consistent with a sclerotic fibroma, with a known association with Cowden syndrome.

As Cowden syndrome is a rare clinical entity with an estimated prevalence of 1 in 250,000, it can pose diagnostic dilemmas when encountered. The accuracy of diagnosis is important, especially as this clinical entity is associated with other malignant conditions.

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