Transplant International

Transplant International ISSN 0934-0874

REVIEW

Nonneoplastic mucocutaneous lesions in organ transplant recipients

Claudio Ponticelli[1] and Pier Luca Bencini[2]

1 Division of Nephrology, Istituto Scientifico Humanitas, Rozzano, Milan, Italy
2 Istituto di Chirurgia e Laser Terapia in Dermatologia (ICLID), Milan, Italy

Keywords
fungal infections, mucocutaneous lesions, transplant complications, transplantation and skin lesions.

Correspondence
Claudio Ponticelli MD, Istituto Scientifico Humanitas, Via Manzoni 56, 20089 Rozzano, Milan, Italy. Tel.: +39 02 26112952; fax: +39 02 26112951; e-mail: claudio.ponticelli@fastwebnet.it

Conflict of interest
CP is a consultant of Novartis Italy.

The authors equally contributed to the preparation of the manuscript.

Received: 27 April 2011
Revision requested: 22 June 2011
Accepted: 6 July 2011
Published online: 2 August 2011

doi:10.1111/j.1432-2277.2011.01308.x

Summary

Nonneoplastic mucocutaneous lesions are frequent in organ transplant recipients. Many of them are caused by a direct toxicity of immunosuppressive drugs, in particular glucocorticoids and cyclosporine. The effects of these agents are dose- and time-dependent. Glucocorticoids can cause acne, Cushingoid appearance, irregular purpuric areas, friable skin, and wide and violaceous stripes. Cyclosporine can cause hypertrichosis, pilosebaceous lesions, and gum hypertrophy. Patients with esthetic changes may show poor adherence to treatment with these immunosuppressive agents that may lead to progressive graft dysfunction. Apart from this direct toxicity, vigorous immunosuppression may render the transplant recipients more susceptible to mucocutaneous infections. Fungal infection, viral warts, and bacterial folliculitis are the most frequent types of mucocutaneous infection. Some fungal infections, such as oral candidiasis and pityriasis versicolor, are relatively trivial, but other mycotic infections can cause severe or disfigurating lesions. Among viral infections, warts and condylomata caused by human papilloma virus are frequent and may favor the development of nonmelanoma skin cancer. Bacterial infections are usually trivial in the early period after transplantation, being represented almost exclusively by folliculitis. However, subcutaneous infections may cause a necrotizing fasciculitis which is a life-threatening disorder, usually sustained by polymicrobial pathogens.

Nonneoplastic cutaneous or mucosal complications are frequent in organ transplant recipients. In a systematic overview made in Leiden, 591 nonmalignant skin diseases were registered in 1768 (33%) organ transplant recipients followed over 13 years [1]. Smaller series reported that the prevalence of nonmalignant skin lesions in transplant recipients may range between 49% and 87% [2–5]. The lesions are mainly related to the prolonged use of immunosuppressive drugs, but an important contributing role may also be played by exposure to sunlight and viral infections. Although the pathogenesis of these lesions is often multifactorial, we will separate them into lesions caused by drugs and by infections.

Drug-related skin lesions (Table 1)

Calcium channel blockers can cause some cutaneous abnormalities, including photo-damage of the head and neck, teleangiectasia, and solar elastosis [6] as well as gingival hyperplasia [7]. However, most skin lesions in renal transplant recipients are caused by immunosuppressive drugs, in particular glucocorticoids and cyclosporine. An important consequence of the esthetic changes caused by these agents is a poor adherence to treatment which represents a major cause of graft failure [8].

Glucocorticoids

Renal transplant recipients given glucocorticoids may show a number of dermatological lesions which are related to the doses and the time of exposure of these agents. While the doses of glucocorticoids used in transplantation were very high in the recent past, the current immunosuppression is based on low doses of glucocorticoids and some units even treat transplant recipients with steroid-free regimens. As a consequence, the skin changes

Table 1. Main skin and mucosal abnormalities related to the use of immunosuppressive drug.

Glucocorticoids	Acne
	Cushingoid appearance
	Bateman's purpura and skin atrophy
	Striae rubrae
	Hair growth
Cyclosporine	Hypertrichosis
	Sebaceous hyperplasia
	Alopecia
	Skin hyperpigmentation
	Gum hyperplasia
Tacrolimus	Alopecia
	Atopic dermatitis
mTOR inhibitors	Aphtous stomatitis
	Acne
	Nail alterations
Azathioprine	Thinning of the hair
Mycophenolate salts	Aphtous ulcers
	Onycholysis

caused by glucocorticoids are today less frequent and severe. The most common complication is acne, which is usually dose-related. Acne occurs early on the cheeks, forehead, chin and chest. Rarely the lesions may progress to nodulocystic transformation (acne conglobata). The severity of acne tends to decrease when the doses of glucocorticoids are reduced. Doxicycline, 100 mg daily, may be effective in reducing acne. Spironolactone is also an effective alternative treatment in women while it should not be used in men because of the risk of gynaecomastia, or in pregnant women because of its teratogenic effects [9]. The most potent agent for treatment of acne is isotretinoin which causes apoptosis of sebocytes by increasing the skin surface levels of neutrophil gelatinase-associated lipocalin [10].

A typical side effect of glucocorticoids is represented by Cushingoid appearance, with facial and neck fullness, buffalo hump, increased supraclavicular and suprasternal fat, and trunkal obesity. These features are caused by abnormalities in fat distribution and are particularly frequent in the post-transplant period, when higher doses of glucocorticoids are used. In the long term, when the doses are reduced, these lesions may spontaneously disappear but some patients may maintain a Cushingoid appearance despite the low dosage of prednisone.

Bateman's purpura and severe skin atrophy are almost constantly seen in patients receiving a prolonged treatment with glucocorticoids. Bateman's purpura consists of irregular purpuric areas that develop spontaneously or after minor trauma on the extensor surfaces of the hands, forearms, and legs, often with spontaneous star-shaped pseudo-scars. Skin atrophy is characterized by increased brittleness and reduced thickness of the skin. Topical retinoic acid at concentrations ranging from 0.01% to 0.05%, may improve skin atrophy. Some patients, however, complain of irritation. Ammonium lactate 6–12% creams are usually better tolerated.

Striae rubrae are wide and violaceous stripes, mainly located over the abdomen, thighs, and buttocks. Children and women receiving high-dose prednisone are particularly prone to this complication. Treatment is difficult. A mild improvement of *striae rubrae* may be obtained with fractional photothermolysis [11], but there is no experience of this treatment in transplant patients. Some patients may have increased hair growth mainly on the face and back.

Cyclosporine

Many skin complications of cyclosporine are dose-dependent and are less frequent today with the lower dosages used by most transplant units. A well-known complication of cyclosporine is hypertrichosis, characterized by thick and pigmented hair appearing over the trunk, back, shoulder, arms, neck, forehead, helices, and malar areas. It is particularly disturbing in black-haired women and in children. Hypertrichosis is usually dose-dependent and is particularly frequent and severe in the pediatric age. Some investigators reported that in children, it is more related to the age than the dosage [12], but others found a strict correlation between hypertrichosis and blood levels of cyclosporine also in children [13]. A possible mechanism for cyclosporine-induced hypertrichosis is the increased activity of alpha-reductase, an enzyme that transforms androgens into dihydrotestosterone in peripheral tissues [14]. Treatment with finasteride, an inhibitor of alpha-reductase successfully used in patients with idiopathic hirsutism may be helpful [15]. Depilatory cream or shaving with an electric razor can also be used to remove excessive hair. Long pulsed lasers emitting wavelenghts targeting hair melanin are very useful in our experience to obtain long-term epilation in kidney transplant patients. In resistant cases, patients may be switched from cyclosporine to tacrolimus which does not cause hypertrichosis [16].

Pilosesebaceous lesions are also quite frequent, probably because cyclosporine, which is highly lipophilic, may partly be eliminated through the sebaceous glands and can exert a direct action on pilosebaceous unit. Sebaceous hyperplasia, epidermal cysts, and pilar keratosis have been reported in 10–20% of patients treated with cyclosporine, but it can be difficult to discern whether these lesions should be attributed to cyclosporine, to glucocorticoids, or to both drugs. Rarely, typical follicular changes different from those observed in hypertrichosis or pilar keratosis can be observed. This particular toxicity is seen after

many months of treatment at excessive plasma concentrations. The disorder may be explained by the fact that cyclosporine extends the anagen phase of the follicular cycle so inducing toxic follicular dystrophy at higher tissue concentrations [17].

Alopecia areata and universalis have also been observed. Accelerated male-pattern balding may occur. Skin hyperpigmentation and bullous or vegetative lesions have also been reported in cyclosporine-treated patients [18]. Cyclosporine may also be responsible for acne.

Gum hyperplasia occurs in about one-third of transplant patients treated with cyclosporine. It is often associated with elevated trough blood levels of cyclosporine and is frequent in children [12]. It is caused by hyperplasia of epithelial and connective tissue components as well as by altered extracellular metabolism. This complication generally occurs after 3 or more months of treatment and can be worsened by the concomitant administration of calcium channel blockers or phenytoin [19]. The incidence of gingival hyperplasia seems to be more frequent in patients with chronic graft dysfunction [20]. Gingival overgrowth is at least partially preventable with careful oral hygiene. Initially, a hyperplasia of the anterior interdental papillae occurs which subsequently spreads to the whole gum also involving the inner side. A 5-day treatment with azythrocin, a macrolide antimicrobial agent, may improve the subjective symptoms and the clinical picture [21,22]. The most severe cases require gingivectomy [23]. The possibility that a gingival Kaposi's sarcoma may mimick a cyclosporine-related gingival hyperplasia should be taken into account.

Tacrolimus

Despite the similar mechanism of inhibition of calcineurin, tacrolimus gives fewer skin abnormalities and does not cause gingival hyperplasia. However, cases of alopecia [24,25] and severe atopic dermatitis [26]. have been reported in transplant patients treated with tacrolimus.

mTOR inhibitors

The use of sirolimus or everolimus is frequently associated with skin disorders and mucositis, [27,28]. Aphtous stomatitis with mouth ulcers can develop immediately after the introduction of a loading dose sirolimus, suggesting that the toxic effect on oral mucosa may be dose-dependent. Oral ulcers have been reported to occur in up to 1/4 of patients treated with mTOR inhibitors in association with mycophenolate [29]. Mucosal ulcers are usually self-limited but they may last for several days and have a high risk of recurrence [28]. This may lead the patient to a poor adherence to treatment. Acne-like eruptions has been reported to occur in 13–46% of patients treated with sirolimus [28]. Follicular acneiform eruptions [30] and ulcerating debilitating maculopapular rash [31] severe enough to necessitate cessation of sirolimus in renal recipients have been described. A high rate of nail alterations, including onychomalacia, onychorrexis, leukonychia, and onycholysys has been reported in renal transplant recipients treated with sirolimus [32].

Azathioprine

Azathioprine may cause thinning of the hair and scalp hair loss [33]. Rarely, it may also be responsible for changes of color or texture of the hair.

Mycophenolate salts

Aphtous ulcers are relatively frequent and often recur in patients treated with mycophenolate particularly in association with sirolimus or everolimus [28,29,34]. Rare cases of mycophenolate-associated onycholysis have also been reported [35].

Infections

Cutaneous infections can occur in 66–80% of transplant patients. [4,5,36,37].

Fungal infection, folliculitis and viral warts are the most frequent types of cutaneous infection [38]. Some infections, such as candidal infection, herpes simplex infection, and impetigo are most frequent during the first post-transplant year. Other infections, such as dermatomycoses, herpes zoster, and folliculitis can affect a substantial number of new patients after the first post-transplant year [36]. The risk of skin infection is related to the intensity of immunosuppression. Of note, however, also the type of immunosuppression may be important. Actually, there is experimental and clinical evidence that mTOR inhibitors may inhibit the replication of several herpes viruses, including cytomegalovirus [39–42].

Mycotic infections (Table 2)

There is wide spectrum of mycotic infections causing cutaneous diseases. Fungal lesions may be typical, but are often aspecific or ambiguous. Cutaneous lesions may be the sign of a trivial mycotic disease or the marker of a disseminated, potentially lethal fungal illness, so great attention should be given to their early recognition [43].

Among the superficial cutaneous fungal infections, candidiasis of the mouth and intertriginous areas of the skin is particularly frequent in the early post-transplant period when the dosage of immunosuppressive drugs is highest

Table 2. Main fungal infections in organ transplant recipient.

Fungus	Signs and symptoms	Treatment
Candida	Stomatitis	Nystatin shallow, Cotrimazole
Pityrosporon	Pityriasis versicolor	Inidazole cream
	Folliculitis	Selenium sulfate shampoo
Aspergillus	Erythematous plaques, papulae, painful subcutaneous nodules	Liposomal amphotericin B. Voriconazole, Posaconazole
Cryptococcus	Nodular masses, maculopapulae, ulcers, abscesses	Polyene, Imidazole
Histoplasma	Erythematous and infiltrating plaques	Itraconazole,Voriconazole
Alternaria	Papulae, smooth and firm nodules	Excisional surgery, Itraconazole
Chromomycetes	Papulae, verrucous nodules, ulcerative plaques	Itraconazole, Posaconazole
Mucormycosis	Skin induration with erythema, necrosis	Amphotericin B, Posaconazole
Paecilomyces	Verrucous nodules	Voriconazole, Posaconazole

[44]. Candida-associated denture stomatitis occurs often in denture wearers taking immunosuppressive therapy [45]. Candidiasis may cause irregular or widespread erythema, erosive changes, or a typical creamy surface. Nystatin swish and shallow every 6 h or cotrimazole may be effective in preventing oral and esophageal fungal infections. Infections caused by dermatophytes, the ringworm-causing fungi, typically occur several months after transplantation. Their clinical appearance is often atypical because of the lack of the erythematous changes. Lesions may present as papules, plaques, ulcers, or subcutaneous nodules [46].

Pityriasis versicolor can occur in more than 30% of transplant patients [47]. This complication, which is caused by the lipophilic yeast Pityrosporon ovale/orbiculare, can involve large areas of the trunk and flexural zones where it causes multiple and widespread small scaly macules either hypopigmented or hyperpigmented. The same fungus can also cause a folliculitis over the shoulders, chest, upper back, and arms. It appears as an acneiform eruption of bland or mildly erythematosus follicular papules and pustules. Treatment rests on imidazole cream or selenium sulfate shampoo.

Seborrheic dermatitis, a common inflammatory dermatosis probably caused by an increased colonization with Malassezia yeast, may occur in 9.5% of kidney transplant recipients, being more frequently observed in male patients and in patients with a long history of transplant. Such a condition may be significantly associated with cutaneous malignancy, in particular squamous cell carcinoma [48].

Primary opportunistic deep cutaneous fungal infections are rare but may cause significant morbidity and mortality in immunosuppressed patients. However, there are few data about their incidence in solid organ transplant recipients. In an Italian series of 3293 consecutive organ transplant recipients with a mean follow-up time since transplantation of 2.5 ± 2.0 years, only 22 cases of deep cutaneous mycoses were detected, an incidence rate of 1.2 cases per 1000 persons-year at risk. Six patients had subsequent systemic involvement and three patients died of systemic dissemination [49].

Primary cutaneous aspergillosis is characterized by painful erythematous plaques and sometimes cellulitis. Papulae, pustules and/or subcutaneous nodules may be seen in case of disseminated aspergillosis [50,51]. Early administration of intravenous amphotericin B or antimold azoles (voriconazole or posaconazole) are recommended in case of aspergillosis.

Cutaneous cryptococcosis usually develops more than 6 months after transplantation and may have varied presentations [52] In a review of 146 organ transplant recipients with cryptococcosis, cutaneous cryptococcosis was documented in 26 (17.8%) patients and manifested as nodules (35%), maculopapule (30%), ulcer/pustule/abscess (30%), and cellulitis (30%). Two-third of the skin lesions occurred in the lower extremities. Localized disease developed in 31% and disseminated disease in 69% of patients [53]. Treatment includes both polyene and imidazole antifungal agents in addition to surgical adjuvant therapy.

Dissemination of previously localized pathogenic agents, such as Histoplasma capsulatum, may lead to erysipela-like lesions. Early cutaneous histoplasmosis consists of painless large erythematous and infiltrative plaque, whereas older lesions are represented by multiple draining ulcers [54,55]. Treatment of histoplasmosis rests on itraconazole or voriconazole.

Subcutaneous pheohyphomicosis caused by dermatiaceous fungi may also occur. Dermal alternariasis can manifest as fleshy papules and nodules, smooth and firm, spreading centrifugally, with an elevated crusted border and a central area slightly depressed and atrophic [56]. During a 20-year period from 1989 to 2008, eight solid organ transplant recipients, all of them highly immunosuppressed, developed Alternaria species infections at the

Mayo Clinic. Wide excisional surgery combined with prolonged itraconazole therapy and reduction in immunosuppressive regimens provided the best chance of cure [57] Phycomycosis of the sinuses may manifest as a facial cellulitis.

Chromomycosis is a mycotic infection that is more frequent in tropical and subtropical regions. It is caused by pigmented fungi that are common saprophytes growing in soil, vegetation, and wood. Several cases of cutaneous chromomycosis have been reported in transplant recipients [58–60]. It is characterized by scaly papules that may progress to verrucous nodules or ulcerating plaques that may be treated with itraconazole or posaconazole. In difficult cases, the diagnosis requires histopathology and isolation of colonies of the dematiaceous mold in culture [60].

Whereas mucormycosis (zygomycosis) is one of the most common causes of opportunistic mycotic infection in immunosuppressed patients, cutaneous mucormycosis is rare. Only 25 cases of primary mucormycosis in organ transplant recipients have been reported in a recent review [61]. Cutaneous zygomycosis may be localized, may extend to deep underlying tissues, or may be disseminated. The most common clinical presentation is induration of the skin with surrounding erythema, rapidly progressing to necrosis. Histological examination and culture of soft tissue are important for the diagnosis of cutaneous zygomycosis. The demonstration of nonseptate hyphae in smears or by culture is the most useful tool for diagnosis. Intravenous amphotericin B followed by oral posaconazole is the recommended treatment [62].

Paecilomyces is a cosmopolitan filamentous fungus. Among the different species of this ubiquitous saprophytic fungus, the most common are *P. lilacinus* and *P. variotii*. Paecilomyces species are an infrequent cause of fungal disease in transplant patients. Cutaneous nodular and verrucous lesions are the most common presentation. In a few weeks, these lesions may become ulcerated, hemorrhagic, and painful [63] To identify these infections, a polymerase chain reaction is usually required [64]. Paecilomyces infections may respond to amphotericin B, but today voriconazole or posaconazole represent the first line therapy in transplant patients [65]. Surgical debridement is often required.

Sporotrichosis is a disease caused by the infection of the fungus Sporothrix schenckii. Cutaneous symptoms include nodular lesions (Fig. 1) or bumps at the point of entry. The lesion starts off small and painless, and ranges in color from pink to purple. In immunosuppressed transplant recipients, the disease may spread to joints, bone, as well as to central nervous system [66].

Fungal infection may also affect the nails. Onychomycosis can occur in about 8% of renal transplant recipients [67]. It is mainly caused by yeast-like fungi. Onychomycosis is more common in patients with a long duration of transplantation. It manifests mainly in distal and lateral sub-ungueal sites. The lesions include longitudinal ridging, distal onycholysis, distal erythema, splinter hemorrhages of the nail plate and transverse leukonychia. Oral terbinafine is an efficacious treatment for onychomycosis [68], athough anecdotal cases of reversible liver dysfunction have been reported [69].

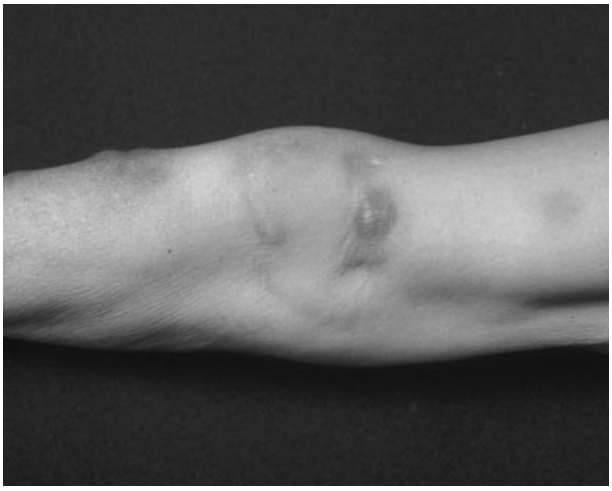

Figure 1 Subcutaneous nodules in a patient with sporotrichosis. Subcutaneous nodules may be the first presentation of severe disseminated fungal or bacterial infections (courtesy of prof. Stefano Veraldi, University of Milan).

Viral infections

Herpes virus infections are frequent in organ transplant recipients. Herpes simplex may have a limited extension without serious consequences but may also cause multifocal, extensive, and hemorrhagic lesions. Ulcers of the mouth and the perioral, perigenital, and perianal skin can occur in the most severe cases [70].

Herpes zoster can be responsible for gangrenous and hemorrhagic lesions, which usually do not extend to other areas. However, atypical herpetic infection may also cause disseminated ulcerative or necrotic skin. The administration of systemic acyclovir (5 mg/kg intravenously every 8 h for 5 days) or valacyclovir (1 g orally three times daily for 7 days) is mandatory for patients with severe lesions.

Varicella can occur in transplant patients and can have a life-threatening course. Varicella zoster virus is often resistant to acyclovir as a result of mutations in virus thymidine kinase, which is the target protein of acyclovir [71]. Children awaiting a renal transplant should receive specific vaccine to prevent this complica-

tion [72]. Reduction, or even withdrawal, of immunosuppressive therapy remains the cornerstone to treatment in severe cases of herpes virus infection [73]. Specific immunoglobulin infusion and acyclovir (10 mg/kg intravenously every 8 h for 7–10 days) may improve the prognosis. Exceptional cases have been described of chronic, localized, verrucous varicella presenting with cutaneous dissemination in varicella-zoster seronegative renal transplant patients [74].

Cutaneous manifestations caused by cytomegaloviruses are very rare. They consist of exanthema with vasculitis, hyperpigmented nodules and plaques, vesicobullae, and buccal and perineal ulcerations. Oral leukoplakia, a typical Epstein–Barr virus lesion, mostly observed in patients affected by acquired immune deficiency syndrome, has also been reported in HIV-negative transplant recipients [75].

Warts and condylomata are frequent in long-term functioning transplant patients, approaching 85% at 5 years [76–78]. Warts develop on sun-exposed areas, mainly in light-skinned patients, and are usually multiple. Their extension may be so widespread as to constitute general verrucosis. Warts are generally caused by human papilloma virus (HPV) and are considered as potential predictors for the development of coincidental non melanoma skin cancer [79]. The types of human HPV found in organ transplant recipients may be different from that seen in the general population. In a study, nine of 10 HPV detected in organ transplant recipients were gamma-PV and one belonged to the genus beta-PV [80]. There is a paucity of information about the oncogenicity of beta-PVs: The role of Beta-PV in the development of cutaneous squamous cell carcinoma was demonstrated by a large multicenter case-control study performed in three countries with different ultraviolet exposure. The presence of 25 beta-PV types in eyebrow hair follicles was determined using a highly sensitive HPV DNA genotyping assay and antibodies for the most prevalent beta-PV types. The presence of beta-PV DNA was associated with an increased risk of squamous cell carcinoma in the Netherlands and Italy, but not in Australia. A positive antibody response against 4 or more beta-PV types was associated with squamous cell carcinoma in Australia, the Netherlands and fair-skinned Italians [81]. In transplant recipients, HPV can also be responsible of anal or genital warts [82], condylomata acuminata [83], or molluscum contagiosum [84]. About 20% of renal transplant patients have antibodies against virus-like particles of epidermodysplasia verruciformis [85], a precancerous condition characterized by several widespread viral warts and pityriasis versicolor-like lesions. Topical keratolytic agents or retinoic acid is the treatments of choice. Imiquimod cream (5%) may be used in resistant warts [86]. Topical cidofovir (1%) may also be useful for treatment of verruca vulgaris or recalcitrant warts [87,88]. Conversion to mTOR inhibitors proved to be a useful strategy for recalcitrant cutaneous viral warts in transplant recipients [89,90].

Bacterial infections

Bacterial infections are usually trivial in the early period after transplantation, being represented almost exclusively by folliculitis. However, subcutaneous abscesses, erysipelas, and impetigo, caused by Gram-positive cocci, may develop in the long term.

Necrotizing fasciculitis is a rare but life-threatening disorder caused by a rapidly spreading subcutaneous infection, usually sustained by polymicrobial pathogens [91]. Clinically necrotizing fasciculitis is characterized by progressive inflammation and extensive necrosis of the skin and soft tissue. Renal transplant patients receiving high-dose glucocorticoids are particularly susceptible to this complication. The presence of a nephrotic syndrome further increases the risk of necrotizing fasciculitis. This infection carries a high rate of mortality, ranging between 33% and 73% [92]. Prompt recognition and aggressive treatment, including surgical intervention with debridement of necrotic tissue and extensive fasciotomy may improve the prognosis.

Not only fungal infections but also Nocardiosis [93] or disseminated tuberculosis [94,95] may present with subcutaneous nodules. The investigation of cutaneous lesions is important to reach a definitive diagnosis for possible future disseminated infections. Rarely, cutaneous tuberculosis may mimick erysipelas [96]. Skin infections caused by atypical mycobacteria may manifest as a spreading cellulitis around joints or as cutaneous or subcutaneous nodules [97]. In particular infections caused by *M. abscessus*, an ubiquitous organism found in the environment and that infrequently gives disease in humans, have increased in the last 5 years, possibly as a result of more focused search for the lesions. However, the exact incidence of *M. abscessus* infection among solid organ transplant recipients is unknown and only anecdotal cases have been reported in the literature [98,99]. Respiratory and cutaneous samples are predominant, with skin lesions being an important site of primary symptom preceding the dissemination of infection. The optimal regimen remains undefined since *M. abscessus* is resistant to most antimycobacterial drugs. The outcome depends mainly on a rapid diagnosis and a prompt treatment based on susceptibility test results.

Parasitic infection

Norwegian scabies is characterized by thick crusted plaques occurring in wide areas of the skin. Several cases of Norwegian cases have been reported in transplant recipients [100–102]. When complicated by brain abscess the outcome of this disease may be fatal [103].

Leishmaniasis is a heterogeneous group of diseases that can range from a solitary, spontaneous healing ulcer, to destructive mucocutaneous disease to generalized visceral involvement which may be lethal if not treated. Leishmaniasis is caused by protozoan parasites and is transmitted by the bite of certain species of sand fly. Mucocutaneous leishmaniasis is a feared form of leishmaniasis because it produces destructive and disfiguring lesions of the face. Although cutaneous leishmaniasis is rare in transplant recipients, the number of published cases has quadrupled since the beginning of the 1990s [104]. Most cases have been observed in patients living in tropical countries or in the Mediterranean basin, but although rarely it has also observed in transplant recipient in the United States [105]. Leishmaniasis is most commonly associated with kidney transplantation (77%) and cases are also recorded among patients undergoing liver, heart, lung, pancreas, and bone marrow transplantation. Early diagnosis is crucial for therapy and outcome; however, this is frequently overlooked or delayed. Mucocutaneous leishmaniasis is treated with long courses (e.g. 30 days) of pentavalent antimonials, including meglumine antimoniate and sodium stibogluconate, in a high dose (20 mg antimony per kg body weight). However, antimonials may be responsible for side effects, such as musculoskeletal pain, gastrointestinal disturbances, headache, electrocardiographic Q-T interval prolongation, renal tubular toxicity, and a mild to moderate increase in liver and pancreatic enzymes [106]. Moreover, not all the cases of mucocutaneous leishmaniasis respond to treatment [107] and complete unresponsiveness to antimony may even develop in endemic areas [108]. Second line treatments in antimony-resistant patients include liposomal amphotericin B [109] and pentamidine. This drug is as toxic as antimonials but proved to be effective in anecdotal antimonial-resistant cases [110]. A new series of monoamidoxime derivatives showed valuable *in vitro* activities toward Leishmania donovani 40 times more selective than pentamidine, and 1.6 times more than amphotericin B, used as reference drug compounds [111].

Funding

None.

References

1. Wisgerhof HC, Edelbroek JR, de Fijter JW, Feltkamp MC, Willemze R, Bouwes Bavinck JN. Trends of skin diseases in organ-transplant recipients transplanted between 1966 and 2006: a cohort study with follow-up between 1994 and 2006. *Br J Dermatol* 2010; **162**: 390.
2. Formicone F, Fargnoli MC, Pisani F, Rascente M, Famulari A, Peris K. Cutaneous manifestations in Italian kidney transplant recipients. *Transplant Proc* 2005; **37**: 2527.
3. Lugo-Janer G, Sánchez JL, Santiago-Delpin E. Prevalence and clinical spectrum of skin diseases in kidney transplant recipients. *J Am Acad Dermatol* 1991; **24**: 410.
4. Alper S, Kilinc I, Duman S, *et al.* Skin diseases in Turkish renal transplant recipients. *Int J Dermatol* 2005; **44**: 939.
5. Zamanian A, Mahjub H, Mehralian A. Skin diseases in kidney transplant recipients. *Urol J* 2006; **3**: 230.
6. Cooper SM, Woinarowska F. Photo-damage in North-European renal transplant recipients is associated with use of calcium channel blockers. *Clin Exp Dermatol* 2003; **28**: 588.
7. Kaur G, Verhamme KM, Dieleman JP, *et al.* Association between calcium channel blockers and gingival hyperplasia. *J Clin Periodontol* 2010; **37**: 625.
8. Butler JA, Roderick P, Mullee M, Mason JC, Peveler RC. Frequency and impact of nonadherence to immunosuppressants after renal transplantation: a systematic review. *Transplantation* 2004; **77**: 769.
9. Rathnayake D, Sinclair R. Use of spironolactone in dermatology. *Skinmed* 2010; **8**: 328.
10. Lumsden KR, Nelson AM, Dispenza MC, *et al.* Isotretinoin increases skin surface levels of neutrophil gelatinase-associated lipocalin in patients treated for severe acne. *Br J Dermatol* 2011; **10**: 1365.
11. Stotland M, Chapas AM, Brightman L, *et al.* The safety and efficacy of fractional photothermolysis for the correction of striae distensae. *J Drugs Dermatol* 2008; **7**: 857.
12. Euvrard S, Kanitakis J, Cochat P, Cambazard F, Claudy A. Skin disease in children with organ transplant. *J Am Acad Dermatol* 2001; **44**: 932.
13. Webb NJ, Coulthard MG, Trompeter RS, *et al.* Correlation between finger-prick and venous ciclosporin levels: association with gingival overgrowth and hypertrichosis. *Pediatr Nephrol* 2007; **22**: 2111.
14. Vexiau P, Fiet J, Boudou Ph, *et al.* Increase in plasma 5 alpha -androstase-3 alpha, 17 alpha-diol glucuronide as a marker of peripheral androgen action in hirsutism: a side-effect induced by cyclosporine A. *J Steroid Biochem* 1990; **35**: 133.
15. Rittmaster RS. Medical treatment of androgen-dependent hirsutism. *J Clin Endocrinol Metab* 1995; **80**: 2559.
16. Walker RG, Cottrell S, Sharp K, *et al.* Conversion of cyclosporine to tacrolimus in stable renal allograft recipients: quantification of effects on the severity of gingival

enlargement and hirsutism and patient-reported outcomes. *Nephrology (Carlton).* 2007; **12**: 607.
17. Leyral C, Beylot-Barry M, Vergier B, *et al.* Cyclosporine-induced follicular eruption. *Ann Dermatol Venereol* 2008; **135**: 58.
18. Ponticelli C, Zorzi F. The skin in renal transplant recipients. In: Massry SG, Glassock RJ, eds. *Textbook of Nephrology*. Philadelphia: Lippincott Williams and Wilkins, 2001: 1685–1688.
19. Spoildorio LC, Spoildorio DM, Neves KA, Gonzaga HF, Almeida OP. Morphological evaluation of combined effects of cyclosporine and nifedipine on gingival overgrowth in rats. *J Periodontal Res* 2002; **37**: 192.
20. Baratynska M, Radwan-Oczko M, Falkiewicz K, Klinger M, Szyber P. Gingival overgrowth in kidney transplant recipients treated with cyclosporine and its relationship with chronic graft nephropathy. *Transplant Proc* 2003; **35**: 2238.
21. Nash MM, Zaltzman JS. Efficacy of azithromicin in the treatment of cyclosporine-induced gingival hyperplasia in renal transplant recipients. *Transplantation* 1998; **65**: 1611.
22. Tokgoz B, Sari HI, Yildiz O. Effects of azithromycin on cyclosporine-induced gingival hyperplasia in renal transplant patients. *Transplant Proc* 2004; **36**: 2699.
23. Gonçalves SC, Díaz-Serrano KV, de Queiroz AM, Palioto DB, Faria G. Gingival overgrowth in a renal transplant recipient using cyclosporine A. *J Dent Child (Chic)* 2008; **75**: 313.
24. Talbot D, Rix D, Abusin K, *et al.* Alopecia as a consequence of tacrolimus therapy in renal transplantation. *Transplantation* 1997; **64**: 1631.
25. Tricot L, Lebbe C, Pillebout E, *et al.* Tacrolimus-induced alopecia in female kidney-pancreas transplant recipients. *Transplantation* 2005; **80**: 1546.
26. Ponte GM, Baidal DA, Romanelli P, *et al.* Resolution of severe atopic dermatitis after tacrolimus withdrawal. *Cell Transplant* 2007; **16**: 23.
27. Ponticelli C. Can mTOR inhibitors reduce the risk of late kidney allograft failure? *Transpl Int* 2008; **21**: 2.
28. Campistol JM, de Fijter JW, Flechner SM, Langone A, Morelon E, Stockfleth E. mTOR inhibitor-associated dermatologic and mucosal problems. *Clin Transplant* 2010; **24**: 149.
29. Van Gelder T, ter Meulen CG, Hené R, Weimar W, Hoistma A. Oral ulcers in kidney transplant recipients treated with sirolimus and mycophenolate mofetil. *Transplantation* 2003; **75**: 788.
30. Kunzle N, Venetz JP, Pascual M, Panizzon RG, Laffitte E. Sirolimus-induced acneiform eruption. *Dermatology* 2005; **211**: 366.
31. Tracey C, Hawley C, Griffin AD, Strutton G, Lynch S. Generalized, pruritic, ulcerating maculopapular rash necessitating cessation of sirolimus in a liver transplantation patient. *Liver Transpl* 2005; **11**: 987.
32. Mahé E, Morelon E, Lechaton S, Kreis H, De Prost Y, Bodemer C. Sirolimus-induced onychopathy in renal transplant recipients. *Ann Dermatol Venereol* 2006; **133**: 531.
33. Lawson DH, Lovatt GE, Gurton CS, Hennings RC. Adverse effects of azathioprine. *Adverse Drug React Acute Poisoning Rev* 1984; **3**: 161.
34. Vermeulen T, Rodrigus IE, Vrints CJ, Conraads V. Severe stomatitis complicating immune-suppressive switch after cardiac transplantation. *Acta Chir Belg* 2010; **110**: 339.
35. Rault R. Mycophenolate-associated onycholysis. *Ann Intern Med* 2000; **133**: 92.
36. Hogewoning AA, Goettsch W, van Loveren H, de Fijter JW, Vermeer BJ, Bouwes Bavinck JN. Skin infections in renal transplant recipients. *Clin Transplant* 2001; **15**: 3.
37. Chen QP, Aw DC. Epidemiology of skin diseases in renal transplant recipients in a tertiary hospital. *Ann Acad Med Singapore* 2010; **39**: 904.
38. Lally A, Casabonne D, Imko-Walczuk B, Newton R, Wojnarowska F. Prevalence of benign cutaneous disease among Oxford renal transplant recipients. *J Eur Acad Dermatol Venereol* 2011; **25**: 462.
39. Johnson RA, Wang X, Ma XL, Huong SM, Huang ES. Human cytomegalovirus up-regulates the phosphatidylinositol 3-kinase (PI3-K) pathway: inhibition of PI3-K activity inhibits viral replication and virus-induced signaling. *J Virol* 2001; **75**: 6022.
40. Kudchodkar SB, Yu Y, Maguire TG, Alwine JC. Human cytomegalovirus infection alters the substrate specificities and rapamycin sensitivities of raptor- and rictor-containing complexes. *Proc Natl Acad Sci U S A* 2006; **103**: 14182.
41. Viganò M, Dengler T, Mattei MF, *et al.* Study Investigators Lower incidence of cytomegalovirus infection with everolimus versus mycophenolate mofetil in de novo cardiac transplant recipients: a randomized, multicenter study. *Transpl Infect Dis* 2010; **12**: 23.
42. Ponticelli C. Herpes viruses and tumours in kidney transplant recipients. The role of immunosuppression. *Nephrol Dial Transplant* 2011; **26**: 1769.
43. Virgili A, Zampino MR, Mantovani L. Fungal skin infections in organ transplant recipients. *Am J Clin Dermatol* 2002; **3**: 19.
44. Ribeiro PM, Bacal F, Koga-Ito CY, Junqueira JC, Jorge AO. Presence of Candida spp. in the oral cavity of heart transplantation patients. *J Appl Oral Sci* 2011; **19**: 6.
45. Golecka M, Oldakowska-Jedynak E, Mierzwinska-Nastalska E, Adamczyk-Sosinska E. Candida-associated denture stomatitis in patients after immunosuppression therapy. *Transplant Proc* 2006; **38**: 155.
46. Miele PS, Levy CS, Smith MA, *et al.* Primary cutaneous fungal infections in solid organ transplantation: a case series. *Am J Transplant* 2002; **2**: 678.
47. Gulec AT, Demirbilek M, Seckin D, *et al.* Superficial fungal infections in 102 renal transplant recipients: a case-control study. *J Am Acad Dermatol* 2003; **49**: 187.

48. Lally A, Casabonne D, Newton R, Wojnarowska F. Seborrheic dermatitis among Oxford renal transplant recipients. *J Eur Acad Dermatol Venereol* 2010; **24**: 561.
49. Tessari G, Naldi L, Piaserico S, *et al.* Incidence and clinical predictors of primary opportunistic deep cutaneous mycoses in solid organ transplant recipients: a multicenter cohort study. *Clin Transplant* 2010; **24**: 328.
50. Gupta A, Khaira A, Lata S, Sharma A, Tiwari SC. Primary cutaneous aspergillosis in renal transplant recipient. *Saudi J Kidney Dis Transpl* 2009; **20**: 848.
51. Ramos A, Ussetti P, Laporta R, Lázaro MT, Sánchez-Romero I. Cutaneous aspergillosis in a lung transplant recipient. *Transpl Infect Dis* 2009; **11**: 471.
52. Abuav R, McGirt LY, Kazin RA. Cryptococcal panniculitis in an immunocompromised patient: a case report and review of the literature. *Cutis* 2010; **85**: 303.
53. Sun HY, Alexander BD, Lortholary O, *et al.* Cutaneous cryptococcosis in solid organ transplant recipients. *Med Mycol* 2010; **48**: 785.
54. Shuttleworth D, Philpot CM, Salaman JR. Cutaneous fungal infection following renal transplantation: a case control study. *Br J Dermatol* 1987; **117**: 585.
55. Marques SA, Hozumi S, Camargo RM, Carvalho MF, Marques ME. Histoplasmosis presenting as cellulitis 18 years after renal transplantation. *Med Mycol* 2008; **46**: 725.
56. Bourlond A, Alexandre G. Dermal alternariasis in a kidney transplant recipient. *Dermatologica* 1984; **168**: 152.
57. Boyce RD, Deziel PJ, Otley CC, *et al.* Phaeohyphomycosis due to Alternaria species in transplant recipients. *Transpl Infect Dis* 2010; **12**: 242.
58. Peña-Penabad C, Durán MT, Yebra MT, Rodríguez-Lozano J, Vieira V, Fonseca E. Chromomycosis due to Exophiala jeanselmei in a renal transplant recipient. *Eur J Dermatol* 2003; **13**: 305.
59. Franco A, Aranda I, Navas F, Olivares J. Follow-up on a transplant recipient with chromomycosis. *Nephrol Dial Transplant* 1997; **12**: 852.
60. Dupont C, Duong TA, Mallet S, *et al.* Unusual presentation of chromoblastomycosis due to Cladophialophora carrionii in a renal and pancreas transplant recipient patient successfully treated with posaconazole and surgical excision. *Transpl Infect Dis* 2010; **12**: 180.
61. Page AV, Evans AJ, Snell L, Liles WC. Primary cutaneous mucormycosis in a lung transplant recipient: case report and concise review of the literature. *Transpl Infect Dis* 2008; **10**: 419.
62. Ashkenazi-Hoffnung L, Bilavsky E, Avitzur Y, Amir J. Successful treatment of cutaneous zygomycosis with intravenous amphotericin B followed by oral posaconazole in a multivisceral transplant recipient. *Transplantation* 2010; **90**: 1133.
63. Ounissi M, Abderrahim E, Trabelsi S, *et al.* Hyalohyphomycosis caused by Paecilomyces lilacinus after kidney transplantation. *Transplant Proc* 2009; **41**: 2917.
64. Van Schooneveld T, Freifeld A, Lesiak B, Kalil A, Sutton DA, Iwen PC. Paecilomyces lilacinus infection in a liver transplant patient: case report and review of the literature. *Transpl Infect Dis* 2008; **10**: 117.
65. Garzoni C, Garbino J. New azoles as first line therapy for Paecilomyces lilacinus in transplant patients. *Transpl Infect Dis* 2008; **10**: 149.
66. Gullberg RM, Quintanilla A, Levin ML, Williams J, Phair JP. Sporotrichosis: recurrent cutaneous, articular, and central nervous system infection in a renal transplant recipient. *Rev Infect Dis* 1987; **9**: 369.
67. Bakr NI, El-Sawy E, Hamdy AF, Bakr MA. Skin infections in Egyptian renal transplant recipients. *Transpl Infect Dis* 2011; **13**: 131.
68. Ghannoum MA, Welshenbaugh A, Imamura Y, Isham N, Mallefet P, Yamaguchi H. Comparison of the in vitro activity of terbinafine and lanoconazole against dermatophytes. *Mycoses* 2010; **53**: 311.
69. Chambers WM, Millar A, Jain S, Burroughs AK. Terbinafine-induced hepatic dysfunction. *Eur J Gastroenterol Hepatol* 2001; **13**: 1115.
70. Balfour Jr HH. Antiviral drugs. *N Engl J Med* 1999; **340**: 1255.
71. Brink AA, van Gelder M, Wolffs PF, Bruggeman CA, van Loo IH. Compartmentalization of acyclovir-resistant varicella zoster virus: implications for sampling in molecular diagnostics. *Clin Infect Dis* 2011; **52**: 982.
72. Furth SL, Fivush BA. Varicella vaccination in pediatric kidney transplant candidates. *Pediatr Transplant* 2002; **6**: 97.
73. Shiley K, Blumberg E. Herpes viruses in transplant recipients: HSV, VZV, human herpes viruses, and EBV. *Hematol Oncol Clin North Am* 2011; **25**: 171.
74. Jeyaratnam D, Robson AM, Hextall JM, Wong W, MacMahon E. Concurrent verrucous and varicelliform rashes following renal transplantation. *Am J Transplant* 2005; **5**: 1777.
75. Ponticelli C, Passerini P. Gastrointestinal complications in renal transplant recipients. *Transpl Int* 2005; **18**: 643.
76. Leigh IM, Glover MT. Cutaneous warts and tumours in immunosuppressed patients. *J R Soc Med* 1995; **88**: 61.
77. Barba A, Tessari G, Talamini G, Chieregato GC. Analysis of risk factors for cutaneous warts in renal transplant recipients. *Nephron* 1997; **77**: 422.
78. Krüger-Corcoran D, Stockfleth E, Jürgensen JS, *et al.* Human papillomavirus-associated warts in organ transplant recipients. Incidence, risk factors, management. *Hautarzt* 2010; **61**: 220.
79. Reuschenbach M, Tran T, Faulstich F, *et al.* High-risk human papillomavirus in non-melanoma skin lesions from renal allograft recipients and immunocompetent patients. *Br J Cancer* 2011; **104**: 1334.
80. Köhler A, Gottschling M, Manning K, *et al.* Genomic characterization of ten novel cutaneous human

papillomaviruses from keratotic lesions of immunosuppressed patients. *J Gen Virol* 2011; **92**: 1585.
81. Bouwes Bavinck JN, Neale RE, Abeni D, *et al.* Multicenter study of the association between betapapillomavirus infection and cutaneous squamous cell carcinoma. *Cancer Res* 2010; **70**: 9777.
82. Patel HS, Silver AR, Levine T, Williams G, Northover JM. Human papillomavirus infection and anal dysplasia in renal transplant recipients. *Br J Surg* 2010; **97**: 1716.
83. Ganguly N, Waller S, Stasik CJ, Skikne BS, Ganguly S. Giant anal condylomatosis after allogeneic bone marrow transplantation: a rare complication of human papilloma virus infection. *Transpl Infect Dis* 2008; **10**: 56.
84. Feldmeyer L, Kamarashev J, Boehler A, *et al.* Molluscum contagiosum folliculitis mimicking tinea barbae in a lung transplant recipient. *J Am Acad Dermatol* 2010; **63**: 169.
85. Stark S, Petridis AK, Ghim SJ, *et al.* Prevalence of antibodies against virus-like particles of epidermodysplasia verruciformis-associated HPV8 in patients at risk of skin cancer. *J Invest Dermatol* 1998; **111**: 696.
86. Gayed SL. Topical imiquimod cream 5% for resistant perianal warts in a renal transplant patient. *Int J STD AIDS* 2002; **13**: 501.
87. Cha S, Johnston L, Natkunam Y, Brown J. Treatment of verruca vulgaris with topical cidofovir in an immunocompromised patient: a case report and review of the literature. *Transpl Infect Dis* 2005; **7**: 158.
88. Kralund HH, Broesby-Olsen S, Bistrup C, Lorentzen HF. Substantial effect of topical cidofovir 1% on recalcitrant warts in a renal-transplanted adolescent: a case report. *Transplantation* 2011; **91**: e52.
89. Dharancy S, Catteau B, Mortier L, *et al.* Conversion to sirolimus: a useful strategy for recalcitrant cutaneous viral warts in liver transplant recipient. *Liver Transpl* 2006; **12**: 1883.
90. Kostaki M, Venetz JP, Nseir G, *et al.* Giant warts in a kidney transplant patient: regression with sirolimus. *Br J Dermatol* 2010; **162**: 1148.
91. Seal DV. Necrotizing fasciitis. *Curr Opin Infect Dis* 2001; **14**: 127.
92. Audard V, Pardon A, Claude O, *et al.* Necrotizing fasciitis during de novo minimal change nephritic syndrome in a kidney transplant recipient. *Transpl Infect Dis* 2005; **7**: 89.
93. Maccario M, Tortorano AM, Ponticelli C. Subcutaneous nodules and pneumonia in a kidney transplant recipient. *Nephrol Dial Transplant* 1998; **31**: 681.
94. Caroti L, Zanazzi M, Rogasi P, *et al.* Subcutaneous nodules and infectious complications in renal allograft recipients. *Transplant Proc* 2010; **42**: 1146.
95. Quirós J, Herrero-Beaumont G, Tornero J, Castañeda S. Subcutaneous nodules: initial manifestation of disseminated hematogenous tuberculosis. *Med Clin (Barc)* 1988; **91**: 237.
96. Sattinger E, Meyer S, Costard-Jackle A. Cutaneous tuberculosis mimicking erysipelas of the lower leg in a heart transplant recipient. *Transplant Int* 2011; **24**: e51.
97. Pandian TK, Deziel PJ, Otley CC, Eid AJ, Razonable RR. Mycobacterium marinum infections in transplant recipients: case report and review of the literature. *Transpl Infect Dis* 2008; **10**: 358.
98. Garrison AP, Morris MI, Doblecki Lewis S, *et al.* Mycobacterium abscessus infection in solid organ transplant recipients: report of three cases and review of the literature. *Transpl Infect Dis* 2009; **11**: 541.
99. Morales P, Gil A, Santos M. Mycobacterium abscessus infection in transplant recipients. *Transplant Proc* 2010; **42**: 3058.
100. Cakmak SK, Gönül M, Gül U, Unal T, Dağlar E. Norwegian scabies in a renal transplant patient. *Australas J Dermatol* 2008; **49**: 248.
101. Abdo A, Kouri V, Burgos D, *et al.* Norwegian scabies associated with herpes simplex infection in a renal transplant patient. *Transplantation* 2009; **87**: 943.
102. Sampathkumar K, Mahaldar AR, Ramakrishnan M, Prabahar S. Norwegian scabies in a renal transplant patient. *Indian J Nephrol* 2010; **20**: 89.
103. Mansy H, Somorin A, el-Sherif M, Eze C, al-Dusari S, Filobbos P. Norwegian scabies complicated by fatal brain abscess in a renal transplant patient. *Nephron* 1996; **72**: 32.
104. Antinori S, Cascio A, Parravicini C, Bianchi R, Corbellino M. Leishmaniasis among organ transplant recipients. *Lancet Infect Dis* 2008; **8**: 191.
105. Mirzabeigi M, Farooq U, Baraniak S, Dowdy L, Ciancio G, Vincek V. Reactivation of dormant cutaneous Leishmania infection in a kidney transplant patient. *J Cutan Pathol* 2006; **33**: 701.
106. Oliveira LF, Schubach AO, Martins MM, *et al.* Systematic review of the adverse effects of cutaneous leishmaniasis treatment in the New World. *Acta Trop* 2011; **118**: 87.
107. Franke ED, Wignall FS, Cruz ME, *et al.* Efficacy and toxicity of sodium stibogluconate for mucosal leishmaniasis. *Ann Intern Med* 1990; **113**: 934.
108. Olliaro PL, Guerin PJ, Gerstl S, Haaskjold AA, Rottingen JA, Sundar S. Treatment options for visceral leishmaniasis: a systematic review of clinical studies done in India, 1980–2004. *Lancet Infect Dis* 2005; **5**: 763.
109. Wortmann G, Zapor M, Ressner R, *et al.* Liposomal amphotericin B for treatment of cutaneous leishmaniasis. *Am J Trop Med Hyg* 2010; **83**: 1028.
110. Pimentel MI, Baptista C, Rubin EF, *et al.* American cutaneous leishmaniasis caused by Leishmania (Viannia) braziliensis resistant to meglumine antimoniate, but with good response to pentamidine: a case report. *Rev Soc Bras Med Trop* 2011; **44**: 254.
111. Paloque L, Bouhlel A, Curti C, *et al.* Synthesis and evaluation of monoamidoxime derivatives: toward new antileishmanial compounds. *Eur J Med Chem* 2011; **46**: 2984.