Prevalence and antibiotic susceptibility of methicillin-resistant Staphylococcus aureus in ocular infections

Prevalência e suscetibilidade antibiótica de Staphylococcus aureus resistente à meticilina em infecções oculares

MÁRIA EUGÉNIA VOLA¹, ÁLICE SILVEIRA MORYAMA¹, RENATO LISBOA¹, MARIA MAGDALENA VOLA², FLÁVIO EDUARDO HIRAI¹, PAULO JOSE MARTINS BISPO¹, ANA LUISA HÖFLING-LIMA³

ABSTRACT

Purpose: To study the prevalence of methicillin-resistant Staphylococcus aureus among S. aureus ocular infections in a tertiary health center in Brazil and compare antibiotic susceptibility patterns between MRSA and methicillin-susceptible S. aureus isolates.

Methods: Electronic records from the ocular microbiology laboratory of the Universidade Federal de São Paulo were retrospectively reviewed. During a 10-year period (between January 2000 and December 2009) all conjunctivitis, keratitis, and endophthalmitis cases with a positive culture for S. aureus were identified. Antibiotic susceptibility was determined using the Kirby-Bauer disk diffusion method.

Results: Five hundred sixty-six S. aureus isolates were identified; of those, 56 (9.9%) were resistant to methicillin. Throughout the 10-year period, Staphylococcus aureus showed a significant increasing trend from 7.55% to 16.18% among overall S. aureus infections (p=0.001) and from 3.7% to 13.16% in conjunctivitis (p=0.001). A significant increasing trend of 7.6% to 16.2% among ocular infections caused by S. aureus (p<0.001) and from 0.5% to 5.7% in conjunctivitis (p=0.001) was also observed. Conversely, we did not observe the same trend among those with keratitis (p=0.38).

Conclusion: We observed an increasing trend in the overall prevalence of Staphylococcus aureus ocular infections and statistically significant higher resistance rates to commonly used antibiotics compared to Staphylococcus aureus. Our data supports the need for constant bacterial surveillance and should be taken into consideration before initiating empiric treatment of ocular infections.

Keywords: Conjunctivitis; Keratitis; Endophthalmitis; Methicillin-resistant Staphylococcus aureus; Fluoroquinolones

INTRODUCTION

Staphylococcus aureus is a major human pathogen responsible for a wide variety of ocular diseases, including sight-threatening infections. Since the first report of a new strain of S. aureus, the so-called methicillin-resistant Staphylococcus aureus (MRSA), its prevalence and morbidity has been increasing worldwide. Moreover, the antibiotic susceptibility is decreasing, introducing new challenges regarding its treatment and making constant antibiotic surveillance a priority.

The mechanism of resistance to semisynthetic penicillins, including oxacillin and methicillin, is based on structural changes of its penicillin-binding proteins. The MRSA phenotype is based on the presence of the mecA gene, which is carried on a 50-kb plasmid, and is responsible for conferring resistance to β-lactams. The mec gene is also responsible for the production of a staphylococcal protein A, which blocks the activity of penicillin-binding proteins and prevents the binding of β-lactams to cell wall precursors.

Staphylococcus aureus is a coagulase-negative staphylococcus, and a wide variety of antibiotics are available for the treatment of ocular infections. However, the widespread use of antibiotics has led to the emergence of drug-resistant strains. The emergence of methicillin-resistant Staphylococcus aureus (MRSA) is a major concern, as it is resistant to almost all available antibiotics, including β-lactams, aminoglycosides, and quinolones.

Conversely, we did not observe the same trend among those with keratitis (p=0.38). The isolates of Staphylococcus aureus resistant to meticillin showed a higher resistance rate to tobramycin, gentamicin, ciprofloxacin, gatifloxacin, and moxifloxacin when compared with S. aureus isolates (p<0.001). All cases were susceptible to vancomycin.

Conclusion: We observed a increasing trend in the overall prevalence of Staphylococcus aureus ocular infections and statistically significant higher resistance rates to commonly used antibiotics compared to Staphylococcus aureus. Our data supports the need for constant bacterial surveillance and should be taken into consideration before initiating empiric treatment of ocular infections.

Keywords: Conjunctivitis; Keratitis; Endophthalmitis; Methicillin-resistant Staphylococcus aureus; Fluoroquinolones

RESUMO

Objetivo: Estudar a prevalência do Staphylococcus aureus resistente à meticilina nas infecções oculares causadas por S. aureus em um centro de saúde terciário no Brasil e comparar o perfil de susceptibilidade antimicrobiana entre as cepas de Staphylococcus aureus resistente à meticilina e S. aureus susceptível à meticilina.

Métodos: Foi realizada uma análise retrospectiva dos arquivos do laboratório de microbiologia ocular da Universidade Federal de São Paulo e selecionados todos os casos de conjuntivite, ceratite e endoftalmite com cultivo positivo para S. aureus, durante um período de 10 anos (entre janeiro de 2000 e dezembro de 2009). Foi avaliada a prevalência de Staphylococcus aureus resistente à meticilina e comparado o perfil de susceptibilidade antimicrobiana dos Staphylococcus aureus resistente à meticilina e S. aureus susceptível à meticilina.

Resultados: Quinhentos e sessenta e seis isolados de S. aureus foram identificados. Desses, 56 (9,9%) apresentaram resistência à meticilina. Durante o período de 10 anos estudado, Staphylococcus aureus resistente à meticilina mostrou uma tendência significativa de aumento de 7,6% para 16,2% entre as infecções oculares causadas por S. aureus em geral (p<0.001) e de 3,7% para 13,2% nas conjuntivites (p=0.001). A mesma tendência não foi observada entre as amostras de ceratite (p=0.38).

Conclusão: Foi observada uma tendência de aumento na prevalência do Staphylococcus aureus resistente à meticilina nas infecções oculares causadas por S. aureus, bem como taxas de resistência significativamente maiores aos antibióticos comumente utilizados na prática oftalmológica. Nosso objetivo é alertar para a necessidade de constante vigilância de resistência bacteriana a antimicrobianos e devem ser considerados na eleição do tratamento empírico das infecções oculares.

Descritores: Conjuntivite; Ceratite; Endoftalmite; Staphylococcus aureus resistente à meticilina; Fluoroquinolonas
ried on a large mobile genetic element called staphylococcal cassette chromosome mec (SCC mec). The meCA gene encodes for an alternative penicillin-binding protein: PBP2a, that has low affinity for β-lactams and allows MRSA strains to survive in different concentrations of these antimicrobial agents\(^6\). As a consequence, the treatment of MRSA infections has been restricted to selected antibiotics, usually glycopeptides. Furthermore, due to the high capability to develop resistance, MRSA strains with reduced susceptibility to vancomycin have been isolated\(^6\).

It is known that MRSA prevalence and antimicrobial susceptibility patterns have substantial geographical variation\(^7\). In the United States, the results from the Antibiotic Resistance Monitoring in Ocular Microorganisms (ARMOR) study showed a prevalence of 39% of MRSA among all \textit{S. aureus} ocular isolates and a considerable increase in the resistance rates to fluoroquinolones\(^8\). Other studies conducted in developing countries showed similar resistance patterns and even higher prevalence rates that ranged from 34% to 53%\(^9,10\). Although these previous studies are important to guide the treatment of ocular infections, their results may not reflect the current prevalence of MRSA in other geographic areas. Therefore, the study of the prevalence and susceptibility of MRSA in Latin America is of major importance in the management of ocular infections.

The purpose of our study was to evaluate the prevalence of MRSA among \textit{S. aureus} ocular infections in a tertiary health center in Brazil and compare antibiotic susceptibility patterns between MRSA and methicillin-susceptible \textit{S. aureus} (MSSA) isolates.

**METHODS**

This was a retrospective study conducted at the Universidade Federal de São Paulo (UNIFESP), from January 2000 to December 2009. The Ocular Microbiology Laboratory receives specimens from emergency services and outpatient clinics referred to the São Paulo Hospital, a tertiary health center in São Paulo, Brazil. For this study isolates were de-identified in order to protect patient identity. Then, we reviewed electronic records from the ocular microbiology laboratory and identified all conjunctivitis, keratitis, and endophthalmitis cases with a positive culture for \textit{S. aureus}. If records showed more than one diagnosis, their results may not reflect the current prevalence of MRSA in other geographic areas. Therefore, the study of the prevalence and susceptibility of MRSA in Latin America is of major importance in the management of ocular infections.

The purpose of our study was to evaluate the prevalence of MRSA among \textit{S. aureus} ocular infections in a tertiary health center in Brazil and compare antibiotic susceptibility patterns between MRSA and methicillin-susceptible \textit{S. aureus} (MSSA) isolates.

<table>
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**RESULTS**

We included in our study 566 \textit{S. aureus} isolates identified from January 2000 to December 2009. Fifty-six isolates (9.9%) were resistant to methicillin. The median age of included subjects was 35.8 years (range from 6 days to 98 years). Patients with positive MRSA samples were significantly younger than patients with MSSA samples (median age of 27.9 vs. 36.7, respectively, \(p=0.014\)). No difference in sex was found between groups.

Table 1 shows the number of MRSA cases per year according to diagnostic category. Throughout the 10-year period, MRSA showed a significant increasing trend from 7.55 to 16.18% among overall \textit{S. aureus} infections (\(p=0.001\)) and from 3.7 to 13.16% in conjunctivitis (\(p=0.001\)). Conversely, we did not observe the same trend among those with keratitis (\(p=0.38\)). The small number of endophthalmitis did not allow us to make statistical inferences.

MRSA was more prevalent in endophthalmitis cases than in conjunctivitis (21.4 vs. 10.0%, respectively, \(p<0.001\)) or keratitis cases (21.4 vs. 8.4%, respectively, \(p<0.001\)). Besides, MRSA was more prevalent in endophthalmitis cases than in the sum of conjunctivitis and keratitis cases (21.4 vs. 9.3%, respectively, \(p=0.036\)).

Figure 1 illustrates the antibiotic susceptibility rates of MRSA and MSSA isolates. Fifty-six point four percent (56.4%) of MRSA strains were susceptible to tobramycin, 70% to gentamicin, 62% to ciprofloxacin, 88.4% to gatifloxacin, and 85.1% to moxifloxacin. For MSSA
Prevalence and antibiotic susceptibility of methicillin-resistant *Staphylococcus aureus* in ocular infections

It is important to highlight that *in vitro* bacterial susceptibility patterns are not fully equivalent to *in vivo* susceptibility. Many variables exist in this equation including factors depending on the antimicrobial pharmacokinetics (PK) and pharmacodynamics (PD), microorganism, site of infection, and host. Moreover, it can be difficult to establish breakpoints in susceptibility tests regarding ocular infections. Although the CLSI recommends breakpoints based on PK/PD index and microbiological data, those values may not represent the concentrations expected in ocular applications. In addition, it is known that antibiotic concentrations differ according to the form of drug delivery. For example, topical antibiotics are associated with higher concentrations of the drug in the ocular surface and cornea, and intravitreal injection directly increases the amount of drug available in the vitreous. It is also important to remember that different components might change the drug efficacy. Benzalkonium chloride, for instance, is a bacteriostatic and bactericidal agent used as preservative in many marketed formulations including fluoroquinolones. It has been demonstrated that gatifloxacin formulated with benzalkonium chloride has better antimicrobial effect than gatifloxacin alone, with a significant reduction in gatifloxacin minimum inhibitory concentration (MIC) against different ocular pathogens.\(^\text{[24]}\)

Direct implication of methicillin resistance on prognosis of ocular infections is still unclear. Although it is obviously influenced by the delay in the introduction of the appropriate antibiotic regimen, virulence factors are also a major concern. Virulence factors are responsible for the capability of the bacteria to cause disease and are correlated with the severity of the disease. Interestingly, the association between increased antibiotic resistance and decreased virulence has already been described for *S. aureus*.\(^\text{[25]}\) Moreover, MRSA showed increased mortality rates compared with MSSA in several studies.\(^\text{[25]-[29]}\) However, little is known about the prognosis associated with MRSA ocular infections. Major et al. evaluated 32 patients with endophthalmitis and reported that the visual acuity after MRSA and MSSA endophthalmitis was similar.\(^\text{[41]}\) Since our study had a cross-sectional design, we were unable to make conclusions about prognosis. Future studies should investigate the real implications and management of MRSA in ocular infections.

In conclusion, our study revealed an increasing trend in the overall prevalence of MRSA ocular infections compared to MSSA. Our results also support previous evidence of an association between resistance to methicillin and resistance to non β-lactam antibiotics, including fluoroquinolones. These findings should be taken in consideration before initiating empiric treatment of ocular infections and illustrates the need for constant bacterial surveillance.

**ACKNOWLEDGEMENTS**

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**REFERENCES**


