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Contact Lenses and Infectious Keratitis: From a Case-Control Study to a Computation of the Risk for Wearers

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Purpose: Contact lens (CL)-related microbial keratitis (MK) has major public health implications, with about 300 million wearers worldwide, and certain potentially modifiable risk factors. This study aimed to identify the risk factors of CL-related MK.

Methods: A multicenter case-control study was conducted between 2014 and 2017. Cases presenting with CL-related MK were submitted to an anonymous 52-item questionnaire, which was also completed by healthy controls. Univariate followed by multivariate logistic regression analysis was performed. Risk factors for CL-related MK were given as odds ratio (OR) with 95% confidence interval and *P*-value.

Results: The study included a total of 2267 patients (1198 cases and 1069 controls). The MK risk factors for the daily disposable lenses group were exceeding the lens renewal period (OR = 9.16, *P* = 0.008) and occasionally wearing CL when sleeping (OR = 15.83, *P* = 0.035). The most important risk factors in the nondaily disposable

lenses group were lens cleaning solution distributed by eye care brands (OR = 3.50, *P* < 0.001) and failure to renew lens cases (OR = 3.39, *P* = 0.001). Statistically and clinically significant variables were used to establish the MK risk equation for CL wearers, allowing an individual calculation of the risk of MK under lenses.

Conclusions: The MK risk equation is a valuable tool for educating patients about the risks associated with wearing CL. It allows the patient to be informed about their overall risk of infection while detailing the precipitating elements of the infectious risk with the aim of modifying risk behavior.

Key Words: microbial keratitis, contact lenses, epidemiology
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Contact lenses (CLs) are medical devices that are primarily used for the correction of ametropia. There were approximately 300 million CL wearers worldwide in 2017, representing a market of \$7.2 billion.^{1,2} It is therefore an important market for manufacturers, but these economic issues should not obscure the complications of wearing CL. Microbial keratitis (MK) is the most feared because it can cause blindness or even in the most serious cases the anatomical loss of the eyeball. Wearing CL is the main risk factor for MK in working-age populations.³ The incidence of MK among CL wearers varies between 1.9 and 4.1/10,000 wearers/yr for daily wearing of soft hydrophilic CLs and 0.2 to 2/10,000 wearers/yr for rigid gas permeable CLs.^{4–6}

In France, the prescription of CLs is legally the prerogative of ophthalmologists. Delivery is performed on prescription by opticians. However, given the difficulties of access to ophthalmologists, patients obtain lenses directly from the internet or after a refractive test at an optician or orthoptist. Moreover, cleaning solutions are usually prescribed by ophthalmologists. There is a right of substitution for pharmacists and opticians, subject to issue an equivalent product. This equivalence is not always respected. Multipurpose solutions can then be delivered in place of oxidizing solutions, for example. Finally, in France, some optical

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groups offer their own cleaning solutions. In addition to the health risks for patients, MK represents a significant cost for our healthcare systems. MK was responsible for almost 1 million specialized consultations (930,000 in medical practices and 58,000 in hospitals), representing approximately \$175 million in direct health costs in 2010 in the United States. Because CLs are the primary risk factor for MK, much of this health expenditure is likely to be secondary to CL-related complications.^{7,8} Epidemiological studies have identified a number of risk factors in recent years. However, these studies are often limited to a reference center and a limited duration of inclusion. In addition, current data on daily disposable lenses (DDLs) are relatively poor. Finally, these studies remain descriptive and do not exploit the data by developing educational tools for prescribers and patients.

The objective of our study is therefore to determine the risk factors for CL-related MK.

METHODS

A retrospective case-control study was conducted between January 2014 and December 2017. The subjects were CL wearers who had an episode of clinically confirmed infectious keratitis (presence of one or more corneal infiltrates associated with epithelial ulceration) or microbiological keratitis (identification of a pathogen on corneal scraping). The control group consisted of healthy wearers who consulted their ophthalmologist for CL renewal and any other purpose.

Patient enrolment was carried out in 22 French universities and regional hospitals (Besançon, Bordeaux, Brest, Caen, Dijon, Epinal, Fort-de-France, Grenoble, Limoges, Lyon, Marseille, Montpellier, Nancy, Nantes, Nice, Paris Kremlin-Bicêtre, Paris XV-XX, Perpignan, Rouen, Saint-Etienne, Toulouse, and Strasbourg) as well as in 11 private ophthalmologists' practices belonging to the French Society of Ophthalmologists Contact Lens Adapters.

The same day as their emergency consultation for MK, all cases completed an anonymous questionnaire of 52 questions developed at Strasbourg University Hospital, under the control of the referent ophthalmologist. This questionnaire made it possible to collect epidemiological data (sex, age, etc.) and information on the characteristics of the CL, its care, and the patient's lifestyle.^{9,10} All patients signed an explicit informed consent form. We conducted our study in compliance with recognized international standards, including the International Conference on Harmonization, the Council for International Organizations of Medical Sciences, and the principles of the Declaration of Helsinki. The study has been validated by a local ethics committee and the Commission Nationale de l'Informatique et des Libertés' (CNIL's) recommendations (declaration 1808523v0).

The statistical analysis was performed by the Professor Nicolas Meyer (Department of Medical Statistics, Strasbourg University Hospital). All the questionnaires were analyzed. Owing to matching cases to controls and also to a few missing data, multivariate stepwise logistic regression was performed by multiple imputation with univariate logistic regression carried out on complete cases, yielding crude odds ratio (OR). Questions that could not be applied to cases and controls were excluded from the analysis (eg, did you sleep while wearing

your lenses the day before infection?). We conducted 2 statistical analyses in parallel: one concerned the DDL group and the second all other renewal frequencies (non-DDL group). The specificities of wearing DDL, including the lack of lens care required, made their comparison with other types of lenses irrelevant, and could even distort the statistical analysis. The questions concerning CL care (massage/rinsing after removal, cleaning solution, etc.) were thus not taken into account for the statistical analysis concerning DDL.

The analysis started with a univariate logistic regression to determine the significant variables (threshold defined at 20%) that would be retained for the multivariate analysis. Variables that were statistically significant, but also those that were clinically relevant but not statistically significant (forced variables) in univariate, were selected for multivariate analysis. These forced variables were retained because they had already been associated in the literature with an increase in the risk of MK or because they strongly appeared to be associated in our clinical experience.

After multivariate logistic regression, statistically ($P < 0.05$) and/or clinically significant variables were used to generate an equation of risk of developing MK in CL wearers using the following formula:

$$P(\text{Microbial keratitis}) = 1 / (1 + \exp(-(b_0 + b_1x_1 + b_2x_2 + \dots + b_nx_n)))$$

with b_0 being the constant of the regression equation, b_n being the decimal logarithm of the OR of the variable n , and X_n being the value of the variable n .

Thus, weighting of each factor was performed using the decimal logarithm of the OR. The number of variables retained for the 2 equations (DDL and non-DDL) could not exceed 10% of the lowest number in the case group or the control group (ie, 12 for DDL and 95 for non-DDL). For numerical variables, cutoffs were determined using receiver operating characteristic curves before univariate analysis.

RESULTS

A total of 2267 patients were included. The daily disposable lens wearers numbered 268, comprising 119 controls and 149 cases. Regarding the non-DDL group, 1999 patients were included, comprising 950 controls and 1049 cases. The average age was 32 ± 12 years for patients wearing DDLs and 33.28 ± 12.6 years for nondaily lens wearers (Table 1). No questionnaire was excluded.

The results of the multivariate analysis for the nondaily disposable lens group are presented in Table 2.

Among the significant results, the following elements were noted: men were more likely to develop infectious keratitis (OR = 1.76, $P = 0.017$). Myopia was a risk factor compared with hyperopia (OR = 2.60, $P = 0.002$), as was wearing lenses for reasons other than myopia or hyperopia (OR = 2.07, $P = 0.031$). Patients who had been wearing lenses for less than 13 years also had a significantly higher risk of MK (OR = 2.19, $P = 0.003$). Wearing lenses less than 5 days a week was a protective factor (OR = 0.30, $P < 0.001$).

TABLE 1. Description of the Study Population

	Control	Cases
Total number	1019	1198
Age (yr)	33.1 (13.0)	32.2 (12.3)
Sex ratio (% male)	69	31
Daily disposable wearers		
N	119	149
Age in yr (Mean [CI])	32.0 (12.0)	33.1 (11.9)
Sex ratio (% male)	55	45
Nondaily disposable lenses		
N	950	1049
Age (yr)	33.3 (13.4)	32.1 (12.4)
Sex ratio (% male)	69	31

CI, confidence interval.

Adaptation by an ophthalmologist was a protective factor (OR = 0.40, $P = 0.037$), as was handling instruction by an ophthalmologist (OR = 0.35, $P = 0.015$) or by their assistant (OR = 0.20, $P = 0.010$). Washing hands with soap and drying them was protective (OR = 0.58, $P = 0.034$). Prescription of a cleaning solution by an ophthalmologist was protective (OR = 0.54, $P = 0.001$), as was the use of multipurpose solutions (OR = 0.62, $P = 0.014$), but the use of lens cleaning solutions distributed by eye care brands was a risk factor (OR = 3.50, $P < 0.001$). Mixing of new and old solution in the same lens case, or “topping off,” was also a risk factor (OR = 2.25, $P = 0.003$). Closure of the cleaning solution cap was a protective factor (OR = 0.29, $P < 0.001$), as was renewal of the lens case every 2.5 months or less (OR = 0.52, $P = 0.003$). Failure to renew the lens case was a significant risk factor (OR = 3.40, $P = 0.001$). Cleaning the lens case every 1.5 days or less was protective against the risk of keratitis (OR = 0.50, $P < 0.001$).

A history of eye infection (OR = 2.29, $P < 0.001$) and other noninfectious ophthalmological conditions (OR = 2.54, $P = 0.034$) were risk factors for MK. General health history was also a risk factor (OR = 2.10, $P = 0.001$). Patients who had a level of education above secondary level had a higher risk of IK, but this risk decreased with the level of studies with OR = 2.24, $P < 0.001$ for a level between completion of secondary education and 2 years of university study, OR = 1.60, $P = 0.034$ for a level between 2 and 4 years of university study and finally OR = 1.18, $P = 0.415$ for a level higher than 4 years of university study even if for the latter statistical significance was not reached.

The results of the multivariate analysis for the daily disposable CL group are presented in Supplemental Table 1 (Supplemental Digital Content 1, <http://links.lww.com/ICO/A962>).

Among the significant results, the following elements were noted: patients who were sleeping with their lenses were more likely to develop infectious keratitis (OR = 15.83, $P = 0.035$). Exceeding the lens renewal period was a risk factor

TABLE 2. Comparative Data With Frequencies in Each Group, Multivariate ORs, and P -value for the Risk Factors Relative to the 1049 Contact Lens-Related Microbial Keratitis Patients Wearing Nondaily Disposable Contact Lenses (Cases) and 950 Healthy Wearers (Controls)

Variable	Control (%)	Cases (%)	OR	P
N	950	1049	NA	NA
Age (yr)	33.3	32.1	0.99	0.466
Male sex	69	31	1.76	0.017
Level of education between completion of secondary education and 2 years of university study (compared with lower than completion of secondary education)	33.7	30.9	2.24	<0.001
Level of education between 2 and 4 years of university study (compared with lower than completion of secondary education)	16.0	20.8	1.60	0.034
Level of study higher than 4 years of university study (compared with lower than completion of secondary education)	22.2	29.7	1.18	0.415
Age of first prescription (yr)	20.2	20.6	1.02	0.230
CL wearer for ≤ 13 years	50.4	73.3	2.19	0.003
CL wearer for corneal pathology	1.3	5.7	10.35	0.225
CL wearer for refractive impairment	98.4	95.5	0.87	0.427
Existence of a refractive problem	100.0	77.8	0.40	0.550
Myopia compared with hyperopia	68.9	76.2	2.60	0.002
CL wearer for a reason other than myopia or hyperopia (compared with hyperopia)	30.4	45.8	2.07	0.031
Rigid lens wearer	11.5	4.6	0.56	0.789
Soft lens wearer	88.3	95.2	6.89	0.485
Silicone hydrogel lens versus hydrogel	23.9	29.5	1.47	0.168
Weekly renewal	1.0	2.2	2.17	0.270
Bi-monthly renewal	16.8	20.4	1.28	0.597
Monthly renewal	63.	69.5	1.85	0.158
Continuous wear	2.1	6.9	1.68	0.201
Daily wear	69.5	80.7	1.17	0.594
Exceeding the lens renewal period	31.0	45.0	1.19	0.276
No. of hours of wear per day ≤ 11 hours	36.6	24.2	0.73	0.088
No. of days of wear per week ≤ 5 days	22.4	12.7	0.30	$P < 0.001$
Has slept while wearing CLs	19.4	44.7	1.65	0.099
Adaptation by an ophthalmologist	95.6	76.3	0.41	0.037
Adaptation by an optician	8.1	25.3	1.03	0.930
Adaptation by another actor	0.1	1.2	3.88	0.453

(Continued)

TABLE 2. (Continued) Comparative Data With Frequencies in Each Group, Multivariate ORs, and *P*-value for the Risk Factors Relative to the 1049 Contact Lens-Related Microbial Keratitis Patients Wearing Nondaily Disposable Contact Lenses (Cases) and 950 Healthy Wearers (Controls)

Variable	Control (%)	Cases (%)	OR	<i>P</i>
Purchase of lenses directly over the internet	0.1	1.2	16.02	0.96
Existence of a dedicated instructive session	72.2	65.8	0.54	<i>P</i> < 0.001
Information on handling lenses	95.6	81.4	0.65	0.122
Handling instruction with an ophthalmologist	58.4	38.4	0.35	0.015
Handling instruction with an ophthalmologist's assistant	15.1	11.9	0.20	0.010
Handling instruction with an optician	32.8	36.0	2.00	0.111
Handling instruction with another actor	0.3	2.9	9.53	0.319
Learning to handle alone	1.8	9.0	1.89	0.264
Duration of information ≤ 14 min	55.7	65.6	1.36	0.039
Time since last consultation ≤ 15 mo	68.5	55.6	0.85	0.601
Last consultation over a yr ago	39.0	49.1	1.06	0.813
Never had an ophthalmologic consultation	8.4	16.3	1.02	0.966
Wash hands with soap and dry before inserting lenses	65.9	51.1	0.85	0.556
Wash hands with soap and dry before removing lenses	60.1	33.7	0.58	0.034
Rub and rinse lenses before inserting	18.6	11.9	0.71	0.096
Cleaning solution prescribed by an ophthalmologist	58.9	29.7	0.54	0.001
Optician/pharmacist's compliance with prescribed product	73.9	53.7	0.90	0.692
Lens cleaning solutions distributed by eye care brands	9.1	27.0	3.50	<i>P</i> < 0.001
Multipurpose cleaning solution	63.9	59.3	0.62	0.014
Oxidizing cleaning solution	5.5	3.3	0.62	0.629
Has used saliva to clean lenses	5.8	3.3	0.41	0.026
Closure of cleaning solution cap	95.6	82.2	0.29	<i>P</i> < 0.001
Period of use of cleaning solution ≤ 2 months	61.4	43.3	0.80	0.311
Mixing of new and old cleaning solution ("topping off")	7.6	24.1	2.27	0.003
Lens case cleaning frequency ≤ 2 days	51.4	29.8	0.50	<i>P</i> < 0.001
Cleaning lens case with water	30.2	32.6	1.17	0.388
Cleaning lens case with CL cleaning solution	39.3	34.9	0.53	<i>P</i> < 0.001

TABLE 2. (Continued) Comparative Data With Frequencies in Each Group, Multivariate ORs, and *P*-value for the Risk Factors Relative to the 1049 Contact Lens-Related Microbial Keratitis Patients Wearing Nondaily Disposable Contact Lenses (Cases) and 950 Healthy Wearers (Controls)

Variable	Control (%)	Cases (%)	OR	<i>P</i>
Never cleaning lens case	4.7	6.4	1.51	0.313
Lens case renewal frequency ≤ 2.5 months	58.6	32.9	0.52	0.003
Never renewing lens case	2.4	13.9	3.40	0.001
Lenses have been in direct contact with sink	18.5	27.5	1.31	0.139
Use of eye drops with lenses	18.8	15.2	0.83	0.391
Patient medical history (except ophthalmological history)	15.9	21.3	2.10	0.001
History of eye infection	29.5	44.3	2.29	<i>P</i> < 0.001
A single previous case of eye infection versus several	40.1	29.8	0.71	0.069
Time since last infection ≤ 365 days	14.7	31.2	1.93	0.038
Other ophthalmologic problem(s)	2.9	5.8	2.54	0.034
Exposure to air conditioning on a daily basis	25.7	30.7	1.36	0.073
Make-up	52.3	61.6	1.04	0.864
Allergy	13.0	9.1	0.74	0.367
Dry eyes	23.8	19.7	0.69	0.079
Sensitivity to atmospheric pollution	25.3	19.8	0.61	0.027
Active smoker	21.8	33.7	1.23	0.501
Live in the countryside	37.9	27.8	0.47	<0.001

Statistically significant results (*p* < 0.05) are in bold characters.

(OR = 9.17, *P* = 0.008). Adaptation by an ophthalmologist was a protective factor (OR = 0.01, *P* = 0.003), to the contrary of an adaptation by an optician (OR = 14.30, *P* = 0.042).

The variables that were statistically significant after the multivariate analysis, and some variables considered clinically relevant, were combined according to the formula: $P(\text{Microbial keratitis}) = 1/(1+\exp(-(b_0+b_1x_1+b_2x_2+\dots+b_nx_n)))$ with b_0 being the constant of the regression equation, b_n being the decimal logarithm of the OR of variable n , and X_n being the value of variable n . We included 12 variables in the DDL equation and 32 variables in the non-DDL equation. An example of a dynamic risk calculation using the equation is presented for 2 extreme situations: a rigid lens wearer (see Supplemental Video 1, Supplemental Digital Content 2, <http://links.lww.com/ICO/A963>) and a soft lens wearer with many risk behaviors (see Supplemental Video 2, Supplemental Digital Content 3, <http://links.lww.com/ICO/A964>). Once the questionnaire will be validated, the patient will be informed of his of developing MK, displayed as a percentage. This percentage reflects the risk of belonging to the CL-related MK group (cases) at the time the questionnaire is completed.

DISCUSSION

This case-control study included more than 2000 patients. Because MK remains a rare disease, a case-control study was more appropriate than the exposed-unexposed type, with all the methodological weaknesses that this implies. This study design has already been used by Schein and Poggio in 1990⁴. One of the main results of this study was that overnight lens use, whether regularly with extended wear lenses or occasionally with daily wear lenses, emerged as the preeminent risk factor for ulcerative keratitis. One of the weaknesses of the study lies in the recruitment of controls, which probably underestimates the proportion of patients providing CLs by the internet or opticians. Odds ratios, and not relative risks (unlike a prospective study of the exposed-unexposed type), have been calculated, but their values are statistically comparable in the case of a rare pathology. For methodological reasons, statistical analysis had to be performed separately for daily disposable and non-DDLs. However, this separate analysis is clinically relevant because the habits and behaviors of both wearers are relatively different.

With 149 cases of daily disposable CLs-related MK and 119 controls, our study makes it possible to highlight some risk factors specific to these lenses. Few studies in the literature have specifically addressed the risk factors for MK in daily disposable CL wearers.^{6,11,12} These lenses have specific features, including the theoretical absence of CL care. Many variables, risk factors for CL-related infection, were significant in univariate analysis but were no longer significant after multivariate analysis. This is probably related to the limited number of DDL wearers in our study. Exceeding the lens renewal period and wearing CLs when sleeping are risk factors that are widely described in the literature.^{6,11-15} Adaptation by an ophthalmologist is protective, which is consistent with the results of the study we conducted on the first questionnaires.^{9,10} More surprisingly, we have also found a protective effect of adaptation by opticians, which diverges from our initial results and results concerning frequent renewal lenses. It can be assumed that these results are related to a recent improvement in the training of opticians on the risks associated with CLs. Because the development of DDL is relatively recent, most questionnaires completed by patients with DDL were collected in the later years of the study. This may explain why optician adaptation is protective in DDL wearers and not in other CL wearers. This result is important in the current context of progressive delegation of the prerogatives of ophthalmologists to paramedical professionals, notably in France.¹¹ Because the development of DDLs has accelerated considerably in recent years, it is therefore likely that a modification of the prescriptions and habits of the wearers appeared during the study. This evolution of practices encourages continued epidemiological surveillance and the realization of new studies on the specific risk analysis in this population.

We also included nearly 2000 patients wearing nondaily disposable CLs over 4 years, which is one of the largest cohorts studied in the literature. Most risk factors have already been described in previous studies. Myopic patients were 2.5 times more likely to develop CL-related IK than hyperopic patients, unlike the results of Dart et al.¹² It may be assumed that myopic patients tend to wear their lenses more often than

hyperopic patients, especially slightly hyperopic patients who often have good vision without correction. However, our study showed that wearing CL 5 days or less a week protected against the risk of MK, as previously published.⁹ Our study also confirms the central place of the ophthalmologist in the prevention of CL-related MK because adaptation by an ophthalmologist is protective, as is receiving handling instructions directly from them or by their assistant (but under their control). These results are consistent with those of our preliminary study^{9,10} but are also weighted with those we observed in the analysis of the DDL group, where we also found a protective effect of adaptation by an optician. It is interesting to note that purchasing lenses directly over the internet was a powerful risk factor (OR = 16) that approached significance without reaching it ($P = 0.096$). If this risk factor seems obvious in our clinical experience, the lack of statistical significance could be related to the relatively recent development of this method of delivery. The phenomenon was marginal at the launch of our study but has grown considerably since its legalization and framework provided by different laws.¹⁶ Hygiene and lens care errors are still major risk factors for infection; the use of a lens cleaning solution distributed by eye care brands and failure to renew the lens case are the most powerful risk factors of our study. We have identified many other factors related to hygiene and lens care, most of which had already been described in the literature.^{3-5,8-10} This further reinforces the need for patient education with basic rules of hygiene and the handling of lenses.

The primary objective of identifying risk factors in our study was to induce a change in risk behavior to reduce the incidence of MK in CL wearers. The rate of poor compliance of CL-wearing patients varies between 50% and 99% in the literature,¹⁷ whereas 90% of the patients consider that they are vigilant wearers.¹⁸ To find an efficient way to transmit our results to wearers was also a goal of this study. The main errors relate to hygiene and renewal procedures.^{19,20} There are many illustrations of this lack of information in the literature, for example, the case of a 67-year-old woman with 27 lenses in one eye.²¹

It is to respond to this lack of information that we have developed the risk equation of CL-related MK. To ensure the dissemination of our new tool to the greatest number, a Web site may be developed. Questions may be answered by the practitioner or the patient himself. The site code will then convert the answers to the questions into binary numeric values "0" (no) or "1" (yes) for each variable in the equation including for numeric values because the cutoffs have been determined beforehand (except for the age of civil majority where the value is kept as such). Once the questionnaire will be validated, the patient will be informed of his developing MK, displayed as a percentage. This percentage reflects the risk of belonging to the CL-related MK group (cases) at the time the questionnaire is completed. The quantified result therefore places the patient in a group with a weighted risk of MK. Taking into account of the detailed results, the ophthalmologist may eventually modify his prescription of lenses or cleaning solution and accurately inform the patient about the errors made (lack of hygiene, renewal period schedules, etc.). His risk factors will then be listed under the result along with recommendations to follow to reduce his risk.

Finally, this study has described the main risk factors for CL-related MK that are consistent with data from the literature. The weighting of these various factors allowed the creation of an equation calculating the risk of infection in wearers. This equation is accessible through the development of a Web site and allows the patient to access information on their overall risk of infection while detailing the precipitating elements of the infectious risk. This tool thus allows for a possible identification and modification of risk behavior with the aim of achieving a reduction in the incidence of CL-related MK.

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