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Outcomes of Pythium keratitis: a meta-analysis of individual patient data

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Abstract

Background: Pythium keratitis is a difficult-to-treat corneal infection.

Methods: A meta-analysis of individual patient data from observational studies of Pythium keratitis was performed. The outcomes of interest were therapeutic penetrating keratoplasty (TPK) and globe removal (evisceration, enucleation, or exenteration); the main exposures were linezolid and azithromycin use.

Findings: Of 46 eligible articles, individual patient data were available for 306 eyes (34 studies). Pythium keratitis was associated with high rates of TPK (80%, 95%CI 70–87%) and globe removal (25%, 95%CI 13–43). In multivariable models adjusting for age and country, fewer TPKs were performed in patients treated with azithromycin (RR=0.80, 95%CI 0.67–0.96; *P*=0.04) and linezolid (RR=0.82, 95%CI 0.67–0.99; *P*=0.02).

Conclusions: Studies of Pythium keratitis reported high rates of TPK and globe removal. Use of azithromycin and linezolid was associated with a lower rate of TPK. While promising, these results should be interpreted with caution given the biases inherent to observational studies.

Keywords

Pythium; pythiosis; corneal ulcer; azithromycin; linezolid; penetrating keratoplasty; systematic review

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INTRODUCTION

Pythium insidiosum is an aquatic oomycete that closely resembles fungus morphologically and histologically.[1] *P. insidiosum* can infect both animals and humans, with published reports of cutaneous, vascular, systemic, gastrointestinal and ocular infections.[2] Corneal infection secondary to Pythium, or Pythium keratitis, has been gaining attention in the past few decades due to its high virulence, challenging diagnosis, lack of effective treatment regimen, high recurrence rate, and poor visual prognosis.[3,4] The majority of cases have been reported mainly in tropical and subtropical countries such as India and Thailand, although there have been scattered cases reported in areas with temperate conditions like the United States, France, New Zealand, Australia, Spain, Israel, and Japan.[5–14] Pythium zoospores develop in swampy areas, and thus agriculture and water-based activities are considered the major predisposing risk factors.[2]

Due to its clinical, microbiological and histological resemblance to fungal keratitis, Pythium keratitis diagnosis is usually delayed, leading to severe complications, including corneal perforation, vision loss, evisceration, enucleation, exenteration and in rare cases, death.[15] Ocular Pythiosis often necessitates early therapeutic penetrating keratoplasty (TPK) due to the high virulence, rapid proliferation of the pathogen, and limited response to medical management.[16] In the past, cases of Pythium keratitis were often treated with antifungal therapy because Pythium was mistakenly grouped as a fungal species. However, several studies have shown that antifungals have limited efficacy against Pythium.[16,17] In the past few years, antibiotics such as azithromycin and linezolid have been reported in some studies as an alternative medical treatment with some efficacy against Pythium.[3,18] However, evidence from individual studies has been limited. Therefore, in this meta-analysis, we collected and analyzed individual patient data from published studies to assess the outcomes of Pythium keratitis and the efficacy of different medical treatment regimens.

METHODS

Literature search.

A literature search was performed on PubMed from inception to August 20, 2022 using the phrase (pythium[tiab] AND (keratitis[tiab] OR “corneal ulcer”[tiab])) OR “ocular pythiosis”[tiab]. Titles and abstracts were screened to select articles reporting cases of human ocular Pythiosis. Only manuscripts available in English were reviewed.

Data extraction.

Two co-authors (BC and VTG) independently assessed the full-text version of all the selected articles and extracted data onto a standardized electronic data collection form. Data was summarized at the individual patient level. If a study reported data only at the group level, the corresponding author was contacted to request the individual-level data. Discrepancies between the two data extractors were resolved by discussing each issue and coming to consensus.

Eligibility criteria.

Patients were included in the study if they had a corneal infiltrate accompanied by positive results for Pythium from at least one of the following tests: (1) microbiological testing (i.e., culture and microscopy), (2) molecular assay (i.e., PCR and sequence homology), or (3) histological assessment. If a patient had bilateral disease, the worst eye was chosen for analyses. Patients who failed to meet one of the above diagnostic criteria for Pythium keratitis were excluded.

Exposure definition.

The main exposures of interest were treatment with linezolid and azithromycin, defined as the use of these medications prior to any surgical therapy.

Outcome measures.

The main outcome measures were therapeutic penetrating keratoplasty (TPK) and the composite outcome of evisceration, enucleation, or exenteration, named globe removal in this report.

Definitions and conventions.

Visual acuity (VA) was converted from Snellen VA measurements to logarithm of the minimum angle of resolution (logMAR) equivalent for statistical analysis. Infiltrate size was calculated as the geometric mean of the reported height and width, assuming a corneal diameter of 11.5 mm to calculate infiltrate size of “total” infiltrates, and assigning the median value from the estimated tertiles when infiltrates were described as “small” or “large.” Medications were recorded as dichotomous variables, based on whether they were used before either of the outcomes had occurred.

Statistical methods.

Statistical analyses were performed using individual patient data in order to address potential confounders. Univariable robust Poisson regression models were created to provide estimates of relative risk, with TPK or globe removal as the response variable and various risk factors at presentation as well as instituted medical treatments as the explanatory variables. Similar multivariable models were constructed to explore the relationship between linezolid/azithromycin use and each of the outcomes, with adjustment for age, country, and visual acuity at presentation. Regression models were performed using the survey commands in Stata to account for the likelihood of intra-cluster correlation within each study (i.e., patients from the same study were likely to be more similar to each other compared with patients from a different study). All regression models were complete case analyses. P-values less than 0.05 were considered statistically significant. Analyses were performed with Stata 17.

RESULTS

Literature search and study characteristics.

A total of 84 articles were identified from the Pubmed search criteria, of which 46 contained data on the exposures and outcomes of interest (Figure 1). Of these manuscripts, 31 contained individual-level data of all participants, 1 contained individual data of some participants, and 6 had only group-level data. The authors of 3 group-level papers provided individual patient-level data upon request. From the resulting dataset, 8 eyes were excluded because of missing data for the outcomes of interest or bilateral disease. The final analysis population consisted of 306 patients (n=306 eyes) from 34 articles.[19–52] Manuscripts were published from 23 different clinical sites of 10 different countries, with the majority coming from India (N=14) and Thailand (N=8) (Table 1). Studies were published between 1993 and 2022, with an increasing number of manuscripts over time (Figure 2). Most of the identified studies were small case series, with a median of 1 (IQR 1–10; range 1–67) patient per study.

Overall, the study population (n=306) had a mean age of 43 years (95%CI 41 – 44 years), and 37% (95%CI 32–42%) were female. The most commonly reported occupation was farming (42%, 95%CI 28–58%, from 166 records with available data), and the most commonly reported risk factor was exposure to vegetative matter (38%, 95%CI 24–54%, from 215 records with available data). Visual acuity was generally poor at presentation (mean logMAR 1.9, 95%CI 1.7–2.2, among 213 records with available data). The median length of follow-up among the 213 records with available data was 82 days (IQR 30–365). Other demographic and clinical data from the initial presentation are shown in Table 2, stratified by country (i.e., India, Thailand, or other).

Medical therapy for Pythium keratitis was variable, and included many classes of antifungals, antibiotics, and antiparasitics (Table 3). Overall, the most commonly use medication was topical natamycin (76%), followed by a topical azole (61%). Use of an oral azole was also relatively common (31%). The most commonly used antibiotic among the entire study population was a topical fluoroquinolone (25%), although in India topical azithromycin and linezolid were more commonly used (29% each). Oral antibiotics were used less frequently than topical forms, and most commonly prescribed in India (oral azithromycin 14%, oral linezolid 4%). Topical antiparasitics were instituted less often than other medications. The proportion of patients treated with a biguanide agent was 3% in India and 5% in Thailand.

Outcomes were also variable, with an average of 80% (95%CI 70–87%) requiring TPK, and 25% (95%CI 13–43%) progressing to evisceration, enucleation, or exenteration (Figure 3). Univariable analyses provided evidence suggesting that disease severity at presentation was associated with subsequent need for TPK (Table 4) and globe removal (Table 5). For example, the mean infiltrate size at presentation was larger in patients who eventually required TPK (6.4mm vs. 4.6mm among 191 records with available data), and the presentation visual acuity worse (logMAR 2.0 vs 1.7). Use of linezolid and/or azithromycin decreased the need of TPK (Table 4) and globe removal (Table 5) in univariable analyses.

Although the amount of missing data limited the complexity of modeling, multivariable models adjusted for country and age found fewer TPKs performed in patients treated with azithromycin (RR 0.82, 95%CI 0.67–0.99; P=0.04) and linezolid (RR 0.80, 95%CI 0.67–0.96; P=0.02) (n=298 observations with non-missing data included in the analysis; Table 6). Fewer globe removal surgeries were also performed in patients treated with azithromycin and linezolid, although this association was not significant (Table 6). Sensitivity analyses restricted to India (i.e., where the vast majority of linezolid and azithromycin was prescribed) that were adjusted for age and presenting vision were consistent, finding fewer TPKs in those treated with azithromycin (RR 0.66, 95%CI 0.42–1.04; *P*=0.07) and linezolid (RR 0.79, 95%CI 0.58–1.07; *P*=0.12) (n=148 observations with non-missing data included in the analysis). Analyses adjusting for corneal ulcer size at presentation in addition to age and presenting vision demonstrated a similar, albeit weaker, association, with fewer TPKs in patients treated with azithromycin (RR=0.63, 95%CI 0.31–1.28; p=0.19) and linezolid (RR=0.8, 95%CI 0.53–1.21; p=0.28) (n=101 observations with non-missing data included in the analysis).

DISCUSSION

This review demonstrated that Pythium keratitis was associated with a poor prognosis, including high overall rates of TPK (80%) and globe removal (25%)—albeit with variability between studies, especially for the globe removal outcome. Topical antifungals were the most commonly reported medical therapies (e.g., natamycin in 76% and an azole in 61%), followed by oral antifungals (e.g., an oral azole in 31%) and topical antibiotics (e.g., a topical fluoroquinolone in 24%). Patients treated with linezolid and azithromycin were least likely to undergo TPK or globe removal, and multivariable models were consistent with a protective effect of these antibiotics, although models could not account for many possible confounders due to missing data. Linezolid/azithromycin therapy was used most commonly in India, and more complex multivariable models restricted to India were also consistent with a protective effect of linezolid/azithromycin, although did not meet criteria for statistical significance.

Surgical interventions have been more commonly reported for Pythium keratitis compared to prior reports of other forms of infectious keratitis. For example, the proportion of patients requiring TPK has been reported in other studies as approximately 6% for bacterial keratitis, 35–44% for fungal keratitis, and 9–43% for acanthamoeba keratitis.[53–57] The proportion of patients requiring evisceration has been reported as approximately 6% for bacterial keratitis, 10% for fungal keratitis, and 5% for acanthamoeba keratitis.[55,57] Although the rates reported in this meta-analysis may have been related to differential practice patterns at each of the study settings (e.g., globe removal more likely in Thailand than India), the findings of approximately 80% TPK and 25% globe removal confirm the clinical impression that Pythium is more difficult to control with medical therapy compared with other corneal infections.

The poor prognosis of Pythium infection reflects multiple challenges in diagnosis and treatment, including its variable clinical presentations, microbiological and histological resemblance to fungal keratitis, and especially, resistance to medical treatment. Although

antifungals were commonly prescribed for Pythium keratitis due to the morphological similarities between Pythium and fungi, clinicians have found antifungals to have limited efficacy, and have sometimes resorted to methods not commonly used in other types of corneal infections, such as cryotherapy and alcohol.[19–21,58] This meta-analysis confirmed that antifungal treatments were not associated with medical treatment success. Azithromycin and linezolid were originally shown to be effective against Pythium in vivo using a rabbit infection model.[59,60] In 2017, azithromycin and linezolid were first used to treat Pythium keratitis, and patients treated with these antibiotics were noted to have a lower rate of TPK and higher rate of healing.[17] The present study, which aggregated all individual patient data currently available, is consistent with these earlier reports, finding a lower rate of TPK among Pythium keratitis patients treated with linezolid and azithromycin. It is important to note that the association between linezolid/azithromycin and TPK was weaker in the multivariable analyses that included presentation visual acuity as a potential confounder. This suggests that there may be some unmeasured confounders that could account for some of the protective effect seen with linezolid/azithromycin, although it should also be noted that these multivariable models included only a subset of the study population due to missing data, and thus may not be representative of the total study population.

Azithromycin, a macrolide, and linezolid, an oxazolidinone, both inhibit protein synthesis by binding to the 50S subunit of the bacterial ribosome. It has been proposed that the likely mechanisms of azithromycin and linezolid against Pythium involve the inhibition of protein synthesis and their immunomodulatory effects.[61] Both azithromycin and linezolid can suppress the production of pro-inflammatory cytokines and may reduce the inflammatory damage.[61] Interestingly, linezolid was shown to have a superior efficacy and safety compared to azithromycin after prolonged treatment for more than 3–4 weeks in a rabbit model.[60] However, since linezolid and azithromycin are used together in most cases reported in this study, it is hard to compare the efficacy of these two antibiotics when used clinically for Pythium keratitis. Further study into the antimicrobial mechanisms of action against Pythium is warranted, especially given the poor outcomes seen in Pythium keratitis.

Limitations of this review include its observational design, which increased the likelihood of biased assessment and reporting of exposure and outcome data, increased the potential for misclassified and missing data, and limited the opportunities to address potential confounding. The study is subject to reporting bias, since centers may not have been willing to report poor outcomes. The vast majority of cases treated with linezolid and azithromycin received both antibiotics together, so it is difficult to know if one of these antibiotics may be superior to the other. No randomized comparative trials were available, although trials may never be performed given the relative paucity of cases. The study drew mainly from Thailand and India, and the associations between linezolid/azithromycin therapy and outcomes derived mostly from the Indian reports. It is unclear if the results are generalizable to other settings.

In conclusion, this meta-analysis of individual patient data found high rates of TPK and globe removal in cases of Pythium keratitis. The study found that patients treated with azithromycin and linezolid had a lower frequency of TPK, suggesting these medications

may be promising therapies for treatment of Pythium keratitis. Additional research is needed to determine the optimal treatments for Pythium keratitis.

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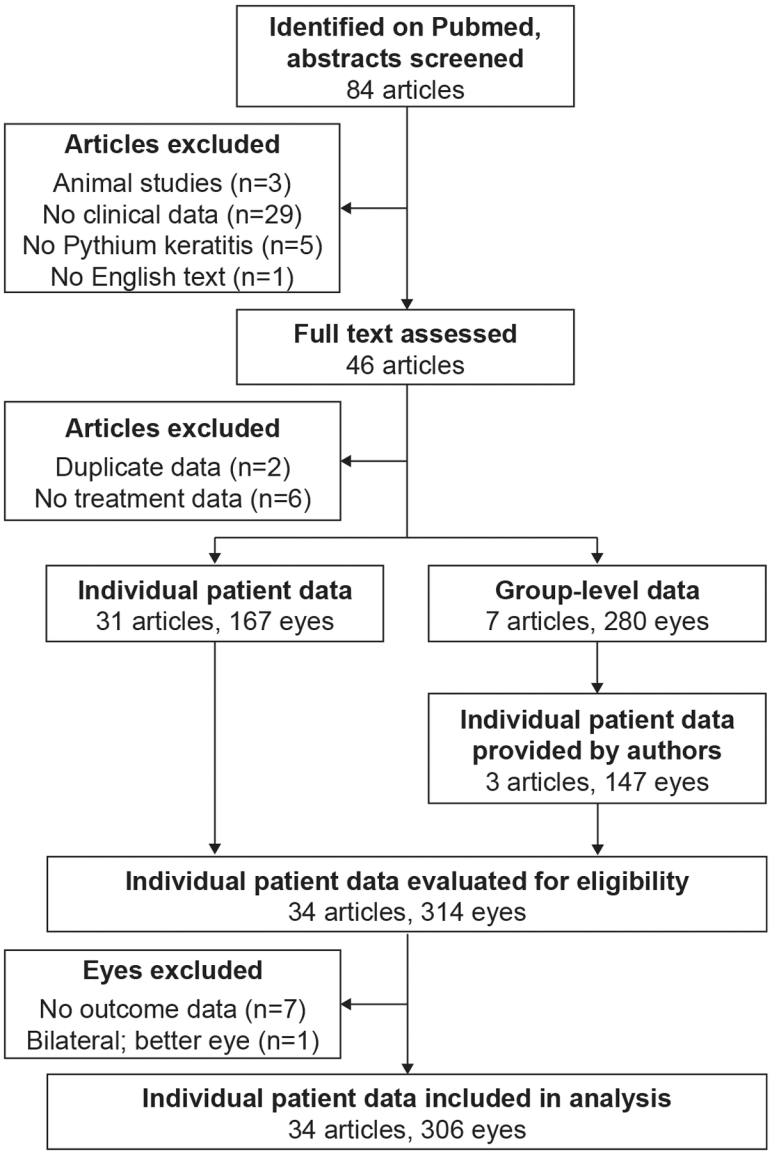

Figure 1:
Study flow.

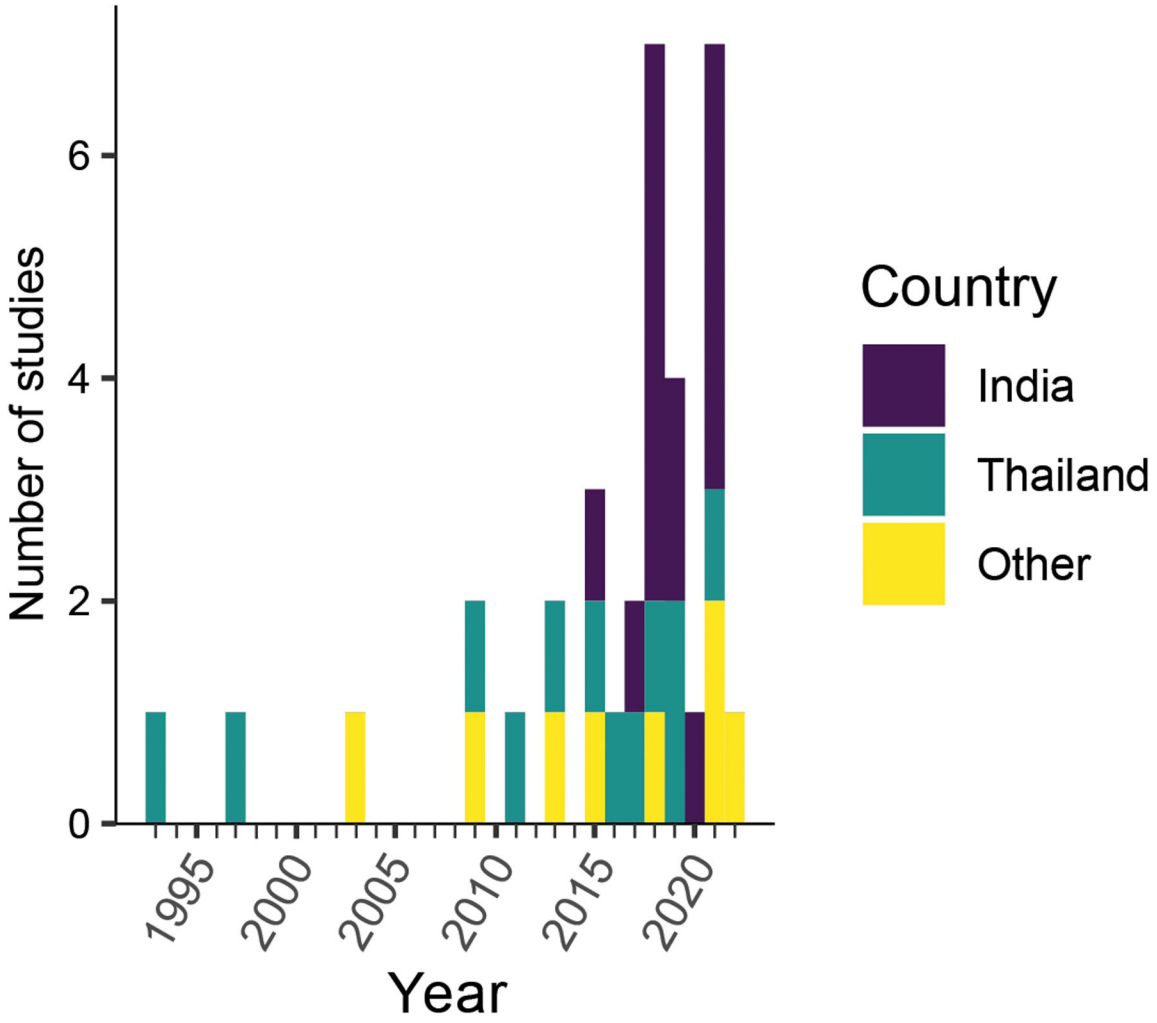

Figure 2: Studies about Pythium keratitis over time.

The number of studies published on Pubmed per year, identified with the search terms: (pythium[tiab] AND (keratitis[tiab] OR “corneal ulcer”[tiab])) OR “ocular pythiosis”[tiab]

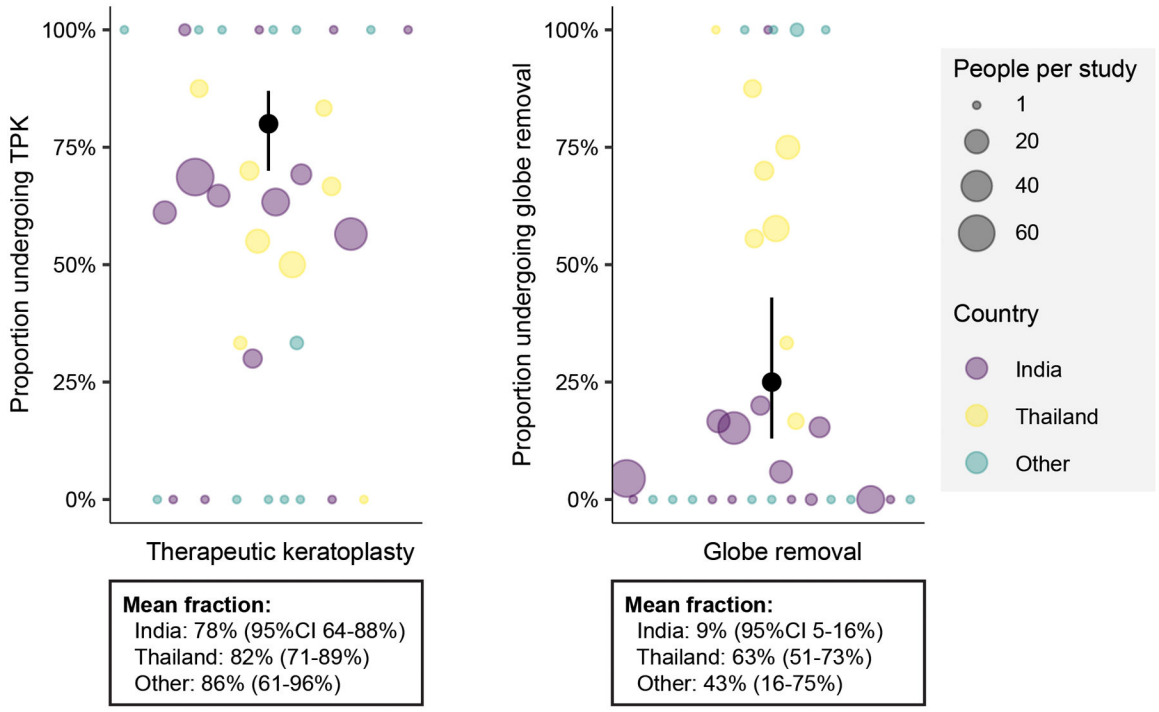

Figure 3: Fraction of patients in studies of Pythium keratitis undergoing therapeutic keratoplasty or globe removal.

Each marker represents a different study, sized relative to the number of patients in the study, and colored by country. The black marker and bars represent the overall mean and confidence intervals.

Table 1.

Demographic and clinical characteristics

Characteristics	Individual-level data		Group-level data only	
	Studies N = 34 (%)	Patients N = 306 (%)	Studies n=4 (%)	Patients n=133 (%)
Countries				
India	14 (41)	209 (68)	3 (75)	103 (77)
Thailand	8 (24)	83 (27)	1 (25)	30 (23)
Others	12 (35)	14 (5)	0	0
Sites				
Aravind (Madurai, India)	1 (3)	67 (22)	0	0
Sitalakshmi (Tamil Nadu, India)	3 (9)	58 (19)	0	0
Chulalongkorn (Bangkok, Thailand)	2 (6)	35 (11)	1 (25)	30 (23)
Srinagarind (Khon Kaen, Thailand)	3 (9)	33 (11)	0	0
LV Pradad (Hyderabad, India)	5 (15)	33 (11)	2 (50)	90 (68)
Aravind (Pondicherry, India)	1 (3)	30 (10)	0	0
LV Prasad (Bhubaneswar, India)	1 (3)	18 (6)	1 (50)	13 (9)
Ramathibodi (Bangkok, Thailand)	3 (9)	15 (5)	0	0
Others	15 (44)	17 (6)	0	0

Table 2.

Characteristics at presentation, Pythium keratitis

	India		Thailand		Other	
	Number with data (n=209)	**Mean or Proportion (95%CI)**	**Number with data (n=83)**	**Mean or Proportion (95%CI)**	**Number with data (n=14)**	**Mean or Proportion (95%CI)**
Age, years	209	43 (41–45)	83	44 (42–47)	14	30 (19–41)
Female	209	34% (27–42%)	83	42% (34–51%)	14	43% (21–68%)
Occupation						
Farmer	104	46% (37–56%)	60	37% (10–75%)	2	0%
Other	104	54% (44–63%)	60	63% (25–90%)	2	100%
Risk factors						
Ocular injury	137	32% (16–60%)	64	28% (13–50%)	14	14% (3–46%)
Vegetative matter	137	40% (22–62%)	64	38% (21–57%)	14	14% (4–39%)
Water exposure	137	7% (3–16%)	64	53% (33–72%)	14	79% (53–92%)
Contact lens use	137	1% (0–7%)	64	11% (2–52%)	14	50% (21–79%)
Days to presentation	147	18 (13–24)	64	13 (7–19)	14	14 (6–22)
Ulcer size, mm	129	6.3 (4.4–8.2)	55	5.5 (4.4–6.6)	7	4.6 (2.9–6.2)
VA at presentation[a]	148	1.9 (1.6–2.2)	57	2.1 (2.0–2.3)	8	1.0 (0.5–1.6)
Days to last follow-up	157	195 (16–374)	42	407 (166–648)	14	1240 (0–3141)

[a]Visual acuity converted into logMAR units

Table 3.

Medical treatment for Pythium keratitis prior to eye surgery

Medical treatment	India		Thailand		Other	
	Number with data n=209	Proportion (95%CI)	Number with data n=83	Proportion (95%CI)	Number with data n=14	Proportion (95%CI)
Topical antibiotic						
Fluoroquinolone	173	21% (6–51%)	75	31% (9–66%)	14	36% (15–63%)
Vancomycin	173	1% (0–5%)	75	4% (2–9%)	14	36% (17–61%)
Cephalosporin	173	1% (0–4%)	75	16% (7–34%)	14	36% (17–61%)
Aminoglycoside	173	5% (2–16%)	75	12% (5–28%)	14	36% (17–61%)
Azithromycin	209	29% (9–61%)	75	7% (1–27%)	14	0%
Linezolid	209	29% (7–67%)	75	4% (1–17%)	14	0%
Topical antifungal						
Natamycin	165	80% (47–95%)	83	75% (55–88%)	14	43% (21–67%)
Azole	165	50% (25–75%)	83	82% (61–93)	14	71% (40–90%)
Amphotericin B	165	2% (0–7%)	83	59% (45–72)	14	21% (6–53%)
Topical antiparasitic						
Biguanide	209	3% (2–5%)	75	5% (2–17%)	14	29% (10–30%)
Diamidine	209	0%	75	4% (1–20%)	14	14% (3–46%)
Oral antibiotic						
Oral azithromycin	209	14% (3–45%)	83	4% (1–11%)	14	0%
Oral linezolid	209	4% (1–22%)	83	1% (0–1%)	14	7% (1–40%)
Other oral antibiotics	209	0% (2–11%)	83	4% (1–11%)	14	7% (1–40%)
Oral antifungal						
Oral azole	209	10% (3–31%)	83	78% (48–94%)	14	57% (33–79%)
Oral terbinafine	209	0%	83	37% (17–64%)	14	0%
Intrastromal injections						
Intrastromal amphotericin	209	0%	83	39% (15–69%)	14	10% (3–32%)
Intrastromal azole	209	0% (0–4%)	83	6% (2–19%)	14	14% (4–39%)
Intravenous medication						
Intravenous antibiotic	209	0% (0–4%)	83	0%	14	21% (6–53%)
Intravenous antifungal	209	0% (0–4%)	83	0%	14	21% (6–53%)
Oral and/or topical						
Linezolid	209	29% (7–67%)	75	4% (1–17%)	14	7% (1–41%)
Azithromycin	209	29% (9–61%)	75	22% (9–46%)	14	8% (2–25%)

Table 4.

Risk factors for therapeutic keratoplasty in Pythium keratitis, univariable analyses.

Factor	TPK- n=62	TPK+ n=244	Univariable Relative Risk	p-value
Feature at presentation				
Country				0.77
India	45/62 (73%)	164/244 (67%)	0.92 (0.71–1.17)	0.48
Thailand	15/62 (24%)	68/244 (28%)	0.96 (0.77–1.19)	0.68
Other	2/62 (3%)	12/244 (5%)	Reference	
Age, years	43 ±18	43 ±16	1.00 (0.99–1.00)	0.88
Female	22/62 (35%)	90/244 (37%)	0.99 (0.89–1.10)	0.81
Farmer	17/40 (43%)	53/126 (42%)	1.00 (0.78–1.29)	0.97
Risk factor				
Ocular injury	12/45 (27%)	51/170 (30%)	1.03 (0.85–1.26)	0.73
Vegetative matter	20/45 (44%)	61/170 (36%)	0.93 (0.78–1.11)	0.38
Water	13/45 (29%)	41/170 (24%)	0.95 (0.81–1.11)	0.50
Contact lens	1/45 (2%)	14/170 (8%)	1.20 (1.00–1.43)	0.05
Days to presentation	12 ±10	16 ±14	1.00 (1.00–1.01)	0.04
Ulcer size, mm	4.6 ±2.0	6.4 ±3.0	1.05 (1.02–1.08)	0.003
logMAR vision	1.7 ±0.9	2.0 ±0.7	1.10 (0.99–1.24)	0.08
Medical treatment				
Topical antibiotic				
Fluoroquinolone	9/61 (15%)	55/201 (27%)	1.17 (1.01–1.34)	0.03
Vancomycin	2/61 (3%)	7/201 (3%)	1.01 (0.69–1.48)	0.94
Cephalosporin	3/61 (5%)	16/201 (8%)	1.11 (0.92–1.33)	0.28
Aminoglycoside	5/61 (8%)	18/201 (9%)	1.02 (0.83–1.26)	0.83
Azithromycin	21/61 (34%)	44/237 (19%)	0.82 (0.69–0.97)	0.03
Linezolid	21/61 (34%)	42/237 (18%)	0.80 (0.70–0.93)	0.004
Topical antifungal				
Natamycin	50/62 (81%)	150/200 (75%)	0.93 (0.77–1.12)	0.44
Azole	32/62 (52%)	128/200 (64%)	1.13 (0.99–1.30)	0.07
Amphotericin B	10/62 (16%)	45/200 (23%)	1.09 (0.98–1.22)	0.11
Topical antiparasitic				
Biguanide	2/61 (3%)	12/237 (5%)	1.08 (0.91–1.28)	0.35
Diamidine	0/61 (0%)	5/237 (2%)	1.26 (1.13–1.42)	<0.001
Oral antibiotic				
Oral azithromycin	11/62 (18%)	21/244 (9%)	0.81 (0.67–0.98)	0.03
Oral linezolid	3/62 (5%)	7/244 (3%)	0.87 (0.67–1.15)	0.32
Other	0/62 (0%)	4/244 (2%)	1.26 (1.13–1.41)	<0.001
Oral antifungal				
Oral azole	18/62 (29%)	76/244(31%)	1.02 (0.85–1.22)	0.82
Oral terbinafine	6/62 (10%)	25/244 (10%)	1.01 (0.86–1.20)	0.88

Factor	TPK- n=62	TPK+ n=244	Univariable Relative Risk	p-value
Intrastromal injection				
Amphotericin	6/62 (10%)	26/244 (11%)	1.02 (0.84–1.24)	0.83
Azole	1/62 (2%)	7/244 (3%)	1.10 (0.79–1.54)	0.56
Intravenous				
Antibiotic	0/62 (0%)	4/244 (2%)	1.26 (.13–1.41)	<0.001
Antifungal				
Oral and/or topical				
Azithromycin	21/61 (34%)	45/237 (19%)	0.82 (0.70–0.98)	0.03
Linezolid	22/61 (36%)	42/237 (18%)	0.79 (0.68–0.91)	0.002

Table 5.

Risk factors for globe removal in Pythium keratitis, univariable analyses.

Factor	EEE- n=229	EEE+ n=77	Univariable Risk Ratio[b]	p-value
Feature at presentation				
Country				<0.001
India	190/229 (83%)	19/77 (25%)	0.21 (0.08–0.57)	0.003
Thailand	31/229 (14%)	6/77 (8%)	1.46 (0.64–3.32)	0.35
Other	8/229 (3%)	52/77 (67%)	Reference	
Age, years	40 ±17	49 ±12	1.03 (1.01–1.04)	0.001
Female	84/229 (37%)	28/77 (36%)	0.99 (0.69–1.42)	0.95
Farmer	45/119 (38%)	25/47 (53%)	1.56 (0.39–6.2)	0.50
Risk factor				
Ocular injury	43/157 (27%)	20/58 (34%)	1.27 (0.59–2.75)	0.53
Vegetative matter	53/157 (34%)	28/58 (48%)	1.54 (0.78–3.07)	0.21
Water	26/157 (17%)	28/58 (48%)	2.78 (1.80–4.30)	<0.001
Contact lens	11/157 (7%)	4/58 (7%)	0.99 (0.34–2.85)	0.98
Days to presentation	16 ±14	15 ±12	1.00 (0.97–1.02)	0.64
Ulcer size, mm	5.8 ±3.0	6.8 ±2.5	1.10 (0.95–1.26)	0.18
logMAR vision	1.8 ±0.8	2.2 ±0.5	1.97 (1.26–3.09)	0.005*
Medical treatment				
Topical antibiotic				
Fluoroquinolone	48/198 (24%)	16/64 (25%)	1.03 (0.47–2.24)	0.94
Vancomycin	5/198 (3%)	4/64 (6%)	1.87 (0.80–4.37)	0.14
Cephalosporin	10/198 (5%)	9/64 (14%)	2.09 (1.02–4.28)	0.04
Aminoglycoside	16/198 (8%)	7/64 (11%)	1.28 (0.68–2.39)	0.43
Azithromycin	59/228 (26%)	6/70 (9%)	0.34 (0.08–1.39)	0.13
Linezolid	59/228 (26%)	4/70 (6%)	0.23 (0.06–0.93)	0.04
Topical antifungal				
Natamycin	142/192 (74%)	58/70 (83%)	1.50 (0.60–3.77)	0.38
Azole	110/192 (57%)	50/70 (71%)	1.59 (0.83–3.06)	0.16
Amphotericin B	23/192 (12%)	32/70 (46%)	3.17 (1.53–6.57)	0.003
Topical antiparasitic				
Biguanide	10/228 (4.4%)	4/70 (6%)	1.23 (0.47–3.22)	0.67
Diamidine	2/228 (1%)	3/70 (4%)	2.62 (1.09–6.29)	0.03
Oral antibiotic				
Oral azithromycin	28/229 (12%)	4/77 (5%)	0.47 (0.15–1.44)	0.18
Oral linezolid	8/229 (3%)	2/77 (3%)	0.79 (0.30–2.10)	0.63
Other	4/229 (2%)	0/77 (0%)	<0.01	<0.001
Oral antifungal				
Oral azole	42/229 (18%)	52/77 (68%)	4.69 (2.19–10.07)	<0.001
Oral terbinafine	16/229 (7%)	15/77 (19%)	2.15 (1.07–4.31)	0.03

Factor	EEE- n=229	EEE+ n=77	Univariable Risk Ratio[b]	p-value
Intrastromal injection				
Amphotericin	7/229 (3%)	277 (32%)	4.12 (2.04–8.31)	<0.001
Azole	5/229 (2%)	3/77 (4%)	1.51 (0.64–3.59)	0.34
Intravenous				
Antibiotic	3/229 (1%)	1/77 (1%)	0.99 (0.15–6.59)	0.99
Antifungal	3/229 (1%)	1/77 (1%)	0.99 (0.15–6.59)	0.99
Oral and/or topical				
Linezolid	60/228 (26%)	4/70 (6%)	0.22 (0.05–0.90)	0.04
Azithromycin	60/228 (26%)	6/70 (9%)	0.33 (0.08–1.36)	0.12

[b] Risk ratio (RR) assessed from log-binomial regression, weighted by number of observations per study. RR indicates the risk of the outcome for each additional 10% of the study population treated with the medication.

Table 6.

Association between topical azithromycin and linezolid with poor outcomes in Pythium keratitis, multivariable analysis.

Values represent odds ratios with 95% confidence intervals.

Factor	Risk Ratio[a]			
	Azithromycin		Linezolid	
Risk factor	TPK (n=298)	Globe removal (n=298)	TPK (n=298)	Globe removal (n=298)
Relevant antibiotic[b]	0.82 (0.67–0.99)	0.66 (0.23–1.85)	0.80 (0.67–0.96)	0.47 (0.14–1.51)
Country				
India	0.98 (0.75–1.27)	0.15 (0.06-.36)	0.98 (0.75–1.27)	0.16 (0.06–0.39)
Thailand	0.97 (0.77–1.22)	0.92 (0.51–1.67)	0.96 (0.77–1.21)	0.92 (0.51–1.65)
Other	Reference	Reference	Reference	Reference
Age, years	1.00 (0.99–1.00)	1.04 (1.02–1.05)	1.00 (0.99–1.00)	1.04 (1.02–1.05)

TPK = therapeutic keratoplasty. Globe removal = evisceration, enucleation, or exenteration.

[a]Risk ratio assessed from robust Poisson regression.

[b]Relevant antibiotic refers to either topical azithromycin (results given in first two columns) or topical linezolid (results given in last two columns.