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ABSTRACT

Cardiovascular diseases are one of the most important global medical challenges because of their high rates of morbidity and mortality. In this narrative review, the authors address the most important dermatologic signs that can be present in patients with cardiovascular disease. The early recognition of these underestimated entities is very important as it may lead to an early diagnosis and timely treatment, thus lessening the effects of long-term disease and possibly improving the prognosis.

Keywords: Cardiovascular Diseases; Skin Manifestations

RESUMO

As doenças cardiovasculares são um dos desafios médicos mais importantes a nível mundial devido às suas elevadas taxas de morbilidade e mortalidade. Neste artigo, é feita uma revisão das manifestações cutâneas mais importantes que poderão estar presentes em doentes com doenças cardiovasculares. O reconhecimento atempado destas entidades clínicas é fulcral, uma vez que permite um diagnóstico e tratamento precoces, minimizando os efeitos destas doenças a longo prazo e possivelmente melhorando o prognóstico destes doentes.

Palavras-chave: Doenças Cardiovasculares; Manifestações Cutâneas

INTRODUCTION

Cardiovascular diseases (CVD) are considered a global priority because of their high rates of morbidity and mortality. Current epidemiologic predictions show that the burden of CVD is increasing significantly, and that only 2% to 7% of the population have no cardiovascular risk.¹ A good amount of information about CVD can be obtained through inspection of the patient, which is a frequently overlooked aspect.² General practitioners, internists and dermatologists may frequently be the first physicians to suspect a diagnosis of an underlying CVD by identification of certain cutaneous abnormalities.³⁻⁵ The prompt recognition of these skin manifestations may lead to an early diagnosis and timely treatment, which would then mitigate the effects of long-term disease and improve the prognosis.

This article aims at providing an overview of the dermatologic signs of CVD, including multisystem disorders and inherited diseases that can affect both the heart and the skin, in addition to cutaneous abnormalities due to cardiovascular therapeutics.

GENERAL DERMATOLOGIC SIGNS OF CARDIOVASCULAR DISEASE

Edema

Edema results from accumulation of excessive fluid in the interstitial space.³ Chronic bilateral peripheral edema is located in dependent areas such as the feet and the lower legs, and the sacral region in bedridden patients. It is usu-

ally caused by right-sided heart failure (HF),^{6,7} regardless of its cause,³ or chronic venous insufficiency,⁶ which would be suggested by the presence of varicosities and stasis dermatitis.⁸ Acute unilateral edema of the limbs is usually caused by local venous obstruction,² as in deep venous thrombosis.⁹ Edema of the head, neck and upper extremities is seen in superior vena cava syndrome, subclavian vein thrombosis, or lymphatic obstruction.²

Cyanosis

Cyanosis is a bluish discoloration of the skin that occurs when there is at least 5 g/dL of deoxygenated hemoglobin. Cyanosis may be central or peripheral.²⁻⁴ Central cyanosis is the result of an abnormal hemoglobin derivative or decreased arterial oxygen saturation (intracardiac right-to-left shunts or intrapulmonary shunts).¹⁰ Therefore, both the mucous membranes and the skin are affected.²⁻⁴ Peripheral cyanosis occurs in patients with normal arterial oxygen saturation, but with decreased blood flow and increased oxygen extraction, and is caused by cold exposure, shock, HF and peripheral vascular disease (PVD). This type of cyanosis is detected on the nose, lips, earlobes, and fingertips,^{2,5} but the mucous membranes are spared.^{4,10} Differential cyanosis involving the lower extremities, but sparing the upper extremities, may occur in patients with patent ductus arteriosus.⁴

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Figure 1 – Digital clubbing: watch-glass nails and drumstick fingers

Digital clubbing

Clubbing is characterized by ‘watch-glass nails’ and drumstick fingers (Fig. 1).^{2,3} The angle between the nail and the cuticle (Lovibond’s angle) becomes convex and the window between the thumbnails when held together in profile is lost (Schamroth’s sign).^{2,11} Digital clubbing is characterized by proliferation of the connective tissue between the nail matrix and the distal phalanx⁴ and is associated with cyanotic congenital heart disease (left-to-right shunts such as tetralogy of Fallot and transposition of the great vessels), myxoma of the left atrium and subacute bacterial endocarditis.^{4,11} Differential clubbing (present on the toes but not fingers) can be seen in patients with patent ductus arteriosus.²

DERMATOLOGIC MANIFESTATIONS OF SPECIFIC CARDIOVASCULAR DISEASES

1. Coronary artery disease

Coronary artery disease (CAD) is rapidly increasing in prevalence around the world and is the leading cause of death in developed and developing countries.¹² Certain cutaneous markers are associated with atherosclerosis and can help identify early asymptomatic CAD in high-risk individuals.¹³

Hyperlipoproteinemia and xanthomas

Xanthomas are localized lipid infiltrates found in the skin, tendons and fascia, and are frequently the first sign of hyperlipidemia, especially familial forms.¹⁴ Their recognition should lead to laboratory evaluation of cholesterol and triglyceride levels,³ as they can be associated with acceler-

ated atherosclerosis and myocardial infarctions.⁴ There are several types of xanthomas. Plane xanthomas are soft yellow plaques that occur on the neck, palms (palmar crease xanthomas), and eyelids (xanthelasmas).^{3,4,13,14} Tendinous xanthomas are painless nodules most frequently involving the Achilles’ tendons, extensor tendons of the elbows and knees.³ Tuberous xanthomas are yellow painless nodules of the elbows, knees, knuckles, buttocks, and heels. They are softer than tendinous xanthomas and not attached to the tendon.³ Eruptive xanthomas are associated with uncontrolled diabetes mellitus and hypertriglyceridemia,¹⁵ and appear as a sudden eruption of multiple erythematous-yellow dome-shaped papules involving the extensor surfaces of the extremities and buttocks. They tend to regress rapidly upon treatment.^{3,4}

Earlobe crease

The association between earlobe crease (Frank’s sign) and CAD remains controversial.^{3,4,16} Some studies suggest that the earlobe crease is merely a result of aging,¹⁷ while others propose that it is an independent marker of CAD, conferring increased risk of acute myocardial infarction and cardiovascular death.^{3,18,19} Clinically, it is an acquired diagonal deep wrinkle in the lobar portion of one or both auricles.¹⁴ Although the pathogenesis remains unknown, biopsies of the earlobe demonstrated small artery arteriosclerosis and generalized elastin loss. These findings may support that the ear lobe crease is a sign of microvascular disease with occlusion of end-arteries, such as in the earlobes and heart.¹⁹



Figure 2 – (A) Acanthosis nigricans: thickened, dark brown, velvety plaques on the posterior aspect of the neck; (B and C) Skin tags (soft fibromas): small, soft skin color papules and nodules over the lateral aspects of the trunk.

Acanthosis nigricans

Acanthosis nigricans (Fig. 2A) is characterized by dark brown velvety and papillomatous plaques in the neck and intertriginous areas.¹⁵ Acanthosis nigricans is not a disease *per se*, but a cutaneous sign of insulin resistance, diabetes and metabolic syndrome, which are great risk factors for CAD. The recognition of this cutaneous sign should lead to a prompt cardiovascular assessment.^{13,20}

Skin tags

Skin tags or soft fibromas (Figs. 2B and 2C) are the most common fibroepithelial tumors of the skin. Clinically, they are small, soft tumors appearing over the lateral aspects of the neck, back, axilla, and trunk. Some studies found an association with hypertension, hyperlipidemia, insulin resistance and diabetes.²⁰

2. Valvular diseases

Mitral valve stenosis

Mitral stenosis is characterized by narrowing of the valve orifice. In advanced disease, patients may have a malar flush, with plethoric cheeks, punctuated by blueish patches: the typical 'mitral facies', which is probably related with impaired cardiac output.^{4,21}

Aortic valve regurgitation

Aortic regurgitation is the diastolic reversal of blood flow from the aorta into the left ventricle. The physical examination in these patients may reveal diagnostic clues: Quincke's pulse, an intermittent flushing of the nail beds that occurs when pressure is applied to the tip of the nail, which is synchronous with the heart rate.^{4,22}

3. Infectious diseases

Infective endocarditis

Infective endocarditis (IE) results from the proliferation of microorganisms in the heart valves (both native and prosthetic), the ventricular septum and intracardiac devices. The characteristic lesion is the vegetation (a mass of fibrin, platelets, and microorganisms). Embolization of vegetation fragments results in distant infection and infarction via the deposition of immune complexes and bacterial antigens.²³ There are several skin manifestations of IE, and a complete dermatologic examination is mandatory.²⁴ Osler nodes are painful erythematous nodules on the pulp of fingers and toes, which disappear after a few days without sequelae. Janeway lesions are nontender, red macules on the palms and soles and tend to last longer. Though less specific, petechiae are the most common cutaneous sign of endocarditis, and they are seen on the conjunctivae, oral mucosa, and upper extremities.^{2-4,25} A prospective observational analysis²⁴ found that patients with dermatologic manifestations had significantly more extracardiac complications, and cerebral complications in particular. The presence of skin lesions may suggest a state of active embolization and be a sign of IE severity.^{24,25}

4. Inherited and/or congenital diseases

Marfan syndrome

Marfan syndrome (MFS) is an autosomal dominant (AD) connective tissue disease.^{3,26} Its major clinical aspects are musculoskeletal, cardiovascular, cutaneous, and respiratory.^{26,27} Patients with MFS are tall and thin, with scarce subcutaneous fat. They have a long and narrow face with crowded teeth, excessively long upper and lower extremities, long fingers (arachnodactyly), hyperextensible joints and altered body segments ratios such as arm span exceeding height. A sunken chest (*pectus excavatum*) or a protruding chest (*pectus carinatum*) are also common features. Other cutaneous manifestations include *striae distensae* located in the chest, shoulders, buttocks and thighs.¹⁵ These patients may also have elastosis perforans serpiginosa (Fig. 3A): a rare skin disorder in which abnormal elastic tissue fibers pass from the dermis to the epidermis, presenting as a cluster of

small papules in a serpiginous pattern.^{2,4,26,27} Cardiovascular manifestations are the main cause of morbidity and mortality.^{26,27}

Ehlers-Danlos syndromes

Ehlers-Danlos syndromes (EDS) (Figs. 3B and 3C) are a genetically heterogeneous group of connective tissue inherited diseases that are characterized by joint hypermobility, anomalous skin texture and tissue fragility.^{4,28} The clinical manifestations vary widely in severity depending on the disease subtype. Cutaneous findings include thin stretchable skin with visible subcutaneous vessels, atrophic and cigarette-paper scars, bruises and hyperpigmentation over the bony prominences and molluscum pseudotumors on the forearms. Cardiovascular manifestations include mitral valve prolapse, aortic root enlargement and bicuspid aortic valve.^{2,4,28}

Cutis laxa

Cutis laxa is an elastin disorder [acquired or inherited (AD, recessive or X-linked)], in which skin loses its elasticity.^{3,5} Clinical manifestations may be present at birth or develop during childhood. Children may appear prematurely aged and there are skin redundant folds hanging from the face and abdomen, with progressive looseness of the skin. These patients may have *cor pulmonale*, as well as aortic aneurysms and pulmonary artery stenosis.^{3,29,30}

Pseudoxanthoma elasticum

Pseudoxanthoma elasticum is an inherited disease of the connective tissue that affects the cardiovascular system, the eyes and the skin, causing fragmentation and calcification of elastic fibers in the mid-dermis and calcification of small and medium size arteries.^{3,4} The typical skin findings are waxy yellow papules that coalesce into plaques on elastic skin, affecting the flexure areas, especially the neck. The skin becomes inelastic and lax, looking like 'plucked chicken skin'.³⁻⁵ Cardiovascular manifestations are common and include mitral valve prolapse and stenosis, CAD, PVD, cardiomyopathy and hypertension.³⁻⁵ In addition, ophthalmologic findings are also hallmarks of the disease, including the development of angioid streaks and neovascularization in the retina followed by a retinal hemorrhage and scarring, with gradual loss of central and night vision and, ultimately, blindness.³¹

LEOPARD Syndrome

LEOPARD syndrome [lentiginos, electrocardiographic (EKG) abnormalities, ocular hypertelorism, pulmonary valve stenosis, abnormal genitalia, retardation of growth and deafness]²⁻⁴ is an AD disease. Its cutaneous findings include multiple lentiginos (Figs. 3D and 3E), mainly on the face, neck and upper trunk, sparing the lips and oral mucosa.¹⁵ They are present in early childhood, and become darker and more abundant with age. A triangular-shaped face with frontal bossing, hypertelorism and low-set ears is typical. These patients may also have axillary ephelides,



Figure 3 – (A) Elastosis perforans serpiginosa: a cluster of small papules grouped in a serpiginous pattern; (B and C) Ehlers-Danlos syndromes: joint hypermobility and hyperpigmentation over bony prominences of the hands; (D and E) LEOPARD syndrome: multiple lentiginos on the upper trunk.

and café-au-lait spots.^{2,3,32} The cardiovascular involvement in these patients is the major cause of morbidity and mortality and the most common heart defect is pulmonary valve stenosis.^{3,4}

5. Vascular diseases

Chronic venous insufficiency

Patients with untreated chronic venous insufficiency may suffer from multiple sequelae including stasis dermatitis, lipodermatosclerosis, and venous ulcerations,^{33,34} with a common mechanism – venous hypertension (from backward venous flow) leading to chronic inflammation.^{33,35,36} Stasis dermatitis is a hallmark of venous disease, and its prevalence increases with age. Clinically, it appears as deficiently demarcated bilateral erythematous-squamous plaques on the lower limbs. Hyperpigmentation results from deposition of hemosiderin from the extravasated erythrocytes. Patients may have pruritus, cramps, restless legs and swelling.^{33,35,37} With progressing disease, lipodermatosclerosis (fibrosis of the skin and subcutaneous tissue) may appear – the skin becomes rigid, indurated, fixed and shiny, contracting the subcutaneous tissue, which leads to shrinking of the lower leg volume, giving it an inverted bottle shape.³⁴ With gradual loss of epithelium, venous ulcers may arise.^{33,34}

Antiphospholipid syndrome

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by venous, arterial and microvascular thrombosis and obstetric complications in the presence of persistent antiphospholipid antibodies. APS is frequently associated with systemic lupus erythematosus (SLE) – secondary APS – but may also occur in the absence of other autoimmune diseases – primary APS.^{38,39} Cutaneous manifestations may be the presenting feature of this disease. Livedo reticularis is the most frequent dermatologic finding of APS, usually widespread. Cutaneous necrosis and skin ulcers occur due to microvascular occlusion and appear as noninflammatory retiform purpura followed by a black necrotic plaque.^{38–40}

MULTISYSTEMIC DISEASES THAT AFFECT THE HEART AND THE SKIN

1. Acute rheumatic fever

Acute rheumatic fever (ARF) is a postinfectious consequence of group A beta-hemolytic streptococcal pharyngitis.^{3,41} ARF occurs because of an autoimmune response in which antibodies against streptococcal antigens cross-react to similar antigens in human tissues – molecular mimicry.^{3,41,42} The clinical manifestations of ARF are summarized in the Jones criteria: fever, migratory arthritis, chorea, rash,

subcutaneous nodules and carditis.^{3,41,43} The cutaneous manifestations of ARF include erythema marginatum and subcutaneous nodules, which are highly specific. Erythema marginatum is characterized by pink evanescent nonpruritic macules and papules involving the trunk and proximal extremities, which spread outwards into annular or polycyclic plaques in a centrifugal manner. As the lesions advance, the edges become raised and red and the center clears, becoming pale. Subcutaneous nodules are firm, painless protuberances seen on the extensor surfaces of the knees, elbows and wrists and are mostly seen in patients who have carditis.^{3,41,43} Carditis is a major manifestation of ARF and may involve the endocardium, myocardium and pericardium – pancarditis. Valvulitis (causing mitral regurgitation) is the most consistent feature,⁴³ and is responsible for the cardiovascular morbidity and mortality in ARF.³ The valvular damage may persist, resulting in chronic rheumatic heart disease.^{41,43}

2. Syphilis

Syphilis is a sexually acquired infection caused by *Treponema pallidum*. It is characterized by a variety of clinical manifestations and involvement of multiple organ systems. If left untreated, chronic syphilis typically has intermittently active disease periods with primary, secondary, and tertiary stages as well as a latent (asymptomatic) period of variable length that occurs between primary and secondary stages (early) or before the onset of tertiary syphilis (late). Mucocutaneous manifestations vary widely. The primary stage of syphilis manifests as an indurated, painless, ulcerative chancre. Secondary syphilis occurs three to 12 weeks after the chancre and is characterized by a diffuse red-brown macular exanthema on the trunk and extremities (typically affecting palms and soles), associated with malaise, myalgia, low-grade fever and generalized lymphadenopathy. Tertiary syphilis is a systemic, multiorgan disease that occurs after a period of years or decades, including neurosyphilis (general paresis or tabes dorsalis), cardiovascular syphilis, or gummatous syphilis (a proliferative granulomatous process). Cutaneous manifestations of this late stage include nodoulcerative or gummatous lesions. Cardiovascular syphilis occurs 15 to 30 years after infection and may cause aortic aneurysms, aortic insufficiency, and myocarditis.^{44,45}

3. Lupus erythematosus

Lupus erythematosus (LE) is an autoimmune disease with a variable clinical course.⁴⁶ LE may cause severe systemic organ involvement (SLE) or affect only the skin – cutaneous lupus erythematosus (CLE).⁴⁷ Cutaneous manifestations in SLE occur in 80% of patients and are the presenting feature in 25%.^{4,5} CLE can be divided into acute, subacute and chronic forms, with decreasing probability of association with systemic disease.⁴⁷ Acute CLE is frequently associated with active SLE, it is sun-induced, transient and resolves without scarring – the malar butterfly erythematous rash is the characteristic feature. Subacute CLE (Fig. 4A)

is characterized by arciform erythematous lesions involving the face, neck, upper trunk and shoulders. The most common form of chronic CLE is discoid lupus (Fig. 4B), which consists of erythematous scaly plaques with central atrophy and hypopigmentation, mainly on the head and neck.⁴⁷ Other nonspecific features of LE include splinter hemorrhages, red lunulae, oral ulcers, and alopecia.^{2,4,47} Cardiac complications occur in half the patients with SLE and cause high morbidity and mortality. Pericarditis with pericardial effusion is the most common cardiac manifestation.^{5,46,48}

4. Kawasaki disease

Kawasaki disease is an immune-mediated vasculitis of children under the age of five years. Although the etiology remains unknown, it is probably caused by an infectious trigger generating an abnormal immune response in genetically predisposed individuals. This disease may resolve without treatment, but serious cardiac sequelae may arise in the absence or delay of adequate treatment.^{49,50} Diffuse maculopapular rash can occur within the first five days after the onset of fever. Extremity changes appear later – edema and erythema of the hands and feet, involving palms and soles, with ensuing desquamation beginning in periungual areas.³ Kawasaki disease is one of the leading causes of acquired cardiac disease in children,⁵⁰ and coronary aneurysms are the most significant cardiac complication, developing in up to 25% of patients.^{3,49}

5. Systemic sclerosis/scleroderma

Systemic sclerosis (SS) is an autoimmune disease characterized by widespread skin and internal organ fibrosis.⁵¹ Cutaneous SS may be classified as limited or diffuse. Scleroderma is a prime feature of this disease. The limited form – symmetrical thickening of distal extremities and the face, with sclerodactyly, calcinosis cutis, and trophic ulcers – does not extend proximal to elbows and knees, or involve the trunk. Diffuse cutaneous SS is characterized by rapid symmetrical fibrosis of the distal and proximal extremities, with face and trunk involvement. Early skin findings on the hands include erythema, Raynaud's phenomenon and dilated nail-fold capillary loops. Typical facial features are shiny skin, loss of wrinkling, and puckering around the mouth. Cutaneous disease subtype has prognostic implications – in diffuse type, internal organ lesion is earlier and more severe.^{2,4,51} Cardiovascular complications may arise with fibrotic visceral damage – fibrosis of the conduction system leads to arrhythmias and sudden death. Pulmonary hypertension with *cor pulmonale*, diastolic dysfunction, and HF may occur.^{4,5,51}

6. Sarcoidosis

Sarcoidosis is a systemic granulomatous disease of unclear etiology. This disorders mostly involves the lungs (90% of patients) and the thoracic lymph nodes, presenting with lung infiltrates and bilateral hilar lymphadenopathy, but the skin and the cardiovascular system may also be involved.^{5,52} Skin features are the most common



Figure 4 – (A) Cutaneous lupus erythematosus: subacute cutaneous lupus erythematosus (erythematous arciform plaques on the upper trunk and shoulders); (B) Cutaneous lupus erythematosus: chronic cutaneous lupus erythematosus (discoid lupus); (C) Dermatomyositis: Gottron's papules on the dorsal aspects of the hands.

extra-thoracic manifestations,¹⁶ and are classified as specific or nonspecific, depending on whether non-caseating granulomas exist on skin biopsy. Erythema nodosum is the most frequent nonspecific and acute cutaneous feature. It is characterized by extremely tender subcutaneous erythematous nodules, mostly on the extensor surfaces of the limbs, often associated with fever and arthralgia. The most common specific lesions are symmetric granulomatous papules and plaques, mainly on the face, trunk, or extremities. Chronic sarcoidosis manifests with lupus pernio (indu-

rated bluish plaques on the nose).^{52,53} Cardiac involvement (cardiomyopathy, conduction disturbances and ventricular arrhythmias) may be occult, but is associated with poor prognosis.⁵²

7. Dermatomyositis

Dermatomyositis (DM) is an idiopathic myopathy, characterized by distinct skin lesions and clinically heterogeneous systemic manifestations. Cutaneous manifestations can be divided into pathognomonic, characteristic,

compatible, less common, rare and non-specific. Pathognomonic manifestations include: Gottron's papules (violaceous plaques overlying the metacarpophalangeal and proximal interphalangeal joints of the hands) (Fig. 4C), Gottron's sign (erythematous plaques over the extensor surfaces of elbows and knees) and heliotrope rash (periorbital erythema with edema). Characteristic skin features include nail-fold changes (periungual erythema and telangiectasias), shawl sign (violaceous plaques on the neck, shoulders and upper back), V sign (erythematous plaques on the lower anterior neck and upper back), and Holster sign (symmetric poikiloderma – hypo- or hyperpigmentation, telangiectasia, and atrophy (reticulated, livedoid or linear) – on the hips and lateral thighs). Other less frequent skin changes are vesiculobullous or ulcerative lesions, cutaneous vasculitis, calcinosis cutis, mechanic's hands (hyperkeratosis and fissuring of fingers and palms), deck-chair sign (erythematous eruption sparing transverse skin folds), and Raynaud's phenomenon. The clinical course of skin lesions does not necessarily parallel that of muscle disease and may precede or follow myositis. Cardiac involvement may develop at any time, with subclinical diastolic dysfunction, myocarditis, myocardial fibrosis, arrhythmias, and HF.^{54,55}

DERMATOLOGIC MANIFESTATIONS OF CARDIOVASCULAR THERAPEUTICS

1. Bypass surgery

Patients who undergo bypass surgery are at risk of developing various cutaneous abnormalities. The great saphenous vein is usually used as conduit in coronary revascularization. Vein graft dermatitis may occur months after bypass surgery: a reddish-brown, scaly, fissured dermatitis along the distal portion of well-healed saphenous vein graft scar.^{3,5,56}

2. Drugs

Many cardiovascular therapeutic drugs may have cutaneous adverse effects. Angiotensin-converting enzyme

inhibitors may cause angioedema. Heparin-induced skin necrosis may occur as a result of hypersensitivity angiitis. Patients with long term use of amiodarone can sometimes develop blue dermal melanosis of the face, mainly in sun-exposed areas. A lupus-like syndrome may occur during treatment with amiodarone, procainamide and hydralazine. Beta-blockers and calcium channel blockers may exacerbate psoriasis or cause new psoriasiform eruptions. Calcium channel blockers such as amlodipine may cause bilateral malleolar edema due to their vasodilatory effect. Thiazide diuretics are classified as sulfonamides and they can produce several types of eruptions in patients previously sensitized to other sulfonamide drugs.^{2,57–59}

AUTHOR CONTRIBUTIONS

CB: Conception of the work, draft of the manuscript, literature review.

RP, CQ: Literature review, critical review of the manuscript.

PF, LMF: Conception of the work, literature review, critical review of the manuscript.

PATIENT CONSENT

Obtained.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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