Corynebacterium

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Corynebacterium infectious keratitis conjunctivitis resistant bacteria fluoroquinolone C. macginleyi

1. Introduction

Corynebacterium species are frequent constituents of the normal bacterial flora of the conjunctival sac and are common as well on human skin and mucous membranes and in the intestines [1][2]. One important species, *Corynebacterium diphtheri*, is the pathogenic bacterium that causes diphtheria, an upper respiratory infection generally characterized by sore throat and high temperature. In severe diphtheria cases, respiratory obstruction due to the inflammation of the tonsils, oropharynx, and pharynx can lead to death as the worst-case scenario. However, in general, *Corynebacterium* species seem to have low pathogenicity; therefore, the isolation of *Corynebacterium* species from infected tissue has been considered to arise as a result of mishandling or contamination [3][4].

Corynebacterium species can be found commonly on the ocular surface, in conjunction with other indigenous bacteria, such as *Staphylococcus epidermidis* and *Propionibacterium acnes* [1][5]. These various commensal bacteria aid in preventing ocular surface from invasion by foreign organisms [6]. However, in immunocompromised patients, many recent reports have demonstrated that *Corynebacterium* species can be potentially pathogenic when present on the ocular surface [7][8][9][10], as this infection has been associated with cases of endocarditis of the aortic and mitral valves [11], granulomatous mastitis [12], and pelvic osteomyelitis [13]. Many reports have been based on the case series [7][14][15][16][17][18][19][20][21]. Therefore, the frequency of occurrence of various *Corynebacterium* species on the ocular surface compared to other organs is not well characterized, and the mechanism by which *Corynebacterium* species function as pathogenic organisms is also unclear. Moreover, the antimicrobial susceptibility pattern in *Corynebacterium* species, as with other bacteria like *Staphylococcus aureus*, has been changing in recent years [22]. Consequently, a full understanding of the pathogenicity of *Corynebacterium* species awaits a systematic review of the various ocular infection cases possibly caused by *Corynebacterium* species.

2. Corynebacterium Species

The genus *Corynebacterium* consists of 137 species, and 10 of these have been isolated from corneal infections (Table 1). *Corynebacterium* species are commonly found in the conjunctiva of healthy adults and have been recognized as non-pathogenic commensal bacteria on the ocular surface [7][8]. One study of 990 patients prior to cataract surgery revealed positive culture results for *Corynebacterium* species in the conjunctival sac in 46.4% (460/990), which was much higher than the results for methicillin-sensitive coagulase-negative staphylococci (MS-CNS), at 22.5% (223/990), or methicillin-sensitive *Staphylococcus aureus* (MSSA), at 4.4% (44/990) [5].

Table 1. Representative cases with ocular surface infection caused by Corynebacterium species.

Authors (Ref. Number)	Year	Country	Age	Disease	Type of Strains	Lipophilic or Non-Lipophilic	Past History	Antibiotic Susceptibilities of Corynebacterium Species (Minimum Inhibitory Concentration; (µg/mL))							
								PCs	EM	CEPs	LVFX	CPFX	GM/TOB	VCM	CP
Badenoch PR et al. [14]	2016	Australia	94	Suture-related keratitis	*C. propinquum*	Non-lipophilic	Diabetes, Corneal transplantation	0.02	>256 (CLDM)	-	-	0.38	-	0.5	-
Duignan ES et al. [15]	2016	Ireland	52	Keratitis	*C. pseudodiphtheriticum*	Non-lipophilic	Corneal inlay	-	-	-	S (MFLX)	-	-	-	S
Todokoro D et al. [16]	2015	Japan	44	Contact-related keratitis	*C. propinquum*	Non-lipophilic	Contact lens wear, Proliferative diabetic retinopathy	-	>256	0.125	1	2	0.5	1	-
Ruoff KL et al. [17]	2010	USA	84	Keratitis	*C. macginleyi*	Lipophilic	Fuchs' endothelial dystrophy	0.016	-	-	-	0.032	0.064	0.5	-
Alsuwaidi AR et al. [18]	2010	Canada	54	Conjunctivitis	*C. macginleyi*	Lipophilic	Health care worker	S	R	S	S	S	S	S	S
Inata K et al. [23]	2009	Japan	23	Contact-related keratitis	*C. mastidis*	Lipophilic	Contact lens wear	-	<0.016	0.125	0.064	0.125	<0.064	0.5	4
Eguchi et al. [8]	2008	Japan	58	Conjunctivitis	*C. macginleyi*	Lipophilic	-	-	-	-	>32	>32	-	-	-
Eguchi et al. [8]	2008	Japan	72	Conjunctivitis	*C. macginleyi*	Lipophilic	-	-	-	-	>32	>32	-	-	-
Eguchi et al. [8]	2008	Japan	58	Conjunctivitis	*C. macginleyi*	Lipophilic	-	-	-	-	>32	>32	-	-	-
Eguchi et al. [8]	2008	Japan	78	Conjunctivitis	*C. macginleyi*	Lipophilic	-	-	-	-	>32	>32	-	-	-

Authors (Ref. Number)	Year	Country	Age	Disease	Type of Strains	Lipophilic or Non-Lipophilic	Past History	Antibiotic Susceptibilities of Corynebacterium Species (Minimum Inhibitory Concentration; (μg/mL))							
								PCs	EM	CEPs	LVFX	CPFX	GM/TOB	VCM	CP
Suzuki T et al. [19]	2007	Japan	74	Suture-related keratitis	*C. macginleyi*	Lipophilic	Corneal transplantation	16	2	0.5	>128	128	<0.13	0.5	-
Suzuki T et al. [19]	2007	Japan	49	Suture-related keratitis	*C. macginleyi*	Lipophilic	Corneal transplantation	16	<0.13	0.25	64	8	<0.13	0.5	-
Giammanco G. M et al. [20]	2002	Italy	65	Corneal ulcers	*C. macginleyi*	Lipophilic	Trauma	S	S	S	-	S (ENX)	S	S	S
Li A et al. [21]	2000	China	86	Keratitis	*C. pseudodiphtheriticum*	Non-lipophilic	Pneumonia, Trichiasis, Lagophthalmos	R	-	R *	-	-	-	S	R
Heidemann DG et al. [24]	1991	USA	80	Keratitis	*C. striatum*	Non-lipophilic	Proliferative diabetic retinopathy	S	S	S *	-	-	-	S	-
Rubinfeld RS et al. [25]	1989	USA	81	Keratitis	*C. striatum*	Non-lipophilic	Contact lens wear, Aphakia	S	S	S *	-	-	-	S	-
Rubinfeld RS et al. [25]	1989	USA	11	Suture related keratitis	*C. xerosis*	Non-lipophilic	Post corneal laceration	-	S	S *	-	-	S	S	S
Funke et al. [7]	1998	Switzerland	47 [a]	Corneal ulcer (*n* = 3), Conjunctivitis (*n* = 12)	*C. macginleyi*	Lipophilic	Contact lens wear, Eyelid closure problems	<0.01–0.125 [b]	<0.03–>64 [b]	0.5–16 [b]	0.125–1 (Ofloxacin) [b]	0.06–0.125 [b]	<0.06–0.5 [b]	0.5–1 [b]	2–4 [b]

Range of , LVFX: phenicol, operative dominant t 2%, C. -specific egel and vo major % of the such as biofilm formation in immunosuppressed persons. In fact, cases of *Corynebacterium*-associated ocular infection, including conjunctivitis, bacteria keratitis, glaucoma bleb-related infections, and endophthalmitis, have been reported [7][8][14][15][16][17][18][19][20][21][24][25][23][26][27][28][29], have led to suspicion of involvement of *Corynebacterium* species in immunocompromised cases. Many case reports have implicated *C. macginleyi* as a main strain that causes conjunctivitis and bacteria keratitis [7][8][17][18][19][20][26][30].

In this review, we have listed the cases of ocular surface infection, including keratitis, corneal ulcer, and conjunctivitis, caused by *Corynebacterium* species (Table 1). The identified species were *C. macginleyi* (*n* = 24), *C. propinquum* (*n* = 2), *C. pseudodiphtheriticum* (*n* = 2), *C. striatum* (*n* = 2), *C. xerosis* (*n* = 1), and *C. mastitidis* (*n* = 1) [7][8][14][15][16][17][18][19][20][21][24][25][23]. Most of the infected patients had risk factors, such as diabetes or long-term use of steroid treatments after corneal transplantation [14][16][19][24] that led to poor immunity, or they had experienced corneal epithelial damage due to trauma [20], contact lens wear [7][16][25][23], lagophthalmos, or trichiasis [21]. Interestingly, mild infectious cases, like conjunctivitis, were more often observed in cases of *C. macginleyi* infection, whereas other *Corynebacterium* strains seem to cause more severe infectious diseases [14][16][21]. In fact, many severe keratitis cases reported from India were caused by strains identified as *C. propinquum* (*n* = 3), *C. pseudodiphtheriticum* (*n* = 1), *C. striatum* (*n* = 1), and *C. bovis* (*n* = 1) [9], suggesting that the causative agents could be either indigenous bacteria or foreign strains.

2.1. C. macginleyi

Riegel and associates reported lipophilic coryneform bacteria from eye specimens that they named *C. macginleyi* [31]. The presence of this species in the normal conjunctiva is not surprising because the meibomian glands produce meibum, an oily substance [31]. In fact, *C. macginleyi* is the most commonly isolated strain in the conjunctiva, and it is also recognized as the most common causative agent of opportunistic ocular infections.

The rDNA sequence of *C. macginleyi* shows a 98.7% similarity to that of *C. accolens*. Eguchi and associates showed that *C. macginleyi* was highly resistant to fluoroquinolones, with 12 of 16 tested isolates showing resistance. They attributed this resistance to overuse of fluoroquinolones eye drops in the ophthalmology field. *C. macginleyi* is an opportunistic pathogen that causes several ocular infections, including conjunctivitis [7][8][18], corneal keratitis [17][19], glaucoma bleb-related infections [28][29], and endophthalmitis [10][27]. *C. macginleyi* can also cause non-ocular infections, such as bladder catheter infections [32], intravenous catheter infections [33][34], and septicemia [35].

2.2. C. accolens

C. accolens (previously CDC group G-1) was first described from human clinical specimens, such as wound drainage, endocervix samples, sputum, and throat swab specimens collected over a 30-year period [3][36]. Hoshi and associates revealed that *C. accolens* was the second most frequent bacterial species, accounting for 7% of the bacteria in the conjunctiva and 44% in the nasal cavity in the healthy volunteers [37]. One case with bacterial conjunctivitis had *C. accolens* identified in the conjunctival sac [8]. However, evidence confirming the *Corynebacterium* isolates as the causative agents of the infection was not provided.

2.3. C. propinquum

C. propinquum was proposed as the CDC coryneform ANF-3 bacterium by Riegel and associates [38]. Two cases of keratitis caused by *C. propinquum* have been reported. One case was a 94-year-old woman who had undergone corneal transplantation for Fuchs corneal dystrophy, and she had used long-term 0.1% fluorometholone eye drops as prophylaxis against graft rejection. Corneal infection had occurred at the loosened suture region of the graft. After medication with 5% cefazolin eye drops and 1% gentamicin eye drop hourly and 0.1% fluorometholone eye drops twice daily, her visual acuity improved to 20/160 [14]. Another case was a 44-year-old woman with a persistent corneal epithelial defect. She had a past history of type 1 diabetes, proliferative diabetic retinopathy, and hemodialysis due to diabetic nephropathy. The ocular infection was attributed to a persistent corneal epithelial defect due to neurotrophic keratopathy, possibly caused by poor diabetes control. The patient was treated with gatifloxacin and cefmenoxime eye drops six times daily and complete eye closure with an eye patch to facilitate reepithelialization. Her final visual acuity recovered to 0.02 (20/1000) [16].

C. propinquum is typically commensal on the human nasopharynx and skin [37][39]. *C. propinquum* has been implicated in various opportunistic infections, such as pulmonary infection [40] and infective endocarditis [41]. The majority of *C. propinquum* strains are constitutively resistant to macrolide drugs [37][42], and both of the above cases were resistant to erythromycin [37].

2.4. C. amycolatum

C. amycolatum is a non-lipophilic and fermentative *Corynebacterium* species, first described by Collins and associates from swabs of the skin of healthy people [43]. One case report has appeared of orbital implant infection after eye evisceration caused by *C. amycolatum* [44], but no reports of conjunctivitis or keratitis have been published. *C. amycolatum* is a normal inhabitant of skin and mucous membranes and promotes the epidermal growth factor receptor-dependent induction of the antimicrobial protein RNase7. The relationship between *C. amycolatum* and RNase7 may control the growth of *Corynebacterium* species on human skin [45].

2.5. C. jeikeium

The species *C. jeikeium* was isolated from bacterial endocarditis following cardiac surgery [46]. *C. jeikeium* is part of the normal flora of the skin, especially in inpatients. Many studies have reported multi-resistance to antibiotics in *C. jeikeium* strains [47][48][49].

2.6. C. mastitidis, C. lowii, and C. oculi

C. mastitidis was first found in sheep with mastitis [50] and this species can stably colonize the ocular mucosa, where it provides a related beneficial local immunity [51]. Bernard and associates analyzed *C. mastitidis* recognized by Eguchi in Japan and Vandamm in Belgium and Switzerland [8][52], and described *C. lowii* and *C. oculi* as two new species, separate from *C. mastitidis*. *C. mastitidis* was detected in contact-related keratitis in Japan; however, unlike *C. macginleyi, C. mastitidis* was very sensitive to both levofloxacin and ciprofloxacin [23].

3. Laboratory Examinations

3.1. The Ocular Manifestations of Corynebacterium Species

Corynebacterium-associated conjunctivitis is characterized by variable symptoms, including hyperemia, foreign body sensation, discharge, and a burning sensation [8][18][26][30]. Bacterial keratitis caused by *Corynebacterium* species shows clinical features by slit lamp microscopy that range from mild cases with a small infiltration on the surface of cornea to severe cases with corneal ulcerations with round to oval shapes at the center of cornea, but the ocular infections show no distinctive findings [9][17][19][24][53][54]. This infection is more frequently found in patients undergoing immunosuppressive therapy after corneal transplantation. As shown in Table 1, age differences do not seem to affect the ocular infection by *Corynebacterium* species. Trauma, contact lens wear, and corneal damage due to trichiasis and severe dry eye can also exacerbate the ocular infection [7][15][20][21][25][23]. However, *Corynebacterium* species isolated as part of the normal flora in the conjunctival sac showed a significant association with age, male sex, and glaucoma eye drop use in a multivariate analysis [5], suggesting that clinical information would be helpful for an accurate diagnosis.

Figure 1 shows the findings for an 89-year-old man who had undergone corneal transplantation for lattice corneal dystrophy eight years previously. He had applied 0.1% fluorometholone eye drops twice daily for the prevention of allograft rejection, accompanied by moxifloxacin eye drops for post microbial keratitis as prophylaxis. At his regular visit, corneal infiltration was found at the suture site. A microbial examination identified *Corynebacterium* species that were resistant to levofloxacin, erythromycin, cefmenoxime, and fosfomycin and were susceptible to arbekacin, vancomycin, and chloramphenicol. The patient was treated with 0.3% chloramphenicol eye drops, 1% vancomycin ointment, and 1% cefmenoxime eye drops, and the keratitis was resolved.

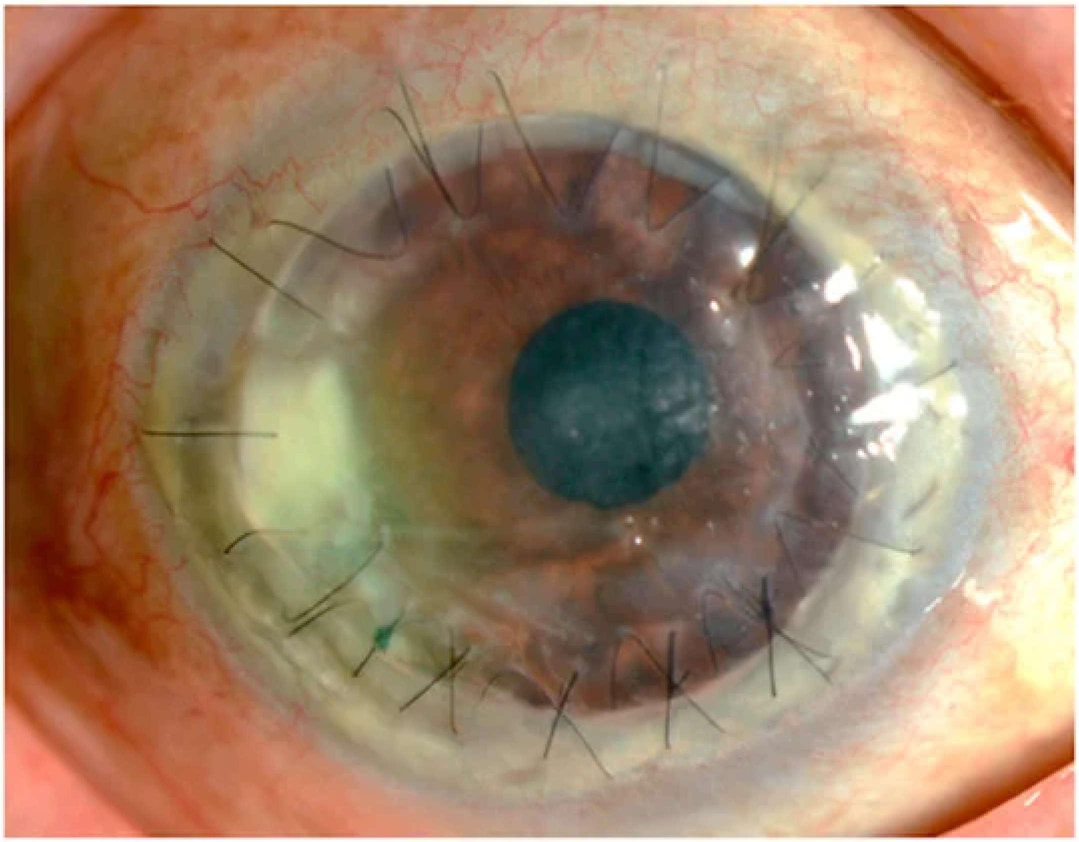

Figure 1. Slit lamp photograph. An 89-year-old man who underwent a penetrating keratoplasty at his age of 81. The corneal infiltration was observed around the graft suture, accompanied with moderate hyperemia.

3.2. Microscopy Examinations

Microscopy examinations of the discharge/fluid from the infected conjunctival sac and of corneal scrapings are helpful for identifying the causative bacteria. *Corynebacterium* species are gram-positive, rod-shaped, non-branching, non-motile, catalase positive, and oxidase negative bacteria. They grow in aerobic conditions, and *Corynebacterium* species are widely present in nature, in water, soil, and plants. The range in size from 0.3–0.8 μm in diameter and 1–8 μm in length. They look like the letters "I, N, T, V, W, or Y" at 1000× magnification, and show the apical growth typical of a bacillus, often exhibiting a club-shaped morphology at one or both ends. *Corynebacterium* species are commonly isolated as indigenous bacteria from the normal ocular flora as well as the mucosa and skin. However, as shown in Figure 2, *Corynebacterium* species are phagocytosed by polymorphonuclear leucocyte, indicating that they can have a potential impact on infection.

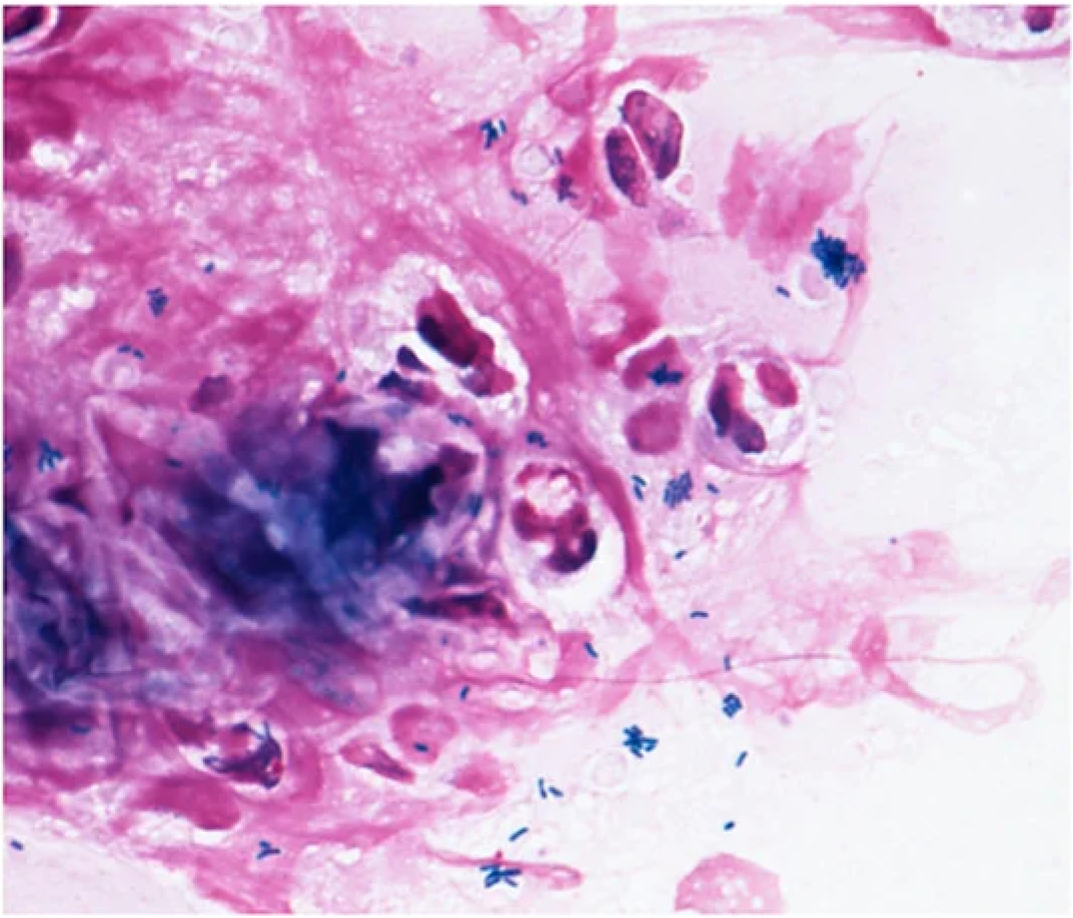

Figure 2. Gram staining. The Gram stain procedure revealed that gram-positive rod-shaped bacteria were phagocytosed by polymorphonuclear leucocyte.

3.3. Culture Tests

Most *Corynebacterium* species can be isolated from a 5% sheep blood agar, and they often form staphylococcal-like colonies. The growth of lipophilic *Corynebacterium* species is enhanced by adding 0.1% Tween 80 to the medium, while blood agar under aerobic conditions helps the growth of non-lipophilic *Corynebacterium* species. C. *macginleyi* is a lipophilic *Corynebacterium* and requires lipid for growth. Clinical laboratories typically report these organisms as “*Corynebacterium* spp.” based on visualization and catalase reactions only, which could lead to misdiagnosis. When other commensal bacteria from the respiratory system material or urinary system material are present, identification of *Corynebacterium* species may not always be necessary, as they are unlikely to be the causative pathogens of an infection. Therefore, *Corynebacterium* should be detected in clinical samples from normally sterile sites. However, the normal bacterial flora on the ocular surface includes *Corynebacterium* species [1], suggesting that the identification of *Corynebacterium* species should be performed with clinical findings in cases when immunity is severely affected, as those patients could develop infections caused by *Corynebacterium* species.

3.4. Antimicrobial Susceptibility Testing

Antimicrobial susceptibility testing is a method for determining possible drug resistance and for assuring the susceptibility to the drugs of choice for a particular bacterial species. Antimicrobial susceptibility testing should be performed for cases highly suspicious for *Corynebacterium* being a causative pathogen based on smear speculation or isolates from sterile materials. The minimal inhibitory concentrations (MIC values) of a drug for lipophilic or non-lipophilic *Corynebacterium* are typically determined using 5% lysed horse blood added to agar and adjusted with Ca and Mg with microfluid dilution. The bacteria are incubated for 24–48 h at 35 °C, with 48 h needed for lipophilic *Corynebacterium* species. Growth on control agar is compared to growth on the drug-containing agar to determine susceptibility or resistance. The disk diffusion method is a standardized technique for testing rapidly growing pathogens. However, many reports suggest some limitations to the use of the disc diffusion method [55][56], as some cases do not accurately display a visual resistance reaction.

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