

Published in final edited form as:

Br J Ophthalmol. 2011 June ; 95(6): 762–767. doi:10.1136/bjo.2009.169607.

Geographic Variations in Microbial Keratitis: An analysis of the Peer-Reviewed Literature

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summary

The epidemiology of microbial keratitis has been investigated in several studies by analysis of organisms cultured from corneal scrapes. However, a comparison of the frequency of different organisms causing keratitis in different parts of the world is lacking. We present a review incorporating an analysis of data from studies worldwide. The data provide a comparison of the frequency of culture-positive organisms found in different parts of the world.

The highest proportion of bacterial corneal ulcers was reported in studies from North America, Australia, the Netherlands and Singapore. The highest proportion of staphylococcal ulcers was found in a study from Paraguay whilst the highest proportion of pseudomonas ulcers was reported in a study from Bangkok. The highest proportions of fungal infections were found in studies from India and Nepal. Possible explanations for these observed geographic variations are discussed.

Keywords

cornea; keratitis; eye; infection; epidemiology

INTRODUCTION

Microbial keratitis is a potentially serious corneal infection and a major cause of visual impairment worldwide. A conservative estimate of the number of corneal ulcers occurring annually in the developing world alone is 1.5-2 million.[1] Permanent visual dysfunction has been reported in a significant proportion of patients in both developing [2] and developed [3] countries. Srinivasan et al [4] comment that ulceration of the cornea in south India 'is a blinding disease of epidemic proportions'.

Various micro-organisms can cause microbial keratitis and predisposing risk factors vary from one geographic region to another. They include pre-existing corneal disease as well as other risk factors such as contact lens wear, surgical or non-surgical trauma and ocular surface disease.[5-7]

There is limited comparative information on international patterns of causative organisms in microbial keratitis. With increasing rates of migration and international travel, an awareness of these geographical variations is relevant for clinicians treating microbial keratitis, and especially for those planning to work in regions where they have not previously practised. The aim of this review is to summarise the published literature that provides information on the worldwide variation in organisms causing microbial keratitis.

METHODS

Search Strategy

A systematic review of the current literature pertaining to the prevalence of causative organisms responsible for microbial keratitis was conducted. Pubmed searches were performed and verified in April 2009 by two independent investigators. The terms 'microbial keratitis', 'bacterial keratitis' and 'infectious keratitis' were entered into Pubmed. Only papers presenting data that were collected after 1st January 1990 were examined, and the search was restricted to English Language and human studies. Only studies that cultured at least 50 organisms in total were included. Titles and abstracts were read and a judgement was made as to whether the paper provided culture results for microbial keratitis in a specified geographical location. If this was felt to be the case then a full text request was made to access the original published data.

Studies looking only at infections related to use of contact lenses were excluded, as were studies looking only at limited age groups.

Extraction and Recording of Data

Papers were read and information was abstracted on the following variables: number of patients in the study, time period of reporting, region, method by which organisms were isolated, method of culture, rate of positive cultures, and number of contact lens wearers in the study sample. These data were then entered then into a Microsoft Excel spread sheet.

With regard to the microorganisms cultured, the total numbers in each of the following categories were abstracted and recorded: gram positive organisms, staphylococcal species, streptococcal species, gram negative organisms, pseudomonal species, protozoa, fungi/ yeasts, aspergillus species and candida species.

Classification of income levels and GNI subheading

The prevalence of different causative organisms was compared according to countries' gross national incomes (GNIs) (source = <http://web.worldbank.org>). Income groups were defined by 2007 GNI per capita, calculated using the World Bank Atlas method.[8] The groups distinguished were: low income, \$935 or less; lower middle income, \$936 - \$3,705; upper middle income, \$3,706 - \$11,455; and high income, \$11,456 or more.

Statistical analysis

Statistical analysis was performed using 'Analyse-it' version 2.20 software. Spearman's correlation coefficients were used to explore associations between:

1. prevalence of certain types of organism and GNI; and between
2. prevalence of contact lens wear and prevalence of pseudomonas.

RESULTS

3883 publications were identified through the preliminary Pubmed search. Of these, 37 papers met the inclusion criteria. One paper was excluded because it included a significant number of cases that the authors deemed to constitute an outbreak of suture-related infections.[9] Twelve of the included papers were from the Indian subcontinent, 7 from North America and Canada, 6 from the Far East, 5 from Australasia, 4 from Europe, 2 from Africa (both from Ghana) and 1 from South America. The mean GNI of the countries studied was \$20834 (range \$470 – \$59880). The number of patients ranged from 73 to 3183. The time periods of study ranged from 3 – 192 months, although three studies did not specify the study period. The proportion of keratitis patients with a recent history of contact lens wear was reported in only 22 studies and ranged from 0.33% (West Bengal [10]) to 50.3% (Paris[11]). Three studies reported on only culture-positive cases and so appear to have 100% culture-positive rates in Table 1. In the remainder of the studies culture-positive rates ranged from 35% - 86%.

Among studies which looked at non-bacterial as well as bacterial organisms, Los Angeles [12] and Adelaide [13] had the highest percentages of bacterial cases (95% in both), with Paraguay [14] having the highest percentage of staphylococcal species (79%), and Bangkok [15] the highest proportion of pseudomonal infections (55%). Tamil Nadu [16] had the highest percentage of streptococcal infections (47%). The highest percentage of protozoal infections (7%) was found in a study from Hong Kong.[5]

East India [10] had the highest proportion of corneal infections attributable to fungi (67%). When considering those countries with a significant proportion of fungal ulcers (we have arbitrarily chosen a cut-off of 10% or more), East India also had the highest percentage of aspergillus (60% of all fungal cultures) whereas the highest percentage of fusarium (73% of all fungal cultures) was found in a study from Hyderabad [17].

Statistically significant correlations were found between Gross National Income and percentages of bacterial, fungal and streptococcal isolates (see Figures 1-3). Surprisingly there was no statistically significant correlation between percentage of pseudomonal isolates and percentage of contact lens wearers (see Figure 4). 95% confidence intervals and p values for these analyses are provided in table 4.

DISCUSSION

We have found a wide variation in the causative organisms for microbial keratitis in different parts of the world. To some degree this variation is explained by economic factors as well as contact lens wear. A high proportion of bacterial ulcers were reported from centres in developed countries (North America, Australia, and Western Europe). In these countries, patients are far less likely to be agricultural workers, and so have a reduced risk of trauma from organic matter, which is known to be a risk factor for fungal infection.[28]

A high percentage of staphylococcus species (79%) was recorded in the study from Paraguay [14] although the reason for this is not clear. Of note, the authors comment that their patients have to make long journeys to their hospital. Thus, their data may reflect more severe cases of microbial keratitis.

The study from Tamil Nadu [16] found the highest proportion of streptococcus species (46.8%). The authors noted that this figure was only 18.5% in 1986 and suggest that the trend might represent a genuine change in the bacterial flora due to changes in the climate and environment.

The study from Bangkok [15] had the highest proportion of pseudomonas infections (55%). Interestingly, this study did not have the highest proportion of contact lens wearers (only 24%). Other studies reported far higher proportions of contact lens wearers, for example 44% in a study from Taiwan [26] and 50% in the study from Paris [11]. When we compared the percentage of contact lens wearers with the percentage of pseudomonal infections (figure 4), the Spearman correlation coefficient was not statistically significant. Interestingly, Cohen et al. [39] at Wills Eye Hospital reported a decline in contact lens-related ulcers: during 1998 to 1991, contact lens wear accounted for 44% of all ulcers, but during 1992 to 1995, it accounted for only 30%. The authors speculated that their figures might reflect a reduction in the number of referrals to their unit due to the increased availability of fluoroquinolones in the community.

Trauma was a major risk factor for corneal infection in certain countries. In Paraguay [14], the percentage of cases with preceding trauma was 48%, in Eastern Nepal[19], 53%, in Madurai, South India[4], 65% and 83% in Eastern India[11] (most commonly from injury by the paddy or its stalk). The authors of this last study noted an increase in keratitis during harvesting season.

The above studies also addressed the frequency of self-medication prior to presentation at a tertiary referral unit. In the Madurai study, 20% of patients had been to a village healer and 87% had been started on topical medication, of whom 8% were on topical corticosteroids. In the study from Eastern India, 18% of patients had used medication before coming to clinic, and in the Paraguay study the proportion was 83%.

Jeng and McLeod[40] commented on the emerging resistance of bacterial infections to fluoroquinolones. In addition to changes in resistance patterns, studies have also demonstrated changing patterns of causative organisms over time in a given geographical location. Varaprasathan et al.[41] reported that the proportion of *S. pneumoniae* and *P. aeruginosa* ulcers in Northern California had decreased over a 50 year period whilst that of *S. marcescens* had increased over the same period. Sun et al.[24] reported a rise in the percentage of gram positive cocci in North China from 25% in 1991 to 70.8% in 1997, as well as a decrease in gram negative bacilli from 69% to 23.4% over a similar period.

Leck et al.[16] have previously compared corneal ulcers in Ghana and South India, whilst Lam et al.[5] have discussed differences between Hong Kong, Europe and North America. However, the present study is the first to present a worldwide comparison of corneal infections.

In interpreting this comparison, a number of limitations must be considered. Variations existed in the definition of microbial keratitis between studies. Lam et al, reporting on cases from Hong Kong [5], included patients with 'the clinical presentation of a corneal stromal infiltrate $>1 \text{ mm}^2$ '. This differs from Srinivasan et al [4] who included patients with 'loss of the corneal epithelium with underlying stromal infiltration and suppuration associated with signs of inflammation with or without hypopyon'. There were variations in methods of culture. For example, one study [21] used Sheep's blood agar, Chocolate, Non-nutrient, Sarbarouds, brain-heart infusion and potato dextrose agar, whilst another [18] used only Chocolate and Sabourauds media. Some studies did not specify the media used [17, 22, 23]. All studies included bacterial infections, but not all included fungal, protozoal and yeast organisms. The majority of studies looked at all cases of microbial keratitis whilst some looked only at patients requiring hospital admission (Wong et al. and Cheung et al. [3,31]). It is likely that in these studies, particularly virulent organisms will be over-represented. Finally, data are only available from centres that have conducted studies on microbial keratitis, limiting the coverage of certain regions of the world.

Despite these limitations, we have presented to our knowledge, for the first time, a worldwide overview of causative organisms in microbial keratitis demonstrating associations between specific types of microbial keratitis and national income.

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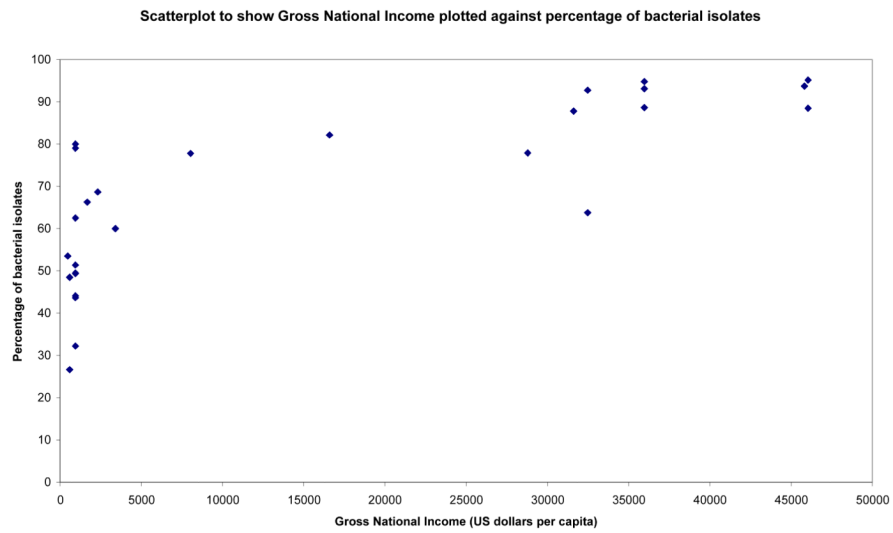


Figure 1. Scatterplot showing percentage of bacterial isolates in studies not looking exclusively at bacterial causes of microbial keratitis plotted against gross national income (US Dollars per capita)

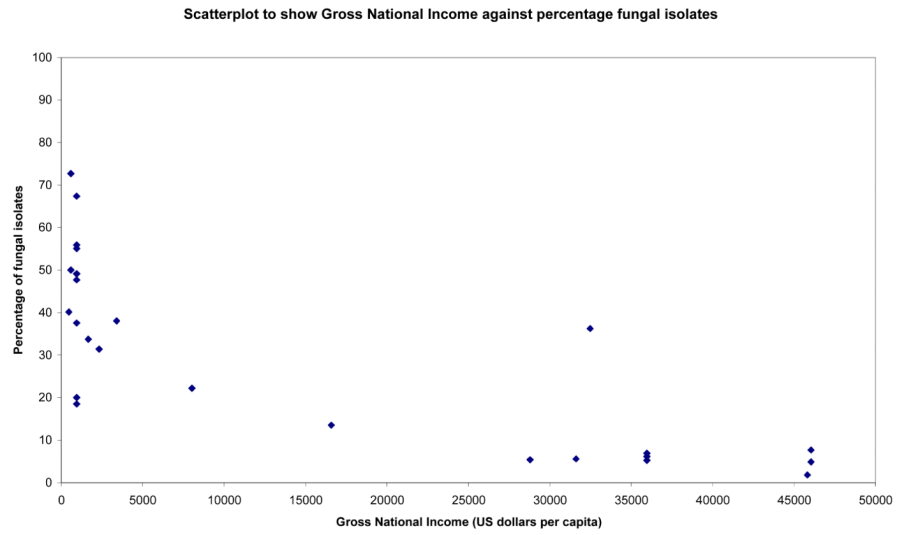


Figure 2. Scatterplot to show percentage of fungal isolates plotted against gross national income (US Dollars per capita)

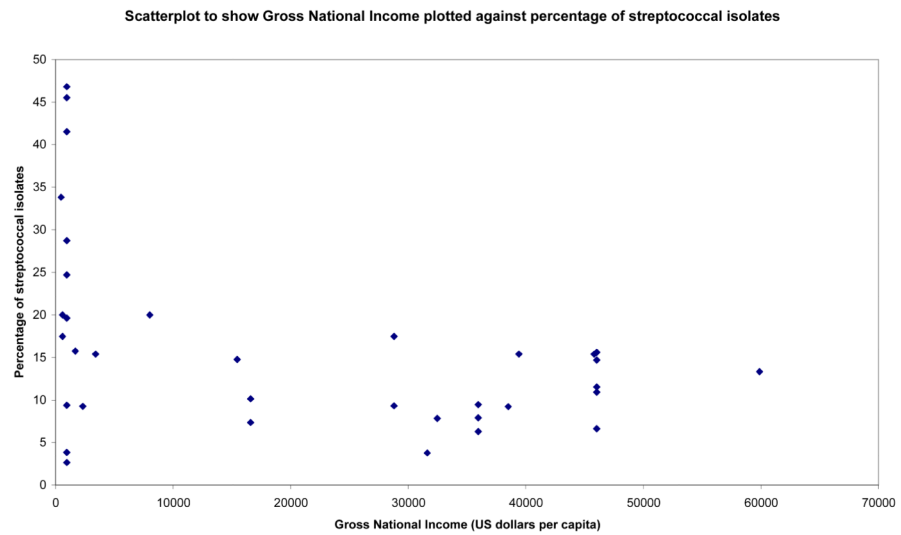


Figure 3. Scatterplot to show streptococcal isolates (expressed as a percentage of total bacterial isolates) plotted against gross national income (US Dollars per capita)

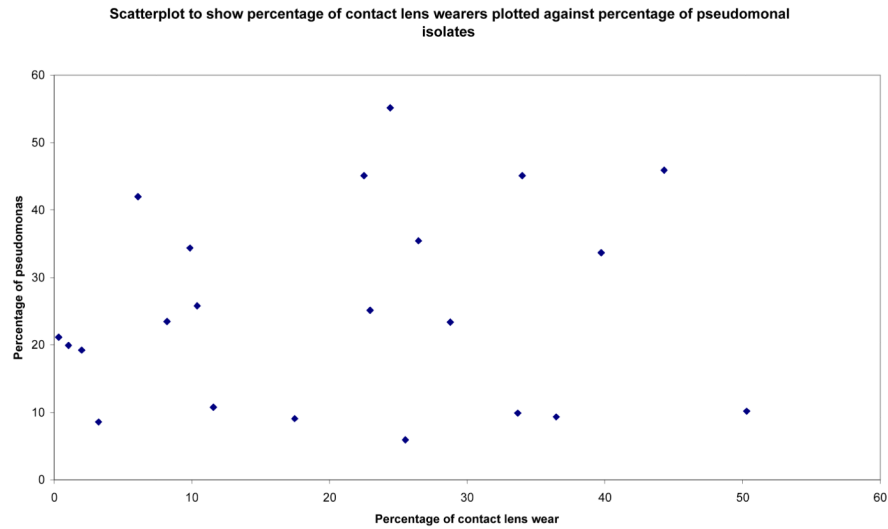


Figure 4. Scatterplot to show pseudomonas isolates (expressed as a percentage of total bacterial isolates) plotted against contact lens wearers (as a percentage of total number of patients included in study)

Table 1
Studies meeting criteria for inclusion in review

Location of study (reference)	GNI per capita (\$)	Time period (months)	Number of patients	Proportion (%) of patients using contact lenses	Method of culture	Proportion (%) of patients with positive cultures
Africa						
Ghana(16)	590	24	290	unspecified	2	50
Accra, Ghana(18)	590	unspecified	199	unspecified	Chocolate, Sabouraud	64
Indian Subcontinent						
Nepal, India(19)	340	36	447	unspecified	Sheep's blood agar, Chocolate, brain-heart infusion, Sabouraud	68
Chittagong, Bangladesh(20)	470	unspecified	151	unspecified	Blood, Chocolate, thioglycollate, Sabouraud	63
Tamil Nadu(16)	950	24	800	unspecified	1	69
East Bengal(10)	950	36	1198	0.33	Blood, chocolate, potatoe dextrose agar, sabarouds dextrose	68
New Delhi(2)	950	unspecified	100	2.0	Blood, chocolate, thioglycollate, sabarouds	65
Madurai, S. India(4)	950	3	434	unspecified	Sheep's blood agar, potatoe dextrose agar, chocolate, brain-heart infusion	68
Hyderabad, India(21)	950	95	1092	unspecified	Sheep's blood agar, Chocolate, Nonnutrient, Sabourauds, brain-heart infusion, potato dextrose agar	35
Tamil Nadu, India (22)	950	36	3183	1.04	unspecified	71
Hyderabad, India (17)	950	15	170	Unspecified	Unspecified	69.4
Delhi, India (23)	950	12	1000	8.2	Unspecified	56.8
Riyadh, Saudi Arabia ^{***} (24)	15440	12	103	17.48	blood, chocolate, Sabouraud's and thioglycollate	unspecified for 2005 ^{**}
Baghdad, Iraq [†] (25)	2320	36	394	6.09	blood, chocolate, Sabouraud's and brainheart infusion	58.6
South America						
Asuncion, Paraguay(14)	1670	162	660	unspecified	Blood, Chocolate thioglycollate, sabarouds	79
Far East						
Taipei, Taiwan(26)	16590	120	453	44.3 [*]	Chocolate, sheeps, sabarouds	56
Taipei, Taiwan(27)	16590	12	314	9.9	Blood, Chocolate, thioglycollate, brainheart infusion	43

Location of study (reference)	CNI per capita (\$)	Time period (months)	Number of patients	Proportion (%) of patients using contact lenses	Method of culture	Proportion (%) of patients with positive cultures
Singapore(28)	32470	60	80	22.5	Blood, chocolate, thioglycollate, sabarouds, brain heart infusion	100
Singapore(29)	32470	22	103	34	Blood,Chocolate, thioglycollate, Sabarouds	50
Hong Kong(5)	31610	17	223	26.5	Blood,Chocolate, thioglycollate, Sabarouds ,non-nutrient Page's saline agar	35
Bangkok, Thailand (15)	34000	47	127	24.4	sterile kimura spatula, blood, chocolate agar, thioglycollate	100
Australasia						
Auckland, NZ(3)	28780	24	98	26	Blood, sabarouds, thioglycollate, brain-heart infusion, Page's amoebic saline	71
Christchurch, New Zealand(30)	28780	60	78	unspecified	Sheep's blood agar, Chocolate	59
Adelaide(14)	35960	61	211	unspecified	Blood, chocolate, sabarouds	64
Victoria, Australia(7)	35960	24	291	33.7	Chocolate, Sabarouds	49
Brisbane, Australia(6)	35960	60	231	22.9	blood, MacConkey, Chocolate, sabarouds	65
North America and Canada						
Toronto(31)	39420	25	95	11.6	Blood, chocolate, inhibitory mould agar, thioglycollate	63
Miami(32)	46040	108	2920	10.4*	Chocolate, sheep, sabouraud, thioglycollate	50
Pittsburgh(33)	46040	60	825	Unspecified	4	100
Los Angeles(12)	46040	31	81	Unspecified	Blood, chocolate, thioglycollate, sabarouds	76
Texas (34)	46040	60	131	28.8	scalpel blade, calcium alginate swabs or cotton tipped applicator, Chocolate, blood, thioglycollate, sabourauds dextrose	52.5
Durham, USA (35)	46040	84	453	unspecified	calcium alginate swabs, blood, chocolate, sabourauds, thioglycollate	68
Europe						
Paris(11)	38500	21	291	50.3*	3	68
Lausanne, Switzerland(36)	59880	21	85	36	Blood, sabourauds, Chocolate, brain-heart infusion	86
Anatolia, Turkey (37)	8020	192	620	3.2	cotton-tipped swabs, chocolate, blood agar, sabourauds	48.4
Amsterdam and Rotterdam	45820	36	156	39.74	blood agar, chocolate agar, cooked meat broth, Sabouraud agar	58

Location of study (reference)	GNI per capita (\$)	Time period (months)	Number of patients	Proportion (%) of patients using contact lenses	Method of culture	Proportion (%) of patients with positive cultures
(38)						

¹ sheeps blood agar, Sabarounds broth and sabarounds glucose agar and at tertiary centre brain heart infusion broth, chocolate agar and cysteine tryptone agar

² sheeps blood agar, Sabarounds broth and inhibitory mould agar and at tertiary centre brain heart infusion broth, chocolate agar and cysteine tryptone agar

³ chocolate polyvitex agar, schaedler broth with globular extract, portagerm amies agar swab and sabouraud-chloramphenicolgentamicin medium

⁴ sheep blood, chocolate, mannitol salt agar, sabourauds dextrose agar supplemented with gentamicin

* paper did not specify the number of contact lens wearers. Instead they report on the number of isolates from contact lens wearers. The figure given in the table therefore represents the percentage of isolates retrieved from cases where CL wear was a risk factor

[†] Estimated to be lower middle income (\$936 to \$3,705), value given in table is midpoint of this range

** This paper presented paper for 1995 and 2005, only 2005 data have been extracted in our study

Table 2

Proportion of culture-positive patients who tested positively for bacteria by location

Location of study	Number of isolates									
	Gram +ve bacteria					Gram -ve bacteria				
	Any	Staphylococci	Streptococci	Other	Any	Pseudomonas	Other			
Africa										
Ghana	17	4	8	5	21	21	0			
Accra, Ghana	34	18	11	5	29	17	12			
Indian Subcontinent	136	102	31	3	21	18	3			
Nepal, India										
Chittagong, Bangladesh	27	2	23	2	39	34	5			
Tamil Nadu	178	63	110	5	57	35	22			
East Bengal	214	174	28	12	84	63	21			
New Delhi	35	28	2	5	17	10	7			
Madurai, S. India	132	26	76	30	35	24	11			
Hyderabad, India	198	92	60	46	45	27	18			
Tamil Nadu, India	814	259	492	63	325	236	89			
Hyderabad, India	80	43	27	0	13	6	7			
Delhi, India	223	200	10	13	152	88	64			
Riyadh, Saudi Arabia	130	75	26	29	45	16	29			
Baghdad, Iraq	88	70	15	3	74	68	6			
South America										
Asuncion, Paraguay	278	210	42	226	132	46	96			
Far East										
Taiwan	67	21	21	25	120	95	25			
Taipei, Taiwan	57	39	12	6	106	56	50			
Singapore	unspecified	4	4	unspecified	41	23	18			
Singapore	9	5	4	0	42	23	19			
Hong Kong	37	9	3	25	42	28	14			
Bangkok	23	11	12	0	unspecified	43	unspecified			
Australasia										
Auckland, NZ	75	41	11	13	13	7	6			
Christchurch, New Zealand	45	19	11	15	18	2	16			
Adelaide	89	65	12	12	38	17	21			
Victoria, Australia	72	56	8	8	29	10	19			

Location of study	Number of isolates										
	Gram +ve bacteria					Gram -ve bacteria					
	Any	Staphylococci	Streptococci	Other	Any	Staphylococci	Streptococci	Other	Any	Pseudomonas	Other
Brisbane, Australia	75	41	11	23	56	44					12
North America and Canada											
Toronto	43	32	10	1	20	7					13
Miami	637	278	89	270	664	345					319
Pittsburgh	797	638	115	44	256	71					185
LA	48	34	9	5	30	13					17
Texas	45	25	12	8	32	18					14
Durham	314	197	57	78	74	40					34
Europe											
Paris	172	116	19	37	35	21					14
Lausanne, Switzerland	57	45	10	2	18	7					11
Anatolia, Turkey	155	115	35	5	20	15					5
Amsterdam and Rotterdam	46	25	16	5	58	35					23

Table 3
Proportion of culture-positive patients who tested positively for protozoa or fungi and yeasts by location

Location of study	Number of isolates						
	Protozoa		Fungi and yeasts				
	Any	Any	Aspergillus	Candida	Other	Other	
Africa							
Ghana	1	82	19	1	62		
Accra, Ghana	unspecified	65	10	1	45		
Indian Subcontinent							
Nepal, India	unspecified	200	75	9	116		
Chitagong, Bangladesh	unspecified	48	24	1	23		
Tamil Nadu	7	296	76	0	220		
East Bengal	4	623	373	7	243		
New Delhi	unspecified	13	6	0	7		
Madurai, S. India	3	155	25	unspecified	116		
Hyderabad, India	unspecified	146	43	2	101		
Tamil Nadu, India	33	1176	294	unspecified	882		
Hyderabad, India	3	22	5	1	16		
Delhi, India	11	358	149	30	179		
Riyadh, Saudi Arabia	unspecified	unspecified	unspecified	unspecified	unspecified		
Baghdad, Iraq	unspecified	74	42	4	28		
South America							
Asuncion, Paraguay	unspecified	209	37	4	168		
Far East							
Taiwan	11	34	5	10	19		
Taipei, Taiwan	unspecified	unspecified	unspecified	unspecified	unspecified		
Singapore	unspecified	29	5	3	21		
Singapore	unspecified	unspecified	unspecified	unspecified	unspecified		
Hong Kong	6	5	unspecified	1	4		
Bangkok	3	46	9	2	37		
Australasia							

Location of study	Number of isolates					
	Protozoa		Fungi and yeasts			
	Any	Any	Aspergillus	Candida	Other	Other
Auckland, NZ	unspecified	7	unspecified	unspecified	unspecified	unspecified
Christchurch, New Zealand	unspecified	unspecified	unspecified	unspecified	unspecified	Unspecified
Adelaide	unspecified	7	3	2	2	2
Victoria, Australia	4	7	unspecified	1	6	6
Brisbane, Australia	unspecified	13	unspecified	unspecified	unspecified	unspecified
North America and Canada						
Toronto	unspecified	unspecified	unspecified	unspecified	unspecified	unspecified
Miami	unspecified	unspecified	unspecified	unspecified	unspecified	unspecified
Pittsburgh	unspecified	Unspecified	unspecified	unspecified	unspecified	unspecified
LA	unspecified	4	unspecified	unspecified	unspecified	4
Texas	4	8	unspecified	3	unspecified	unspecified
Durham	unspecified	unspecified	unspecified	unspecified	unspecified	unspecified
Europe						
Paris	unspecified	unspecified	unspecified	unspecified	unspecified	unspecified
Lausanne, Switzerland	unspecified	unspecified	unspecified	unspecified	unspecified	unspecified
Anatolia, Turkey	unspecified	50	10	15	25	25
Amsterdam and Rotterdam	unspecified	2	0	2	0	0

Table 4
95% confidence intervals and p values for Spearman's Correlation analysis

Variables analysed	Correlation coefficient	95% confidence limit	2 tailed p value
Prevalence of bacteria, GNI	0.83	0.68 to 0.91	<0.0001
Prevalence of fungi, GNI	-0.81	-0.90 to -0.66	<0.0001
Prevalence of Streptococci, GNI	-0.43	-0.66 to -0.12	0.009
Prevalence of pseudomonas, prevalence of contact lens wearers	0.13	-0.31 to 0.52	0.6