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REVIEW

Management and treatment of contact lens-related *Pseudomonas* keratitis

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Abstract: Pubmed and Medline were searched for articles referring to *Pseudomonas* keratitis between the years 2007 and 2012 to obtain an overview of the current state of this disease. Keyword searches used the terms "Pseudomonas" + "Keratitis" limit to "2007–2012", and ["Ulcerative" or "Microbial"] + "Keratitis" + "Contact lenses" limit to "2007–2012". These articles were then reviewed for information on the percentage of microbial keratitis cases associated with contact lens wear, the frequency of *Pseudomonas* sp. as a causative agent of microbial keratitis around the world, the most common therapies to treat *Pseudomonas* keratitis, and the sensitivity of isolates of *Pseudomonas* to commonly prescribed antibiotics. The percentage of microbial keratitis associated with contact lens wear ranged from 0% in a study from Nepal to 54.5% from Japan. These differences may be due in part to different frequencies of contact lens wear. The frequency of *Pseudomonas* sp. as a causative agent of keratitis ranged from 1% in Japan to over 50% in studies from India, Malaysia, and Thailand. The most commonly reported agents used to treat *Pseudomonas* keratitis were either aminoglycoside (usually gentamicin) fortified with a cephalosporin, or monotherapy with a fluoroquinolone (usually ciprofloxacin). In most geographical areas, most strains of *Pseudomonas* sp. (≥95%) were sensitive to ciprofloxacin, but reports from India, Nigeria, and Thailand reported sensitivity to this antibiotic and similar fluoroquinolones of between 76% and 90%.

Keywords: *Pseudomonas*, keratitis, contact lens

Introduction

Microbial keratitis (MK), epithelial loss from the cornea with underlying stromal infiltration by white blood cells and disintegration of the stroma, occurs when one of the protective mechanisms of the ocular surface is disrupted. It is a vision-threatening condition that requires rapid and appropriate management and antibiotic treatment if vision loss is to be prevented. MK caused by *Pseudomonas aeruginosa* is commonly associated with contact lens wear (Table 1).[1–21] Predisposing risk factors for microbial keratitis can vary with geographical location and can depend on the penetration of contact lens wear. The differences may also be associated with the incidence of single nucleotide polymorphisms (SNPs) in cytokine genes in different populations. Recently, SNPs in the gene for interleukin (IL)-10 have been associated with severity of and predisposition to MK.[22] In developing countries, trauma to the eye may be a predominant risk factor,[23] whereas in developed countries, contact lens wear is often the most important risk factor.[24] A study from Malaysia suggested that as *P. aeruginosa* is also a common inhabitant of soil, water, and vegetation, it may also be the main pathogen following vegetation-related corneal injury in certain regions.[15]

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Table 1 Percent of microbial keratitis cases associated with contact lens wear

Geographical location	Country	% MK associated with contact lens wear
North America	USA[1]	55
	USA[2]	26.5
South America	Brazil[3]	12.8
Europe	UK[4]	31
	UK[5]	32
	UK[6]	30.3
	Ireland[7]	41.1
	The Netherlands[8]	39.7
	Turkey[9]	3.2
	Italy[10]	46.1
Indian subcontinent	India[11]	17.14
	India[12]	8.2
Asia	Japan[13]	54.5
	Nepal[14]	0
	Malaysia[15]	21
	Thailand[16]	18.6
	Thailand[17]	32.4
Australasia	New Zealand[19]	29.4
	Australia[20]	21.7
	Australia[21]	21

The incidence of contact lens-related microbial keratitis has been estimated over the past 20 years, and has remained almost constant at 1/2500 contact lens wearers who wear lenses on a daily wear basis (that is removing lenses each night and placing in disinfecting solution prior to re-wearing the lens the next day), or 1/500 wearers if the lenses are worn on a continuous or extended wear basis (ie, the person wears lenses for 24 hours, sleeping in lenses overnight).[25] It is now common for lens wearers to discard their lenses after 2 weeks or 1 month of wear.[25] In a study from North America, it was found that the incidence of all ulcerative keratitis was 2.76 per 10,000 person-years (95% confidence interval [CI]: 2.46–3.09) but the incidence of contact lens-associated keratitis was 13.04 per 10,000 person-years (95% CI: 11.13–15.17), with an adjusted relative risk of 9.31 (7.42–11.7; $P < 0.001$) compared with non-contact lens wearers.[1] Another study put the incidence of MK at 1.1 per 10,000 persons/year in the US[24] but a different study found an incidence of 79.9 per 10,000 persons/year in Nepal.[23] The risk with therapeutic contact lenses is higher at approximately 52/10,000 yearly.[26] A study of armed forces of the UK evacuated because of keratitis from the Middle East showed an incidence of MK of 35 per 10,000 (with 74% being associated with soft contact lens wear).[27]

The percentage of microbial keratitis cases caused by *Pseudomonas* species (most likely *P. aeruginosa*) is shown in Table 2 for different geographical locations.[1–13,15–18,28–44] Whilst

Table 2 Frequency of *Pseudomonas* sp. as a causative agent of microbial keratitis in different geographical regions

Geographical region	Country	Frequency (%) of *Pseudomonas* sp. as a total of all MK isolates
North America	USA[1]	0
	USA[2]	20.2
South America	Brazil[3]	12
	Brazil[28]	12 (41% of these caused by *P. aeruginosa*)
Europe	UK[29]	6 (1995–1998); 15 (2004–2007)
	UK[4]	12
	UK[5]	21
	UK[6]	28.5 (24.3% of total cases caused by *P. aeruginosa*)
	UK[30]	20.9
	Ireland[7]	33.3 (56.2 of CLMK)
	The Netherlands[8]	22.4
	Turkey[9]	6.6 (*Pseudomonas* sp.)
	Italy[10]	72.2
Middle East	Iraq[31]	42 (100% of those associated with contact lenses caused by *Pseudomonas* sp.)
	Kingdom of Bahrain[32]	54 (95% of those associated with contact lenses caused by *P. aeruginosa*)
	Various[27] (predominantly Iraq)	71
	Oman[33]	28.8 (all CLMK)
Africa	Sierra Leone[34]	40
	Nigeria[35]	22.4
Indian subcontinent	India[36]	71 (only cases of CLMK examined, all *Pseudomonas* species were *P. aeruginosa*)
	India[37]	52
	India[11]	1
	India[12]	24.4
Asia	Japan[38]	2.8
	Japan[18]	20
	Japan[13]	1
	Thailand[16]	59
	Thailand[17]	55
	Malaysia[15]	58.6
	Hong Kong[39]	42.9 (85.7 of culture proven) for CLMK
	China[40]	20.07
	Taiwan[41]	47
Australasia	New Zealand[42]	3.4 (all *P. aeruginosa*)
	Australia[43]	8
	Australia[21]	17 (55% of these caused by *P. aeruginosa*)
	Australia[44]	35 (CLMK; 49.2 of culture proven cases)

P. aeruginosa/Pseudomonas sp. are usually a predominant causative agent, temperate zones tend to have a higher incidence of Gram-positive bacteria causing the disease and less aggressive keratitis.[44] In most studies, *Pseudomonas* sp. are usually isolated in monoculture from cases of MK, however, a study

from Thailand demonstrated that in 46% of MK cases caused by *Pseudomonas* sp. other Gram-negative bacteria including *Escherichia coli, Acinetobacter calcoaceticus, Klebsiella pneumoniae, Serratia marcescens*, and *Enterobacter* sp. could also be cultured.[16] However, the predominance of *P. aeruginosa* during contact lens-associated MK is not always seen. For example, even though 29.4% of MK cases were associated with contact lens wear in a study from Wellington, New Zealand, no cultures of *P. aeruginosa* were reported.[19] The predominant Gram-negative bacteria isolated was *Moraxella* sp. (12.5% of all bacterial isolates),[19] and this predominance of *Moraxella* sp. from MK scrapes has been reported from a study in Christchurch, New Zealand.[45] Climate may also affect the incidence of *P. aeruginosa* keratitis. In Australia, the incidence of *P. aeruginosa* contact lens microbial keratitis (CLMK) is increased in tropical compared to temperate zones, whereas the incidence of *Serratia marcescens* CLMK is higher in temperate zones.[44]

Determinants of the clinical outcome of MK include distance of the ulcer from the limbus and the minimum inhibitory concentration (MIC) of the first antimicrobial used or lowest MIC if combination therapy was used.[5] A large multicenter clinical trial with participants from India and the US has shown that *P. aeruginosa* ulcers were significantly worse for visual acuity than patients with other bacterial ulcers, but interestingly showed significantly more improvement in 3-month best-spectacle-corrected visual acuity than those with other bacterial ulcers.[46] *Pseudomonas* sp. are often associated with the largest ulcers.[5]

Ideally, every case of presumed MK should be scraped for microbiological investigations, especially with the possibility of increasing isolation of antibiotic-resistant microbes. However, it must be borne in mind that there is often a small ulcer and so relatively little material might be obtained. Corneal scrapings obtained with a surgical blade (eg, Bard-Parker blade #15), Kimura spatula, or 21-gauge disposable needle should be inoculated on chocolate agar, sheep blood agar, and into thioglycolate broth, and incubated at 35°C. Sabouraud's agar plates should also be used and these are maintained at 25°C to enhance fungal growth. Samples may also be inoculated onto non-nutrient agar and into brain heart infusion broth. Scraping of small lesions (smaller than 2.0 mm^2) is probably not worthwhile, and patients with such lesions can be empirically treated. Scrapes should not only be sent for microbial culture, but also smeared onto microscope slides and examined by Gram stain (and potassium hydroxide if fungal keratitis is suspected). However, as there is often only a small amount of material, cultures on agar plates for bacteria and fungi, as well as Gram stain, are most often used. The following clinical parameters are useful in monitoring the clinical response to antibiotic therapy: blunting of the perimeter of the stromal infiltrate, decreased density of the stromal infiltrate, reduction of stromal edema and endothelial inflammatory plaque, reduction in anterior chamber inflammation, re-epithelialization, and cessation of corneal thinning.

Therapies used in different geographical locations are shown in Table 3.[4,5,8,9,12,16,31,39,42,47–49] Monotherapy with ciprofloxacin (0.3%; or another fluoroquinolone) is commonly used. In severe cases, subconjunctival injections of gentamicin may be used.[31] The combination of two fortified antibiotic preparations, 1.5% gentamicin and 5% cefuroxime, covers almost the entire range of common bacterial pathogens causing

Table 3 Most common topical antimicrobial therapies used to treat *Pseudomonas* keratitis by geographical location

Geographical region	Country	Antibiotics commonly prescribed
Europe	The Netherlands[8]	Cefazolin and tobramycin/gentamicin; ofloxacin monotherapy
	Ireland[9]	Ceftazidime and vancomycin; ofloxacin
	UK[4]	Ciprofloxacin
	UK[5]	Ciprofloxacin or ofloxacin (84% monotherapy; 9% combination therapy)
Middle East	Iraq[31]	Ciprofloxacin
	Iran[47]	Fortified ceftazidime and vancomycin; ciprofloxacin for small (<2 mm) ulcers
Indian subcontinent	India[12]	Fortified cefazolin; tobramycin (modified depending on sensitivity analysis and clinical response)
Asia	Hong Kong[39]	Levofloxacin or gentamicin monotherapy; fortified gentamicin
	Thailand[16]	Fortified antibiotics (gentamicin or amikacin or ceftazidime and/or cefazolin); ciprofloxacin and/or tobramycin
Australasia	New Zealand[48]	Severe cases fortified gentamicin or Tobramycin; ciprofloxacin; mild cases ciprofloxacin; chloramphenicol
	New Zealand[42]	Fortified cefuroxime and tobramycin; ciprofloxacin in cases where scrape results show Gram-negative organisms resistant to tobramycin
	Australia[49]	Fluoroquinolone monotherapy; ceftazidime/gentamicin

corneal ulcers. Randomized controlled trials have demonstrated that monotherapy with fluoroquinolones has non-inferiority and fewer side effects compared with combination therapy.[50,51] A study from Iran recommended the concurrent use of ceftazidime and amikacin or ceftazidime and ciprofloxacin as the initial treatment based on antibiotic sensitivities of isolates, and as all *P. aeruginosa* isolates were resistant to chloramphenicol, trimethoprim, vancomycin, and cefazolin, these antibiotics should probably not be included in any empirical antibiotic regimen in that country.[47] Data from Taiwan[41] demonstrate that ciprofloxacin was statistically significantly more effective against *P. aeruginosa* than the combination of cefazolin and gentamicin. Whilst therapy is most often, if not always, commenced prior to results of cultures being obtained, a study from Japan has shown that the therapeutic outcome was better when antimicrobial agents were selected based on culture results, thus reemphasizing the importance of culture studies.[18] Sometimes a combination of piperacillin/tazobactam might be effective with unresponsive *P. aeruginosa* MK.[52]

The use of steroids in conjunction with antibiotics has been a source of controversy for many years, despite the demonstration in an animal trial that the combination of tobramycin and dexamethasone was safe and resulted in the reduction of clinical scores and lower bacterial numbers in the cornea.[53] However, a recent large scale multicenter clinical trial that enrolled subjects in India and US found that the use of moxifloxacin combined with prednisolone phosphate did not improve overall clinical outcome.[46]

Sensitivity of *Pseudomonas* sp. to antibiotics by geographical region is shown in Table 4.[2,7,8,16,20,21,28–31,35,37,40–42,47,54] Generally *P. aeruginosa* is sensitive to fluoroquinolones, but there have been reports of multi-resistant *P. aeruginosa* strains, for example, from Australia where the strains were resistant to ciprofloxacin, gentamicin, tobramycin,

Table 4 Sensitivity to antibiotics of *Pseudomonas* sp. in different geographical regions

Pseudomonas type	Country	Percentage of strains sensitive to antibiotic				
		Ciprofloxacin	Gentamicin	Cephalosporin	Tobramycin	Chloramphenicol
P. aeruginosa	USA[2]	100 (levofloxacin = 100)	93.7[a]	ND	93.7[a]	ND
P. aeruginosa	Brazil[28]	100 (ofloxacin = 100; gatifloxacin = 100)	97	ND	100	ND
Pseudomonas sp.	Brazil[54]	95 (ofloxacin = 95; gatifloxacin = 95)	ND	ND	ND	ND
Pseudomonas sp.	Ireland[7]	100 (ofloxacin = 100)	100	73 (cefotaxime); 100 (ceftazidime); 18 (cefuroxime)	ND	ND
P. aeruginosa	UK[30]	98.6 (levofloxacin = 99.3; moxifloxacin = 100)	96.4	99.3 (ceftazidime)	ND	ND
Pseudomonas sp.	UK[29]	100	100	100 (1995–1998); 0 (2004–2007) (cefuroxime)	ND	ND
P. aeruginosa	The Netherlands[8]	100	ND	ND	ND	ND
Pseudomonas sp.	Iraq[31]	62	55	2 (cefazolin)	ND	0
P. aeruginosa	Iran[47]	100	93	0 (cefalozin); 100 (ceftazidime)	ND	3
P. aeruginosa	India[37]	85 (norfloxacin = 82; ofloxacin = 87; gatifloxacin = 88; moxifloxacin = 79)	33	0 (cefalozin); 64 (cephotaxime); 80 (cetazidime)	30	60
P. aeruginosa	Nigeria[35,b]	90 (ofloxacin = 80)	90	20 (cephalexin)	ND	10
P. aeruginosa	Taiwan[41]	99	91	99 (ceftazidime)	ND	ND
P. aeruginosa	Thailand[16]	100 (data for ofloxacin)	100	100 (ceftazidime)	ND	ND
Pseudomonas sp.	China[40]	76 (ofloxacin = 89; levofloxacin = 96)	ND	ND	87	ND
P. aeruginosa	New Zealand[42]	99[c]	ND	99.7 (cefuroxime)	100	ND
P. aeruginosa	Australia[20]	100	100	ND	ND	100
P. aeruginosa	Australia[21]	100	100	100 (ceftazidime or cefotaxime)	ND	ND

Notes: [a]Data supplied as 'intermediate or resistant to gentamicin or tobramycin'; [b]all ocular infections not just MK; [c]data supplied for all Gram-negative microbes combined.

Abbreviations: MK, microbial keratitis; ND, not given or determined.

and amikacin but was sensitive to ceftazidime, imipenem, meropenem, and timentin.[55] Recent data examining possible synergistic activity between different classes of antibiotics against *P. aeruginosa* has shown that a combination of meropenem/ciprofloxacin gave the lowest mean fractional inhibitory concentrations (ie, best synergy) for *P. aeruginosa* isolates, with 90% of isolates showing an additive or synergistic effect[56] and so this may be a promising therapy for the more resistant strains.

Comparisons between Tables 3 and 4 demonstrate that ciprofloxacin is the most commonly prescribed antibiotic to treat MK in Iraq, however only 62% of *Pseudomonas* sp. are sensitive to it. Likewise for India, tobramycin is one of the most commonly prescribed antibiotics but only 30% of *Pseudomonas* sp. are sensitive to it. This is different from all other most commonly prescribed treatments in other geographical locations which are >95% effective. Whilst there are no true cut-off points for sensitivity or resistance for topically applied antibiotics, it is perhaps important for those countries where there are high levels of apparently resistant strains of *P. aeruginosa* to monitor the clinical outcome of MK very carefully.

In conclusion, *Pseudomonas* sp. (predominantly *P. aeruginosa*) is often isolated from cases of contact lens-induced microbial keratitis. The most commonly used therapies to treat this disease are either monotherapy with a fluoroquinolone or fortified aminoglycosides. Strains of *P. aeruginosa* isolated from contact lens-induced MK are commonly still sensitive to these antibiotics, but geographic differences in sensitivity exist and should be taken into account when recommending treatment options.

Disclosure

The author reports no conflicts of interest in this work.

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