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NATIONAL INSTITUTE OF PUBLIC HEALTH AND THE ENVIRONMENT

RIVM report 640300 003

Skin infections in renal transplant recipients and the relation with solar UVR

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December 2000

This investigation has been performed by order and for the account of the Inspectorate for Health Protection, Commodities and Veterinary Public Health, within the framework of project 640300, “Influence of UVB on the immune system and repercussions for the resistance to infections and tumours and vaccination responses in humans” and by order and for the account of the Dutch National Research Programme on Global Air Pollution and Climate Change, project 952276, “Impact of UV-B irradiation on the resistance to infectious diseases and efficacy of vaccination”.

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Samenvatting

UV blootstelling heeft effecten op het immuunsysteem van mens en dier. Dergelijke effecten zouden kunnen leiden tot verminderde weerstand tegen infecties in de bevolking. Wij hebben in een retrospectieve cohort studie met 137 post-niertransplantatiepatiënten onderzocht of er een verband tussen blootstelling aan zonlicht en het optreden van verschillende huidinfecties aangetoond kon worden.
De klinische gegevens werden verkregen uit de patiënten dossiers van de deelnemers aan deze studie. Een schatting van de blootstelling aan UV gedurende het gehele leven werd gemaakt op basis van zelf-gerapporteerde gegevens in een vragenlijst. Het seizoen waarin de diagnose van de betreffende infectie werd gesteld werd gezien als ruwe maat voor de blootstelling aan UV vlak voor of op het moment van infectie. Deze blootstelingsvariabelen werden opgenomen in een multivariaat Poisson regressie model voor herhaalde waarnemingen, samen met andere klinisch relevante gegevens (o.a. aanwezigheid van diabetes, gebruik prednison).
Het hoogste voorkomen van huidinfecties per tijdseenheid werd gevonden in de eerste 6 maanden na niertransplantatie. Er werd geen consistente correlatie gevonden met de maat voor de cumulatieve zonlichtblootstelling gedurende het gehele leven. In de zomermaanden werden de hoogste incidenties van virale en schimmel/ gist- infecties en de laagste van bacteriële infecties gevonden. Herpes Simplex infecties werden vooral in de lente, terwijl Herpes Zoster infecties vooral in de zomer gediagnosticeerd werden.
Eventuele interindividuele verschillen in de gevoeligheid voor en de rapportage van huidinfecties zouden de associatie met de cumulatieve maat voor zonlichtblootstelling vertekend kunnen hebben. Verder zou een gebrek aan gedetailleerde informatie de associatie met het gebruik van immuunsuppressieve middelen en met het aantal behandelingen voor rejectie vertekend kunnen hebben. Daar seizoen als een betrouwbare en tijdsafhankelijke variabele in het Poisson model geïncludeerd kon worden, gaan deze bezwaren zeer waarschijnlijk niet op voor de gevonden associatie tussen het optreden van infecties en seizoen.
De conclusie die uit deze studie kan worden getrokken is dat er seizoensverschillen ten aanzien van het voorkomen van infecties in deze groep niertransplantatie patiënten zijn. Deze zouden gedeeltelijk kunnen worden toegeschreven aan het jaarritme voor UV belasting. Daarnaast zouden andere jaarritmes in immuunresponsen, die niet noodzakelijkerwijs verband behoeven te hebben met UV belasting, een rol kunnen spelen bij de seizoensinvloed op het voorkomen van infecties in de bevolking.

Summary

In view of the immune suppressive effects of ultraviolet B radiation (UVR) we examined whether an association exists between exposure to solar UVR and the rate of different skin infections in a retrospective cohort study of 137 renal transplant recipients.
The clinically data were extracted from the patient's medical charts. An estimate of lifetime cumulative exposure to sunlight was calculated on the basis of self-reported data. Season of diagnosis was regarded as a rough estimate of the exposure just prior to or at the time of the infection. These variables were included in a Multivariate Poisson Regression Model for repeated measurements among other clinically relevant parameters (age at renal transplantation, diabetes, and dose of immune suppressive treatment etc.).
The highest rates of infection were observed in the first 6 months since renal transplantation. No consistent correlation was found with the estimate of lifetime cumulative exposure to sunlight. In summer the highest rates of viral and fungal/ yeast and the lowest rates of bacterial skin infections were found. For Herpes Simplex infections the highest rates were found in spring, for Herpes Zoster infections the highest rates were found in summer.
It is discussed that inter-individual differences in the susceptibility to and the reporting of infections may hamper the interpretation of the observed associations with the lifetime cumulative estimate of sunlight. Furthermore, lack of detailed information on a daily basis may have biased the association with the use of immune suppressive medication and the number of treatments for rejections.
As season was introduced as time dependent variable the objections do probably not apply to the observed seasonal influence on the occurrence of skin infections. This result may indicate that seasonal differences in ambient UVR triggers a circannual rhythm in immune responses and hence in the resistance to certain infections in human populations.

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1. Introduction

Experimental animal data show that ultraviolet radiation (UVR) at doses relevant to outdoor exposure may affect specific cellular immune responses and reduce the resistance to viral, bacterial and parasitic agents [1,2]. It has also been shown that exposure to artificial UVR or sunlight may suppress important immune parameters in humans [3,4,5]. It is still an unresolved issue whether this acute UVR-induced immune suppression is associated with an increased risk of infections or with a more severe clinical course after infection in human populations [6,7]. We may assume that the possible subtle effects of UVR on the occurrence or severity of infections in humans will come to light more easily in persons who already are immune suppressed. It has been shown that renal transplant recipients are at increased risk of non-melanoma skin cancer [8]. Both immune suppressive therapy and the cumulative life time exposure to sunlight are believed to be important risk factors for the development of skin cancers in these patients [9]. Furthermore, it is known that transplant recipients are at an increased risk of acquiring infections due to their immune suppressive therapy [10,11]. In a cohort of renal transplant recipients, who were initially included in a study on skin cancer, we retraced the medical records and checked them for the presence of viral, bacterial and fungal/ yeast skin infections since the time of renal transplantation [9,12]. A description of the infections found in these charts and their occurrence in the course of time since the renal transplantation has been described [12]. The purpose of the present analysis was to examine the possible association between exposure to solar UVR and the occurrence of different skin infections.

It appears from experimental studies (both animal and human) that UVR may have a short term and possibly reversible suppressive effects on the immune system [3,13]. For this reason, it is expected that in our present study on infections the acute short term exposure to solar UVR is of greater importance than the cumulative life time exposure, which is associated with cumulated DNA damage in the skin and as a consequence induction of skin malignancies. We hypothesised that in these immune suppressed patients a high, probably short-term exposure to solar UVR is associated with an increased risk of skin infections.

2. Methods

2.1 Study group

The cohort maintained at the Transplant Unit of the Leiden University Medical Centre consisted of 137 renal transplant recipients, who had received their first transplant between July 20, 1967 and December 22, 1980 and who were still alive with a functioning graft on August 1, 1989. The selection of this group of patients has been described before [9,14]. For the study on infections the follow-up of the cohort was extended to July 1, 1996. All but three charts could be retraced from the Transplant Unit. Patients' characteristics are given in *table 1a* [12].

2.2 Assessment of exposure to sunlight

Between August 24, 1988 and December 31, 1989 a retrospective questionnaire on sunlight exposure was administered [9,14]. Each patient's life-time cumulative exposure to sunlight was calculated by adding the hours of exposure associated with occupational activities to those associated with non-occupational activities, such as outdoor recreation, holidays and residence in the tropics. This was done to explore the association between the cumulative life time exposure to solar UVR and the risk for skin cancer [9]. It is well known that there is a strong association between season and exposure to ambient UVR in human populations [15,16]. As the short-term exposure to sunlight could not be measured day-by-day in these patients, the season of the year at the time of the diagnosis of an infection was regarded as indicative of the exposure at the time of or prior to that infection.

2.3 Statistical analysis

We explored the association between the occurrence of skin infection and various possible risk factors by means of a Poisson regression-analysis for repeated measurements. Rate ratios (RR) and their statistical significance were calculated to estimate the relative risk of exposure to/ presence of each possible determinant. In case of multi-categorical variables the RR's were calculated with regard to a reference category, which was chosen arbitrarily or according to the expectation of the lowest risk associated with that level of the risk factor. As it is known from our former analyses and clinical practice that time since renal transplantation is an important determinant of infection, at first the analyses were performed bivariately with period since renal transplantation as co-variable [10,11,12]. Time since renal transplantation was subdivided in: the first month, 1 month – 6 months, 6 months – 1 year and longer than 1 year. Determinants bivariately associated with the risk of infection as statistically expressed by a p-value of 0.10 (90% Confidence Interval, CI) or lower were included in the final multivariate model. In the multivariate model a p-value of 0.05 (95%-CI) was regarded as the level of statistical significance. All analyses were performed separately for infections of viral, bacterial and fungal/ yeast origin [12].

The following independent variables were included in the analysis:
- Time since renal transplantation (< 1 month, 1 month – 6 months, 6 months – 1 year, >1 year). If the precise date of diagnosis of a skin infection was unknown, that infection was excluded from the analysis.
- Gender
- Age at renal transplantation
- Diabetes (yes/ no)
- Skin type (I, III, III/IV) was assessed using standard criteria [17].

- Use of azathioprine (mg/kg/day), the personal mean daily dose was calculated and categorised (low/ intermediate/ high) for every above mentioned post-transplantation period separately
- Use of prednisone (mg/kg/day), idem.
- Cumulative number of treatments for rejection (categorised)
- Lifetime cumulative exposure to sunlight. The cumulative number of hours exposed was divided by the number of lifetime days to give the average life time exposure per day.
- Cumulative exposure to sunlight since renal transplantation. The number of hours exposed since the time of renal transplantation only could be estimated from the questionnaires and by dividing this number by the number of days between renal transplantation and the filling out of the questionnaire the average exposure per day since renal transplantation was estimated.
- Season of infection.

3. Results

In *table 1b* an overview of all registered skin infections is given. A total of 340 infections in 105 patients were detected. The infections were 97 times of viral, 97 times of bacterial and 146 times of fungal/ yeast origin. Infections with Herpes Zoster and Herpes Simplex formed the greatest part of viral infections.

In *table 1c* the number and the rate (number per person year) of registered skin infections are given by period since renal transplantation. The first half-year after the transplantation was associated with the highest rate of (registered) skin infections, irrespective of the microbial origin. The first month after renal transplantation was associated with the highest rate of fungal and yeast infections. The period from the second through the sixth month after renal transplantation was associated with the highest rate of viral and bacterial infections.

In *table 2* the results of the bivariate Poisson-analysis are shown. Younger age at renal transplantation and a darker skin were statistically significantly associated with a lower rate of skin infections of viral origin.
The presence of diabetes was associated with a higher rate of skin infections of bacterial and fungal/ yeast origin.
After adjusting for the possible confounding effect of time since renal transplantation no statistically significantly higher rates of infections were found during periods with comparatively high doses of azathioprine or prednisone. For prednisone a strong correlation between time since renal transplantation and the mean dosage was found with the highest dosage immediately after the transplantation and decreasing doses thereafter (*figure 1*), which is in agreement with the dosage regimen after transplantation. Periods with low or intermediate doses of azathioprine even tended to be associated with higher rates of infection, especially in case of fungal/ yeast infections.
A higher cumulative life time exposure to sunlight tended to be associated with a higher rate of infection, but no clear gradient was established with the highest rate of infections in the group of participants with intermediate life time sunlight exposure.
A clear seasonal fluctuation could be established. Summer months (third quarter) were associated with the highest rates of viral and fungal/ yeast infections and the lowest rates of bacterial infections.
Those variables bivariately associated with the risk for viral, bacterial or fungal/ yeast infections were included in a multivariate Poisson model. Results are shown in *table 3*. The same associations as were found in the bivariate analysis could be established. In case of viral infections the association with skin type and season did not reach the level of statistical significance (p=0.05).

As it is known that exposure to solar UVR may facilitate the recurrence of herpes viruses, particularly Herpes Simplex, the above-described analysis was performed separately for Herpes Simplex and Herpes Zoster. The multivariate model is shown in *table 4*. For Herpes Zoster a clear association with age at renal transplantation could be established. For both Herpes Simplex and Herpes Zoster a seasonal fluctuation was found. Spring (second quarter) was associated with the highest rates of Herpes Simplex. Summer (third quarter) was associated with the highest rates of Herpes Zoster.

4. Discussion

In a cohort of post renal transplant recipients we examined the association between exposure to solar UVR and the incidence of skin infections among other clinically important parameters. This was done by using a rough estimate of short-term exposure and by a questionnaire-based estimate of lifetime cumulative exposure. We regarded 'season' as surrogate measure for short-term exposure to UVR.

In the analyses we took the clinically important determinants of infection like time since renal transplantation, diabetes and immunosuppressive medication into account. It is already known that the highest rates of infection are found in the first months after renal transplantation [12]. The highest rate of fungal/ yeast infections was found in the first month since renal transplantation, possibly reflecting the higher risk of candidal infections seen in surgical patients, irrespective of the state of immunosuppression [10]. The highest rates of viral and bacterial infections were found in the second through sixth month after renal transplantation. This may reflect the influence of the immunosuppressive therapy, which is determined mainly by its duration and less by the particular dose of drugs being administered on a given day or over a few days [11]. Furthermore, the first months after renal transplantation are possibly associated with more frequent visits to the clinic and so a higher probability for an infection being diagnosed and registered in the medical chart.
Diabetes appeared to be associated with statistically significantly higher rates of bacterial and fungal/ yeast infections, which is in accordance with clinical data [18,19].
Although it is well known that therapy with prednisone and azathioprine is associated with a higher risk of infections [11,20,21,22], a consistent correlation with the dose of prednisone, azathioprine, or the combination of both could not be established in this cohort. Periods with low and intermediate doses of azathioprine even were associated with higher rates of fungal/ yeast infection. Furthermore, although a strong correlation between prednisone dose and time since renal transplantation was observed (*figure 1*), the correlation between the rate of infections and the time since renal transplantation was not modified by taking into account the effect of prednisone dose. These results may indicate that the association between the prescribed dose of immunosuppressive medication and the risk for infections is not clear-cut or can be evaluated only when detailed information on the daily use of medication and adjustments of therapy regimen is included in the analysis.

We found a clear seasonal influence on the incidence of skin-infections. High summer (July through September) was associated with the highest rates of Herpes Zoster ('shingles') and fungal/ yeast infections, whereas these months were associated with the lowest rates of bacterial skin infections. The highest rates of Herpes Simplex were found in spring and early summer (April through June). It is already known that UVR may induce the recurrence of Herpes Simplex, although we found no studies in which a clear seasonal variation could be established [23,24,25,26]. In one study the greatest part of episodes of Herpes Simplex-induced keratitis was found from January through June, which coincides with our finding of highest incidences in spring [24]. In a population-based study a statistically significant seasonal influence on the referred number of patients with acute Herpes Zoster viral infection was found. The highest rates were found in summer, lower rates in autumn and winter and the lowest rates in spring, which is in accordance with our findings [27]. In another study it was also found that summer months were associated with the greatest number of patients with Herpes Zoster [28]. In other studies increasing incidences of Herpes Zoster infection with age

were found, which is also in accordance with our finding [29,30]. This finding may indicate selective decline in cellular immunity to varicella virus with age [30]. As both humoral and cellular immune responses are important to maintain control of viral replication, it is possible that the observed seasonal fluctuation of Herpes infections is related to circannual variations in immune responses [28,31]. Further research is needed to examine whether circannual variations of immune responses and the occurrence of infections are due to seasonal differences in ambient UVR. For Herpes Simplex and Herpes Zoster the established seasonal variation may indicate an effect of UVR on the cellular immunity and hence the recurrence rate. For the superficially localised fungal/ yeast infections we cannot rule out that the seasonal fluctuation is due to seasonal differences in ambient and skin temperature and/ or humidity.

Differences in infection rates between categories of patients characterised by the estimate of lifetime cumulative exposure to sunlight could be established. This questionnaire-based estimate of lifetime cumulative exposure to sunlight appeared to be correlated with the risk for skin cancer in the same cohort in a former analysis [9].
A tendency towards higher rates of bacterial and fungal/ yeast infections was observed in the intermediate exposed group. No association with the cumulative exposure since renal transplantation could be established. UVR induced DNA damage can accumulate in the skin and may be an important mediator of UVR induced immune suppression [32,33]. Hence, it is plausible that the association with the lifetime cumulative exposure is stronger than the association with the cumulative exposure during a shorter time interval, as is the case with exposure since renal transplantation only. On the other hand, the association with the estimate of lifetime cumulative exposure could not be established consistently, as there were no statistically significant differences in infection rates between the highest and the lowest exposed participants. Inter-individual differences in the number of visits to the clinic for medical examination (‘reporting-bias’) or differences in susceptibility to infections may have confounded the association with the life-time cumulative exposure or may have introduced spurious differences between the low and intermediate exposure categories.

This retrospective cohort study has many limitations. Inter-individual differences in number of visits to the clinic or susceptibility to infections may have confounded the correlation with the time-independent variables as the life-time cumulative estimate of exposure to sunlight and the cumulative number of treatments for rejection. Lack of detailed information on a daily basis may have biased the association with immune suppressive medication and the number of treatments for rejection.
On the other hand, as the patients were followed for many years and the date of diagnosis of the infections used in the analysis was known, season was introduced as a reliable time dependent variable. Hence, the above objections to the retrospective design of our study do probably not apply to the observed seasonal effects.
Furthermore, we may exclude that the observed seasonal fluctuations are due to seasonal differences in the reporting of infections or the use of immune suppressive medication, as an association between these factors and season is unlikely.
Still, whether the higher rates of viral and fungal/ yeast infections in spring and summer are due to the immune suppressive effect of UVR remains to be established [16].
We may hypothesise that in immunocompromised patients exposure to an immunosuppressive dose of UVR will lead to a higher rate of certain clinical infections more readily than in healthy persons. This may explain why in our cohort a seasonal fluctuation has

come to light easily. Although our finding is possibly of no relevance in healthy non-immunocompromised persons, it indicates that ambient UVB may have a subtle influence on the resistance to infections in human populations.

References

1. Goettsch W, Garrsen J, Slob W, De Gruijl FR , Van Loveren H. Risk assessment for the harmful effects of UVB radiation on the immunological resistance to infectious diseases. Environ Health Perspect 1998; 106(2): 71-76.
2. Garssen J, Norval M, El-Ghorr A, Gibbs NK, Jones CD, Cerimele D, De Simone C, Caffieri S, Dall'Acqua F, De Gruijl FR, Sontag Y, Van Loveren H. Estimation of the effect of increasing UVB exposure on the human immune system and related resistance to infectious diseases and tumours. Photochem Photobiol 1998; 42: 167-179.
3. Hersey P, Hasic E, Edwards A, Bradley M, Haran G, McCarthy WH. Immunological effects of solarium exposure. Lancet 1983; I: 545-548.
4. Hersey P, Haran G, Hasic E, Edwards A. Alteration of T cell subsets and induction of suppressor T cell activity in normal subjects after exposure to sunlight. J Immunol 1983; 31(1): 171-174.
5. Falkenbach A, Sedlmeyer A. Travel to sunny countries is associated with changes in immunological parameters. Photodermatol Photoimmunol Photomed 1997;13: 139-142.
6. Chapman RS, Cooper KD, De Fabo EC et al. Solar ultraviolet radiation and the risk of infectious disease: summary of a workshop. Photochem Photobiol 1995; 61(3): 223-247.
7. Norval M, Garssen J, Van Loveren H, El-Ghor AA. UV-induced changes in the immune response to microbial infections in human subjects and animal models. J Epidemiol 1999; 9(6): S84-S92.
8. Hartevelt MM, Bouwes Bavinck JN, Kootte AMM c.s. Incidence of skin cancer after renal transplantation in the Netherlands. Transplantation 1990; 49: 506-9.
9. Bouwes Bavinck, JN, De Boer A, Vermeer BJ, Hartevelt MM, Van der Woude FJ, Claas FHJ, Wolterbeek R, Vandenbroucke JP. Sunlight, keratotic skin lesions and skin cancer in renal transplant recipients. Br J Dermatol 1993; 129: 242-249.
10. Fishman JA, Rubin RH. Infection in organ-tranplant recipients. New Engl J Med 1998; 338(24): 1741-1751.
11. Rubin RH. Infection in the Organ Transplant Recipient. In: *Clinical Approach to Infection in the Compromised Host* 1994. (Edited by Rubin RH and Young LS), pp 629-686. Plenum Medical Book Company, New York and London.
12. Hogewoning AA, Goetstsch W, Van Loveren H, De Fijter JW, Vermeer BJ, Bouwes Bavinck JN. Skin infections in renal transplant recipients. Clin Transplant, 2000, in press.
13. Goettsch W, Garssen J, Timmerman HH, Dortant P, Kuper F, De Gruijl FR and Van Loveren H (1993) Systemic effects of UVB irradiation on basal immune parameters in the rat. In: *Biological Effects of Light* 1993. (Edited by E.G. Jung and M.F. Holick), pp. 637-641. Walter de Gruyter, Berlin.
14. Bouwes Bavinck JN, Vermeer BJ, Van der Woude FJ cs. Relation between skin cancer and HLA antigens in renal-transplant recipients. N Engl J Med 1991; 325: 843-848.
15. Diffey BL, Larkö O. Clinical climatology. Photodermatol 1984; 1: 30-37.
16. Termorshuizen F, Boland GJ, De Gruijl FR, Garssen J, Van Loveren H, Van Hattum J. Influence of season on antibody response to high dose rDNA hepatitis B vaccine: effect of exposure to solar UVR? [Abstract] Eur J Gastroenterol Hepatol 1999; 11(2): A94-5.
17. Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. Arch Dermatol 1988; 124: 869-71.
18. Romano G, Moretti G, Dibenedetto A, Giofre C, DiCesare E, Russo G, Califano L, Cucinotta D. Skin lesions in diabetes mellitus: prevalence ans clinical correlations. Diabetes Res Clin Pract 1998; 39(2): 101-106.

19. Trilla A, Miro JM. Identifying high risk patients for Staphylococcus aureus infections: Skin and soft tissue infections. J Chemother 1995; 7(S3): 37-43.
20. Hollander AAMJ, Hene RJ, Hermans J, Van Es LA, Van der Woude FJ. Late prednisone withdrawal in cyclosporine-treated kidney transplant patients: a randomized study. J Am Soc Nephrol 1997; 8(2): 294-301.
21. Virgili A, Zampino MR, La Malfa V, Strumia R, Bedani PL. Prevalence of superficial dermatomycoses in 73 renal transplant recipients. Dermatology 1999; 199(1): 31-34.
22. Vincenti F, Amend W, Feduska NJ, Duca RM, Salvatierra O. Improved outcome following renal transplantation with reduction in the immunosuppression therapy for rejection episodes. Am J Med 1980; 69(1): 107-112.
23. Taylor JR, Schmieder GJ, Shimizu T, Tie C, Streilein JW. Interrelationship between ultraviolet light and recurrent herpes simplex infections in man. J Dermatol Sci 1994; 8: 224-232.
24. Brandt BM, Mandleblatt J, Asbell PA. Risk factors for herpes simplex-induced keratitis: a case-control study. Ann Ophthalm 1994; 26(1): 12-16.
25. Liesegang TJ, Melton LJ, Daly PJ, Ilstrup DM. Epidemiology of ocular herpes simplex. Incidence in Rochester, Minn, 1950 through 1982. Arch Ophthalmol 1989; 107(8): 1155-1159.
26. Davis LE, Redman JC, Skipper BJ, McLaren LC, Albuquerque NM. Natural history of frequent recurrences of herpes simplex labialis. Oral Surg Oral Med Oral Path 1988; 66(5): 558-561.
27. Glynn C, Crockford G, Gavaghan D, Cardno P, Price D, Miller J. Epidemiology of shingles. J R Soc Med 1990; 83(10): 617-619.
28. Gallerani M, Manfredini R. Seasonal variation in herpes zoster infection. Br J Dermatol 2000; 142: 588.
29. Cooper M. The epidemiology of Herpes Zoster. Eye 1987; 1: 413-421.
30. Ragozzino MW, Melton LJ, Kurland LT, Chu CP, Perry HO. Population-based study of herpes zoster and its sequelae. Medicine Baltimore 1982; 61(5): 310-316.
31. Lévi FA, Canon C, Touitou Y, Reinberg A, Mathé G. Seasonal Modulation of the Circadian Time Structure of Circulating T and Natural Killer Lymphocyte Subsets from Healthy Subjects. J Clin Invest 1988; 81: 407-413.
32. Sontag Y, Guikers CLH, Vink AA, De Gruijl FR, Van Loveren H, Garssen J, Roza L, Kripke ML, Van der Leun JC, Van Vloten WA. Cells with UV-specific DNA damage are present in murine lymph nodes after in vivo UV irradiation. J Invest Dermatol 1995: 104(5): 734-738.
33. Garssen J, Van Steeg H, De Gruijl FR, De Boer J, Van der Horst GTJ, Van Kranen H, Van Loveren H, Van Dijk M, Fluitman A, Weeda G, Hoeijmakers JHJ. Transcription-Coupled and Global Genome Repair Differentially Influence UV-B-induced Acute Skin Effects and Systemic Immunosuppression. J Immunol 2000; 164: 6199-6205.

Appendix 1 Tables and Figure

Table 1a. Basic Characteristics of the Study Population included in the present analysis

Number of patients		134
Gender	male	80
	female	54
Age at renal transplantation (mean, min. – max.)		32.6 years (12.7 – 53.2)
Diabetes	yes	12
	no	122
Skin type	I	4
	II	39
	III or IV	85
	unknown	6
Number of treatments for rejections		
	0-1	44
	2-3	61
	4-6	20
	unknown	9
Cumulative life-time exposure to sunlight		
	<0.52 hours/ day	39
	0.52 – 0.77 hours/ day	44
	>0.77 hours/ day	46
	unknown	5
Cumulative exposure to sunlight since renal transplantation		
	<0.52 hours/ day	38
	0.52 – 1.17 hours/ day	45
	> 1.17 hours/ day	46
	unknown	5
Follow-up time included in the present analysis (mean, min. – max.)		19.1 years (0.06 – 29.0)

Table 1b The number and type of skin infections registered in the medical records since the time of renal transplantion

		All infections together	
	First infection per patient	Number of patients	Number of infections
Infection			
Viral			
Herpes Zoster	24 (22.8%)	48	55 (16.2%)
Herpes Simplex	9 (8.6%)	17	26 (7.6%)
Molluscum Contagiosum	4 (3.8%)	9	16 (4.7%)
Bacterial			
Impetigo vulgaris	7 (6.7%)	14	19 (5.6%)
Ecthyma	2 (1.9%)	3	3 (0.9%)
Folliculitis	15 (14.3%)	29	50 (14.7%)
Erysipelas	4 (3.8%)	12	22 (6.5%)
Erythrasma	0 (0.0%)	3	3 (0.9%)
Fungal			
Candida	18 (17.1%)	28	46 (13.5%)
Dermatomycosis	13 (12.4%)	40	63 (18.5%)
Onychomycosis	4 (3.8%)	12	18 (5.3%)
Tinea Versicolor	5 (4.8%)	11	19 (5.6%)
	105 (100%)		
No infections	**29**		
Charts not retraced	**3**		
	137 patients		**340 infections**

Table 1c. The number of infections(A), the number of follow-up years in which these infections were observed(B) and the rate of infection (A/B), by type of infection and time since renal transplantation. Those infections are shown that were included in the Poisson-analysis.

	Number of infections	Number of follow-up years	Rate of infection (number/yr)
Viral infections			
- all			
< 1 month	0	10.50	0.000
1 month - 6 months	8	53.20	0.150
6 months - 1 year	1	63.28	0.015
> 1 year	78	2432.29	0.032
- Herpes Simplex			
< 1 month	0	10.50	0.000
1 month – 6 months	4	53.20	0.075
6 months - 1 year	1	63.28	0.015
> 1 year	18	2432.29	0.007
- Herpes Zoster			
< 1 month	0	10.50	0.000
1 month - 6 months	4	53.20	0.075
6 months - 1 year	0	63.28	0.000
> 1 year	47	2432.29	0.019
Bacterial infections			
< 1 month	2	10.50	0.190
1 month - 6 months	11	53.20	0.206
6 months - 1 year	5	63.28	0.079
> 1 year	74	2432.29	0.030
Fungal/ yeast infections			
< 1 month	4	10.50	0.381
1 month - 6 months	14	53.20	0.263
6 months - 1 year	8	63.28	0.126
> 1 year	114	2432.29	0.046

Table 2. Results of the Poisson-analysis on determinants of skin infections since renal transplantation (RTP)(bivariate)

	Viral		Bacterial		Fungal/ yeast	
	RR	90%-CI	RR	90%-CI	RR	90%-CI
1. Time since renal transplantation [a]						
< 1 month			**5.95**	**2.01 - 17.61**	8.11	**3.46 - 18.99**
1 month - 6 months	**4.68**	**2.64 - 8.30**	**6.65**	**3.49 - 12.66**	5.61	**3.46 - 9.07**
6 months - 1 year	0.49	0.09 - 2.61	**2.51**	**1.17 - 5.40**	2.69	**1.17 - 6.20**
> 1 year	1.00	.	1.00	.	1.00	.
2. Gender						
Female	1.28	0.84 - 1.95	1.37	0.71 - 2.62	1.09	0.74 - 1.61
Male	1.00	.	1.00	.	1.00	.
3. Age at RTP						
< 26 years	**0.44**	**0.27 - 0.73**	0.78	0.34 - 1.81	1.20	0.75 - 1.92
26 – 39 years	1.01	0.64 - 1.60	0.91	0.44 - 1.87	1.03	0.68 - 1.57
>39 years	1.00	.	1.00	.	1.00	.
4. Diabetes						
Yes	0.99	0.48 - 2.04	**5.05**	**2.34 - 10.91**	1.66	**1.05 - 2.63**
No	1.00	.	1.00	.	1.00	.
5. Skin type						
Dark (III/ IV)	**0.53**	**0.35 - 0.81**	1.00	0.21 - 4.73	0.59	0.32 - 1.07
Intermediate (II)	**0.48**	**0.32 - 0.73**	2.04	0.40 - 10.24	0.68	0.35 - 1.30
Light (I)	1.00	.	1.00	.	1.00	.
6. Azathioprine						
<1.36 mg/kg/day	1.00	.	1.00	.	1.00	.
1.36 - 2.04 “	0.76	0.47 - 1.24	0.87	0.42 - 1.77	**1.17**[b]	0.74 - 1.85
> 2.04 “	0.91	0.48 - 1.74	0.58	0.28 - 1.24	**0.62**	0.36 - 1.08
7. Prednison						
<0.22 mg/kg/day	1.00	.	1.00	.	1.00	.
0.22 - 0.42 “	0.52	0.16 - 1.67	0.93	0.38 - 2.30	1.31	0.52 - 3.27
> 0.42 “	0.71	0.17 - 2.90	2.38	0.69 - 8.15	1.43	0.47 - 4.35
6./7. Combination 6/7						
Low	1.00	.	1.00	.	1.00	.
Intermediate	0.77	0.34 - 1.70	0.74	0.40 - 1.38	**0.56**	**0.35 - 0.89**
High	1.50	0.57 - 3.95	1.49	0.51 - 4.37	0.72	0.32 - 1.62

8. Number of treatments for rejections						
0-1	1.00	.	1.00	.	1.00	.
2-3	1.09	0.66 - 1.81	0.60	0.27 - 1.32	0.81	0.51 - 1.27
4-6	0.67	0.37 - 1.21	0.56	0.26 - 1.21	1.05	0.60 - 1.83
9. Cumulative life-time exposure to sunlight						
< 0.52 hours/ day	1.00	.	1.00	.	1.00	.
0.52 – 0.77 "	1.37	0.88 - 2.13	**2.96**	**1.42 - 6.18**	**1.67**	**1.04 - 2.69**
> 0.77 "	1.15	0.70 - 1.89	1.63	0.82 - 3.25	1.14	0.70 - 1.87
10. Cumulative exposure to sunlight since RTP						
< 0.52 hours/ day	1.00	.	1.00	.	1.00	.
0.52 – 1.17 "	1.00	0.61 - 1.63	1.59	0.74 - 3.42	1.48	0.88 - 2.47
> 1.17 "	1.09	0.63 - 1.88	1.20	0.65 - 2.22	1.16	0.70 - 1.93
11. Season						
January – March	1.00	.	1.00	.	1.00	.
April – June	1.23	0.72 - 2.11	**1.47**	**1.05 - 2.05**	**1.54**	**1.03 - 2.29**
July – September	**1.58**	**1.00 - 2.50**	**0.81**[c]	0.54 - 1.22	**2.05**	**1.36 - 3.09**
October – December	1.27	0.76 - 2.11	1.12	0.69 - 1.82	1.39	0.89 - 2.17

a No other co-variables were included.
b The difference between the rate at a daily dose of '1.36 - 2.04 mg/kg/day' and the rate at a daily dose of '> 2.04 mg/kg/day' reached the level of statistical significance (risk ratio = **1.88, 90%-CI: 1.05 – 3.37**, '>2.04 mg/kg/day' = reference category).
c The difference between the rate in 'July – September' and the rate in 'April – June' reached the level of statistical significance (risk ratio = **1.82, 90%-CI: 1.19 – 2.78**, July – September = reference category).

Table 3. Results of the Poisson-analysis on determinants of skin infections since renal transplantation (RTP)(multivariate)

	Viral		Bacterial		Fungal/ yeast	
	RR	95%-CI	RR	95%-CI	RR	95%-CI
1. Time since renal transplantation						
< 1 month			**6.47**	**1.96 - 21.35**	**7.13**	**2.62 - 19.39**
1 month - 6 months	**4.61**	**2.32 - 9.17**	**6.75**	**3.17 - 14.40**	**6.00**	**3.38 - 10.67**
6 months - 1 year	0.49	0.07 - 3.60	**2.54**	**1.04 - 6.18**	**3.24**	**1.22 - 8.59**
> 1 year	1.00	.	1.00	.	1.00	.
3. Age at RTP						
< 26 years	**0.45**	**0.25 - 0.81**				
26 – 39 years	0.99	0.56 - 1.73				
>39 years	1.00	.				
4. Diabetes						
Yes			**5.50**	**2.50 - 12.10**	**1.69**	**1.00 - 2.87**
No			1.00	.	1.00	.
5. Skin type						
Dark (III/IV)	0.64	0.36 - 1.14				
Intermediate (II)	0.64	0.38 - 1.09				
Light (I)	1.00	.				
6. Azathioprine						
<1.36 mg/kg/day					1.00	.
1.36 - 2.04 "					**1.16**[a]	0.67 - 1.99
> 2.04 "					**0.57**	0.29 - 1.12
9. Cumulative life-time exposure to sunlight						
< 0.52 hours/ day			1.00	.	1.00	.
0.52 – 0.77 "			**3.06**	**1.28 - 7.31**	1.71	0.96 - 3.05
> 0.77 "			1.99	0.77 - 5.09	1.07	0.56 - 2.05
11. Season						
January – March	1.00	.	1.00	.	1.00	.
April – June	1.23	0.65 - 2.33	**1.47**	**0.98 - 2.19**	1.54	0.96 - 2.48
July – September	1.58	0.92 - 2.73	**0.82**[b]	0.50 - 1.37	**2.06**	**1.27 - 3.36**
October – December	1.27	0.69 - 2.33	1.13	0.64 - 1.99	1.39	0.82 - 2.37

a The difference between the rate at a daily dose of '1.36 - 2.04 mg/kg/day' and the rate at a daily dose of '> 2.04 mg/kg/day' reached the level of statistical significance (risk ratio = **2.04. 95%-CI: 1.04 – 3.99**. '>2.04 mg/kg/day' = reference category).

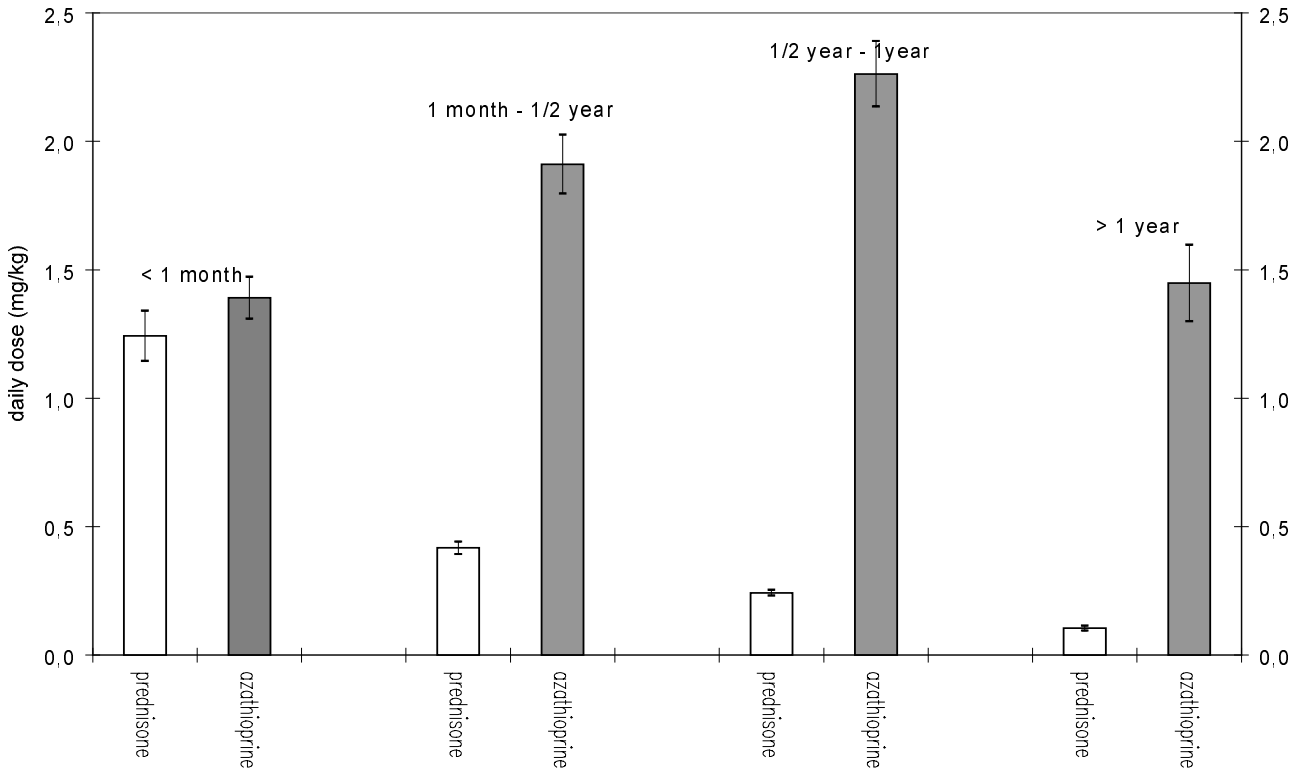
b The difference between the rate in 'July – September' and the rate in 'April – June' reached the level of statistical significance (risk ratio = **1.78. 95%-CI: 1.06 – 3.00**. July – September = reference category).

Table 4. Results of the Poisson-analysis on determinants of Herpes Simplex- and Herpes Zoster-skin infections since renal transplantation (RTP)(multivariate)

	Herpes Simplex		Herpes Zoster	
	RR	95%-CI	RR	95%-CI
1. Time since renal transplantation				
< 1 month				
1 month - 6 months	**6.72**	**1.56- 28.95**	**3.66**	**1.32 - 10.14**
6 months - 1 year	1.26	0.17 - 9.17		
> 1 year	1.00	.	1.00	.
2. Gender				
Male	2.50	0.88 - 7.13		
Female	1.00	.		
3. Age at RTP				
< 26 years			**0.30**	**0.14 - 0.62**
26 – 39 years			0.74	0.44 - 1.24
>39 years			1.00	.
6./7. Combination 6/7				
Low	0.39	0.09 - 1.68		
Intermediate	**0.17**	**0.03 - 0.94**		
High	1.00	.		
11. Season				
January – March	1.00	.	1.00	.
April – June	**4.09**	**1.15 - 14.47**	**0.64**	0.25 - 1.65
July – September	2.06	0.59 - 7.23	**1.62**[a]	0.75 - 3.50
October – December	0.66	0.12 - 3.68	1.32	0.61 - 2.88

a The difference between the rate in 'July – September' and the rate in 'April – June' reached the level of statistical significance (risk ratio = **0.39. 95%-CI: 0.17 – 0.92**. July – September = reference category).

Figure 1. Daily dosages of prednisone (white bar) and azathioprine (grey bar) by time since renal transplantation



Appendix 2 Mailing list

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3. Prof.Dr. J.J. Sixma,Voorzitter van de Gezondheidsraad
4. Prof.Dr. J.C. van der Leun, Universiteit Utrecht
5. Dr.F.R. de Gruijl, Universiteit Utrecht
6. Prof.Dr. B.J. Vermeer, Universiteit Leiden
7. Depot Nederlandse Publikaties en Nederlandse Bibliografie
8. Directie RIVM
9. Prof.Dr.Ir. D. Kromhout, directeur sector 2
10. Dr.Ir. G. de Mik, directeur sector 3/4
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12. Prof.Dr. J.G. Vos, hoofd LPI
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