

Epidemiological study of infectious keratitis in inpatients of a tertiary hospital center – revision of 5 years

Estudo epidemiológico das queratites infecciosas internadas num centro hospitalar terciário - revisão de 5 anos

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ABSTRACT

Objective: Infectious keratitis is a pathology with a high incidence and is responsible for a large number of prolonged stay hospital admissions. The purpose was to analyze the epidemiological and clinical data associated with high risk microbial keratitis at a central hospital in Portugal. **Methods:** A retrospective study of all inpatients presenting with corneal abscess in Centro Hospitalar Universitário do Porto, from April 2013 to March 2018 was performed. Target population was characterized by risk factors, clinical features, length of stay, culture results, in vitro antibiotic resistance, treatment and outcome. **Results:** This study included 105 patients. The main risk factors were previous corneal surgery, contact lenses wear and recent history of ocular trauma. 74.3% of patients had a positive culture, 87.9% of these corresponding to a pure bacterial culture, with *Pseudomonas aeruginosa* and *Streptococcus pneumoniae* being the most common pathogens. 27.9% of positive cultures were resistant to 3 or more classes of antibiotics. All patients began treatment with fortified drops. 29.5% of patients required a corneal transplant. After 6 months of follow-up, only 20.9% presented a VA>20/40. **Conclusion:** Most cases were caused by bacteria. A considerable number of multi-resistant bacteria was identified. Despite most cases having improved after treatment, a large number of patients had a significant visual acuity sequelae.

Keywords: keratitis/microbiology; Drug resistance; Eye infections

RESUMO

Objetivo: A queratite infecciosa é uma doença de incidência relativamente elevada e é responsável por um número importante de internamentos. Neste estudo pretende-se estudar diversas características epidemiológicas e clínicas associadas às queratites infecciosas de alto risco num hospital terciário em Portugal. **Métodos:** Realizou-se um estudo retrospectivo, onde foram incluídos todos os doentes internados por abscesso da córnea no Centro Hospitalar Universitário do Porto (CHUP), entre Abril de 2013 a Março de 2018. Caracterizou-se a população em relação aos fatores de risco, apresentação clínica, tempo de internamento, resultados de culturas, resistência antibiótica in vitro, tratamento efetuado e resultado funcional. **Resultados:** O estudo incluiu 105 doentes. Os principais fatores de risco foram antecedentes de cirurgia de córnea, uso de lentes de contacto e história recente de trauma ocular. 74,3% dos doentes tiveram cultura positiva com 87,9% a corresponderem a cultura bacteriana pura, sendo a *Pseudomonas aeruginosa* e o *Streptococcus pneumoniae* os agentes etiológicos mais frequentes. 27,9% das culturas positivas eram resistentes a 3 ou mais classes de antibióticos. Todos os doentes iniciaram tratamento com colírios fortificados. 29,5% dos doentes necessitaram de realizar transplante de córnea. Ao final de 6 meses de seguimento, apenas 20,9% apresentavam AV>20/40. **Conclusão:** Na maioria dos casos, a etiologia foi bacteriana. Observou-se um número considerável de bactérias multirresistentes. Apesar do tratamento ter permitido uma melhoria da visão na maioria dos casos, um número considerável de doentes ficou com sequelas visuais importantes.

Descritores: Ceratite/microbiologia; Resistências microbiana a medicamentos; Infecções oculares.

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INTRODUCTION

Infectious keratitis is characterized by the presence of a stromal inflammatory infiltrate usually associated with epithelial defect originated by the invasion of corneal tissue by microorganisms.⁽¹⁾ This is an important cause of visual impairment and blindness, often affecting populations socially excluded from access to health care.⁽²⁾ The incidence is relatively high⁽³⁾ and is responsible for a significant number of hospitalizations in our hospital. In many cases, it may be associated with poor functional prognosis, especially if not properly diagnosed and treated. Proper treatment can reduce the incidence of severe vision loss and restrict corneal damage.⁽⁴⁾

Infectious keratitis is rare in the absence of predisposing factors. Until recently, most cases of bacterial keratitis were associated with ocular trauma or eye surface disease.⁽⁵⁾ However, widespread use of contact lenses has dramatically increased the incidence of keratitis related to contact lens, and is a major risk factor in the United States, while in developing countries it is more common to be caused by ocular trauma during agricultural activities.⁽²⁾

The most consensual diagnosis method is ocular exudate collection for microbiological study, although sensitivity is around 40-70% consistently over the past 10 years.⁽⁶⁻⁸⁾ Microorganisms isolated from severe cases of keratitis and their treatment sensitivities also vary geographically and over time.⁽⁹⁾ The emergence of drug resistance and availability of new antimicrobials has made it essential to constantly update knowledge about treatment protocols.⁽⁴⁾

The pattern of infectious keratitis varies significantly from country to country, and even from region to region. The present study aims to study various epidemiological variables and clinical characteristics associated with high-risk infectious keratitis in a tertiary hospital in Portugal, allowing to evaluate diagnostic issues, treatment resistance, and possible prevention strategies.

METHODS

A retrospective study was carried out including all patients hospitalized for corneal abscess at Centro Hospitalar Universitário do Porto (CHUP) from April 2013 to March 2018. All hospitalization records, previous emergency episodes, previous and post-hospitalization records, microbiological results were analyzed, as well as surgical reports when applied to each case.

The ocular exudate was collected at the emergency department before patients were admitted. The decision to admit required at least one of the following severity criteria: central lesion; infiltrate greater than 2mm of larger diameter; therapeutic failure (non-resolution or clinical worsening); and suspicion of atypical body (through clinical history and characteristics of biomicroscopy).

The following culture media were used per protocol for the microbiological study: blood agar (non-selective medium for isolation of gram negative and positive bacteria), chocolate agar (nutrient medium for isolation of demanding microorganisms), Sabouraud agar (culture and growth of fungal species), and thioglycolate (enriched liquid medium). When viral keratitis (characteristic dendritic appearance) was suspected, polymerase chain reaction (PCR) analysis was invariably used.

Depending on the microorganism isolated, the susceptibility test carried out included the following therapeutic agents: B-lactams (amoxicillin + clavulanic acid, penicillin, ampicillin, oxacillin, piperacillin + tazobactam, imipenem), fluoroquinolones (ciprofloxacin, levofloxacin), cephalosporin (ceftazidime, cefepime), aminoglycosides (tobramycin, gentamycin, neomycin, amikacin), chloramphenicol, tetracycline (minocycline), polymyxins (polymyxin B and colistin), glycopeptides (vancomycin, teicoplanin), macrolides (erythromycin), bacteriostatic (fusidic acid), lincosamides (clindamycin), and sulfonamides (sulfamethoxazole + trimethoprim).

The study population was characterized by gender, age, laterality, risk factors, clinical presentation, length of stay, culture results, in vitro antibiotic resistance, treatment carried out, and functional outcome.

Data was analyzed using SPSS Statistics, version 22.0. Statistical analysis of quantitative data including descriptive statistics and parametric and nonparametric comparisons were carried out for all variables. Frequency analysis was carried out using the Chi-square test. P values lower than 0.05 were considered statistically significant.

RESULTS

EPIDEMIOLOGICAL CHARACTERISTICS

The study included 105 patients, 52.4% right eyes, and 47.6% left eyes. Most patients were women (60.0% vs 40.0%). The average age was 58.4±19.9 years. The age group between 60 and 80 years had a higher number of patients involved (43.8%), with females representing the vast majority of cases (65.2% - Figure 1). The average age was similar over time (Kruskal-Wallis test, $p = 0.711$), although there is a trend towards increasing age, as shown by the trend line (Figure 2).

The main risk factors identified were history of corneal surgery (26.7%), use of contact lens (24.8%), and recent history of eye trauma (10.5% - Figure 3).

Of the patients with history of corneal surgery, 71.4% underwent penetrating keratoplasty (PQ - Figure 4).

Of the subgroup previously submitted to PQ, 60% of cases had graft failure as a previous surgery pathology, and 15% of cases had perforated decemetocoele. Regarding the suture technique, about 94% of patients were sutured with single stitches, as opposed to the continuous suture present in the remaining 6% of cases, although this distribution also reflects the most frequently used technique in our service. Regarding the time elapsed between the date of PQ and the appearance of the abscess, it was found that it took on average 1.6±3.1 years, and in more than half of cases the abscess appeared during the first year after surgery (Figure 5).

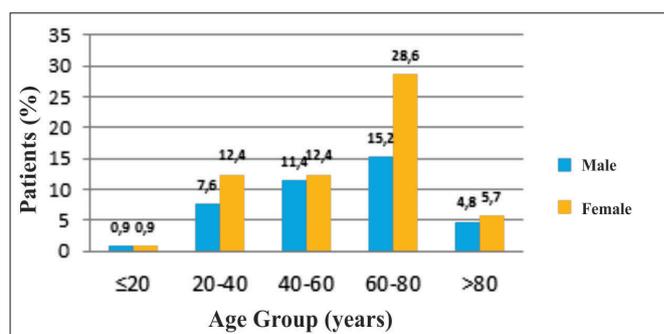


Figure 1: Distribution of patients per age group and gender.

In addition, at the time of corneal abscess diagnosis, 63% of this subgroup of patients were still on topical immunosuppression, and 10% on systemic immunosuppression to prevent graft rejection.

The following were considered as risk factors in the category of “systemic disease”: immunosuppression, diabetes mellitus, and psoriatic arthritis. The category “ocular surface alteration” included rosacea, keratoconus, facial paralysis, and ocular herpes. The average time elapsed between symptom onset and first observation at CHUP was 6.2 ± 7.1 days, with no statistically significant difference between the 2 genders (t test, $p = 0.787$). Patients over 40 years old tend to see their ophthalmologist later (on average 7 days) after symptom onset than patients aged 40 years or less (on average 3.3 days) (t test, $p = 0.049$).

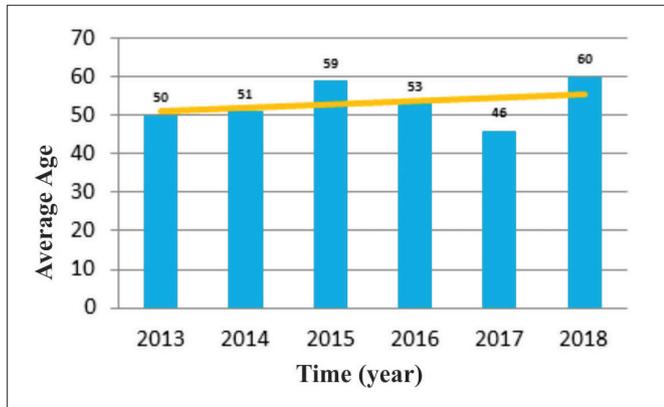


Figure 2: Average age of patients per year, with trend line.

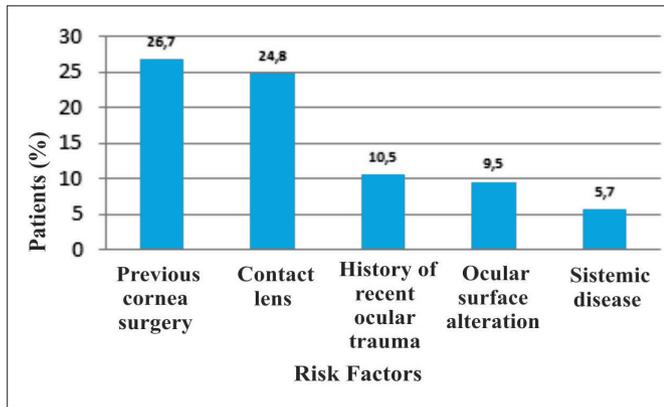


Figure 3: Distribution of risk factors.

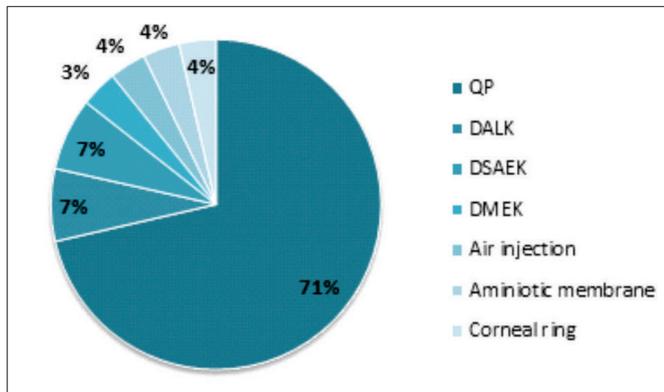


Figure 4: Previous corneal surgery.

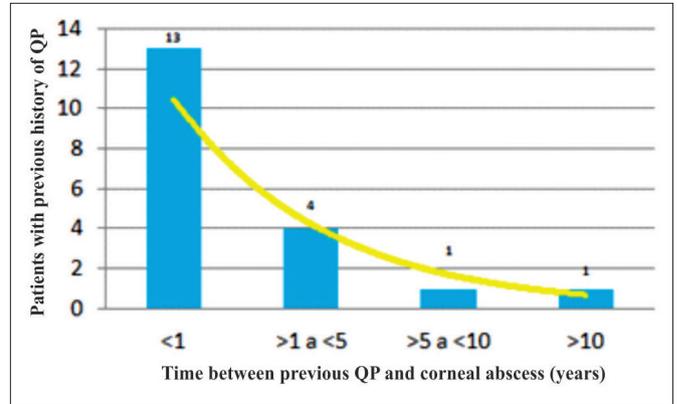


Figure 5: Time elapsed between previous PQ and the appearance of corneal abscess.

MICROBIOLOGICAL RESULTS

Of the 78 (74.3%) patients who collected exudate for microbiological analysis, 58 (74.4%) had positive culture. Of the positive results, 87.9% corresponded to bacterial culture, 6.9% to fungal culture, 3.4% to Acanthamoeba culture, and 1.7% to mixed culture (one species of bacteria and one fungus). (Figure 6)

The most common bacterial isolate was Pseudomonas aeruginosa with 22.6%, followed by Streptococcus pneumoniae with 12.9% (Figure 7); 61.3% of bacterial isolates were gram positive, with Staphylococcus being the most common species. Within gram negative (39%), the predominantly isolated species was Pseudomonas (58.3% - Figure 8). There were no statistically significant differences in the average age (T-test, $p = 0.406$) and symptom duration (t, test $p = 0.301$) between patients with gram positive and negative exudates.

Regarding the risk factors, positive cultures in patients who underwent ocular trauma were 50% positive for coconut gram positive; in patients with contact lens it was 56.2% for gram negative bacillus; and in patients who underwent previous penetrating keratoplasty it was 50% for coconut gram positive.

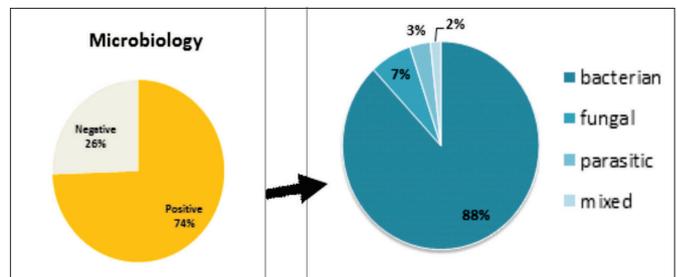


Figure 6: Microbiological result.

The most common fungal isolates were Fusarium spp and Candida spp, with 40.0% each. For parasites, only 2 cases (3.4% of patients) of Acanthamoebawere identified. The main risk factor identified for fungal and parasitic infectious keratitis was the use of contact lenses.

There are no statistically significant differences in the average age (Kruskal-Wallis test, $p = 0.116$) and the average duration of symptoms (Kruskal-Wallis, $p = 0.235$) among patients with bacterial, fungal or parasitic exudates (test).

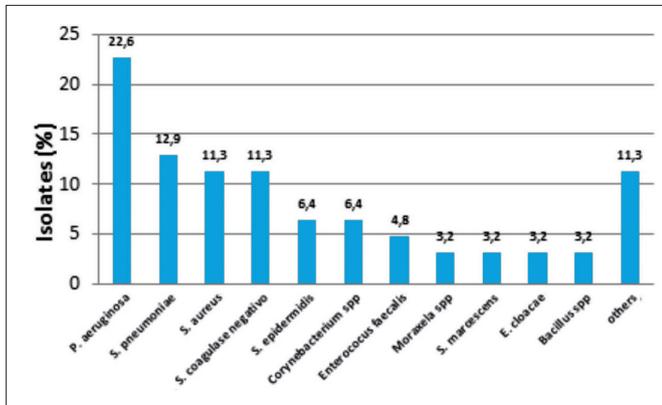


Figure 7: Distribution of bacterial species

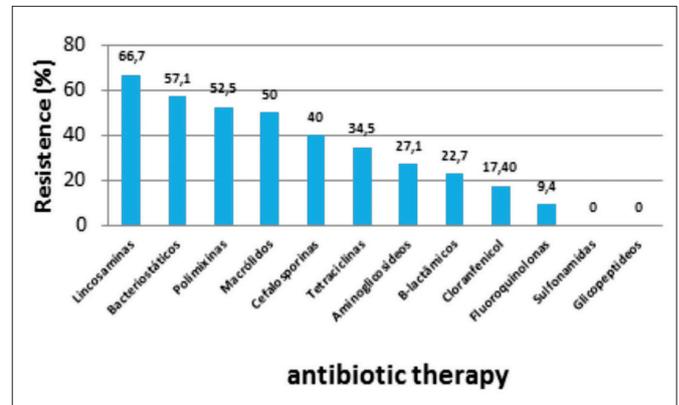


Figure 9: Resistances per antibiotics.

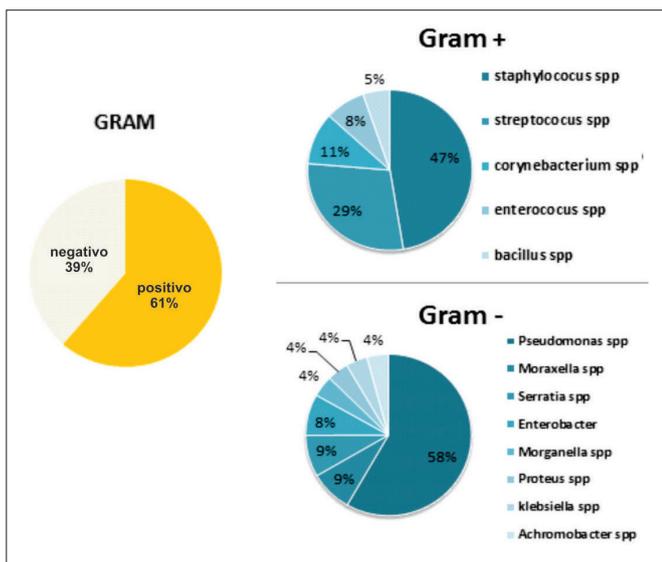


Figure 8: Gram negative vs gram positive

The most resistant in vitro antibiotics were colistin (60.9%), and fusidic acid (57.1%). In terms of classes, lincosamines and bacteriostats were the most resistant. Glycopeptides (including vancomycin), sulfonamides and fluoroquinolones have resistance below 10%. The distribution of resistances by therapeutic class can be better observed in figure 9.

We observed that 27.9% of positive cultures were resistant to 3 or more classes of antibiotics, without statistically significant differences between gram positive and gram negative (Chi-square test, $p = 0.703$), average ages (Mann-Whitney test, $p = 0.841$) and duration of similar symptoms (Mann-Whitney test, $p = 0.799$).

MEDICAL AND SURGICAL TREATMENT

The average length of stay was 10.6 ± 6.1 days. Patients with multidrug-resistant ocular exudate did not show a higher number of days of hospitalization (Mann-Whitney Test, $p = 0.512$). Patients older than 60 years had on average a higher number of days of hospitalization, but no statistical significance (t, test, $p = 0.093$).

All patients started empirical treatment with fortified eye drops (Ceftazidime 50mg/dL (5%), Gentamicin 15mg/mL (1.5%), Vancomycinat 50mg/mL (5%), and/ or Voriconazole 10mg/mL (1%), since only high-risk infectious keratitis was included in this

study; 29.5% of patients required corneal transplantation (87.1% underwent penetrating keratoplasty, and 12.9% underwent deep anterior lamellar keratoplasty); and 38.7% of these patients had previous corneal transplantation. In 71.0% of cases, the transplant was performed in the first month with curative intent (abscesses resistant to medical treatment and/or associated with perforation), and 27.3% needed to have a new graft later. Two patients were eviscerated by painful eye after prolonged follow-up. At admission, 4.3% of patients had VA $\geq 20/40$, whereas after 6 months 25.6% had this VA (Figure 10).

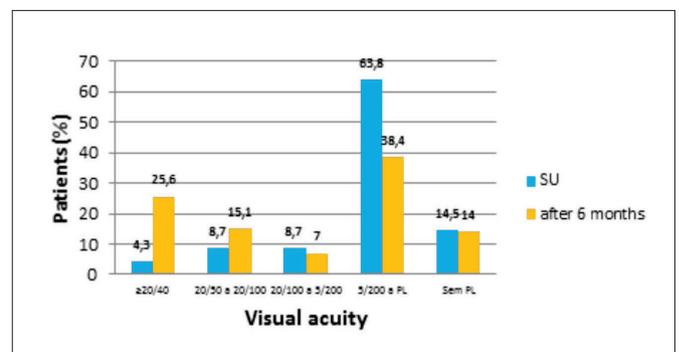


Figure 10 : Visual acuity in the Emergency Department (SU) and 6 months after hospitalization.

DISCUSSION

High-risk infectious keratitis occurred most often in women and in the age group between 60-80 years. The most frequent risk factors were previous corneal surgery, use of contact lens, and history of ocular trauma, probably following the overall trend of decreasing the cases associated to ocular trauma (risk factor most commonly identified in developing countries).⁽²⁾ There was also a later clinical search in the older age groups, which may indicate the presence of a risk population with less immediate access to health care. It was possible to isolate the causative agent of keratitis in most cases, with microbiology presenting a sensitivity above the average described in most studies published in the literature.^(1,2,6,7) In the vast majority of cases, the etiology was bacterial, with *Pseudomonas aeruginosa* and *Streptococcus pneumoniae* being the most common pathogens.⁽¹⁰⁾ The large percentage of isolations of *Pseudomonas aeruginosa* may be influenced by the presence of a considerable

number of contact lens wearers in the present study. According to some studies, this association can be explained by the ability of this species to adhere to the contact lens material,⁽¹¹⁾ and by the type of lens preservation solutions used.⁽¹²⁾ Knowledge of the potentially less effective drugs by resistance pattern is very important for the treatment of this disease.⁽¹³⁾ In our study, it was found that the antibiotics used in the empirical treatment of high-risk infectious keratitis still have acceptable resistance patterns, but therapeutic adjustment should be considered after the antibiotic susceptibility test result to avoid the onset of multi-resistances. In addition, we also found that the fluoroquinolone group had low resistance rates, which may become an option for initial empirical treatment, as it is already done in other hospitals.⁽¹⁴⁾ Cornea was transplanted in 29.5% of cases, as opposed to the 5% that Kaye et al reported in their study.⁽¹⁵⁾ Regarding transplants, 71.0% were performed in the first month due to the presence of corneal perforation and/or infection refractory to medical treatment. However, it is a state-of-the-art characteristic given the high graft failure rate, which explains the need for new grafts in 27,3% of cases in our series. Although treatment improved vision in the vast majority of cases, a considerable number of patients had significant visual sequelae at the end of the follow-up period.

CONCLUSION

Conducting epidemiological studies in a given region is essential for proper monitoring of etiological trends and for the adequacy of the treatments instituted. Regarding the severe infectious keratitis, our study has enabled us to understand the microbial agents most frequently involved in our region, the incidence of multiresistant bacteria over time, and validate our appropriate treatment protocol, i.e., the rates of acceptable resistance for the drugs we use as the first line. This monitoring does not end with this paper. And it would be important to be started and compared with other similar studies. As it is a condition that can have catastrophic outcomes and antimicrobial resistance is increasing worldwide, close monitoring and sharing of local experiences can be of great value in the success of therapy in these cases.

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