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Ocular Infections Caused by *Corynebacterium* Species

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Additional information is available at the end of the chapter

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1. Introduction

1.1. The history of *Corynebacterium* species

The most well-known *Corynebacterium* species, *Corynebacterium diphtheriae*, causes diphtheria. However, in 1970, the clinical value of identification of *Corynebacterium diphtheriae* became less medically significant owing to the development of diphtheria toxoids and a decrease in the prevalence of diphtheritic infection in developed countries. Other *Corynebacterium* species have been considered contaminants when found in clinical samples because they are organisms normally found in the skin, mucous membranes, and other human tissues. Given that *Corynebacterium* species are one of the most commonly isolated bacteria from the ocular surfaces [1, 2], they are also considered non-pathogenic in the ophthalmic field.

Currently, in a clinical setting, many bacteriological laboratory technicians in hospitals report *Corynebacterium* species as “Gram-positive rods”. Sometimes, the presence of *Corynebacterium* species is not reported because it is considered to be contaminants. As a result, it is not possible for ophthalmologists to determine whether *Corynebacterium* species are present in clinical samples by using laboratory tests. This makes the *Corynebacterium* species to be nonpathogenic for ophthalmologists leading to therapeutic failure.

2. Bacteriological characteristics of *Corynebacterium* species

Morphology: The size of *Corynebacterium* species varies from $0.3\text{--}0.8 \times 1\text{--}8 \mu\text{m}$. They exist in a variety of shapes, even in pure cultures. In the clinical samples, they mostly appear as rod-shaped bacteria in palisade-, ring-, or ‘I, N, T, V, W, or Y’ letter-shaped arrangements.

Lipophilicity: Few *Corynebacterium* species generally have high lipophilicity. In vitro, they can be easily become unculturable if the final concentration of Tween 80 (polysorbate 80) in the medium is slightly different from the optimal concentration. Presumably, this is the reason why particular *Corynebacterium* species prefer the ocular surfaces as these are area where fatty acids are always present because they are secreted from the meibomian gland. This requirement may also explain why *Corynebacterium*-induced endophthalmitis is very rare.

3. *Corynebacterium* species as a pathogen: Case presentations

Case 1: In 2003, the author encountered the case of an elderly patient who had clear infectious conjunctivitis in his right eye. He had experienced mild conjunctival hyperaemia and mucopurulent discharge after cataract surgery performed 2 years before consultation (Fig. 1). He had continued to use a quinolone ophthalmic solution postoperatively, but had not undergone any ophthalmic examination. He had eye discomfort for more than 3 months. Gram staining smear of the discharge showed that many polymorphonuclear leukocytes phagocytizing Gram-positive rods (Fig. 2). Culture of the discharge sample detected quinolone resistant *Corynebacterium* species, and the strain was susceptible to cephem antibiotics. Switching the quinolone ophthalmic solution to a cephem antibiotic resolved of the patient's symptoms. The author determined this to be a clear case of conjunctivitis due to *Corynebacterium* species. Thereafter, the author encountered a large number of cases of *Corynebacterium* conjunctivitis in geriatric patient as well as several cases of *Corynebacterium* keratitis in patients who underwent keratoplasty. Thus, in 2012, *Corynebacterium* species still appear to be pathogens of the ocular surface.

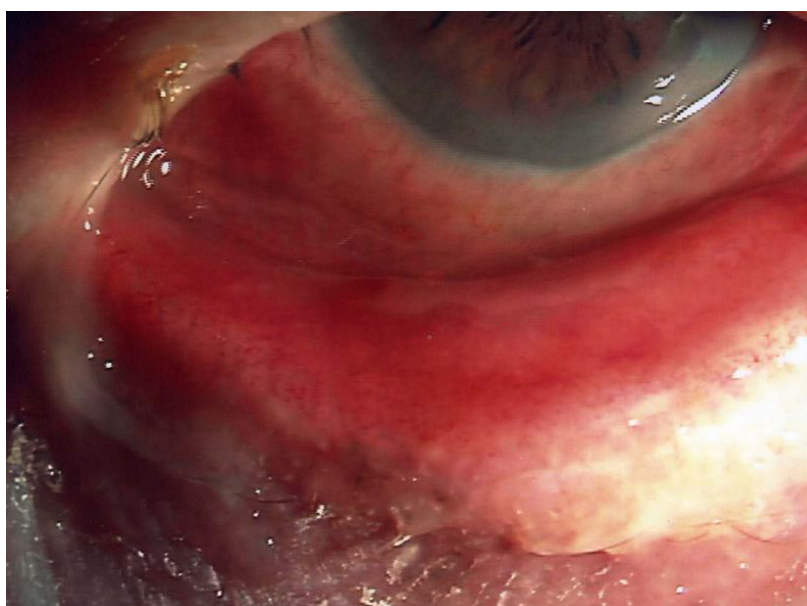


Figure 1. Infectious conjunctivitis occurred in case 1. A mild infectious conjunctivitis was found.

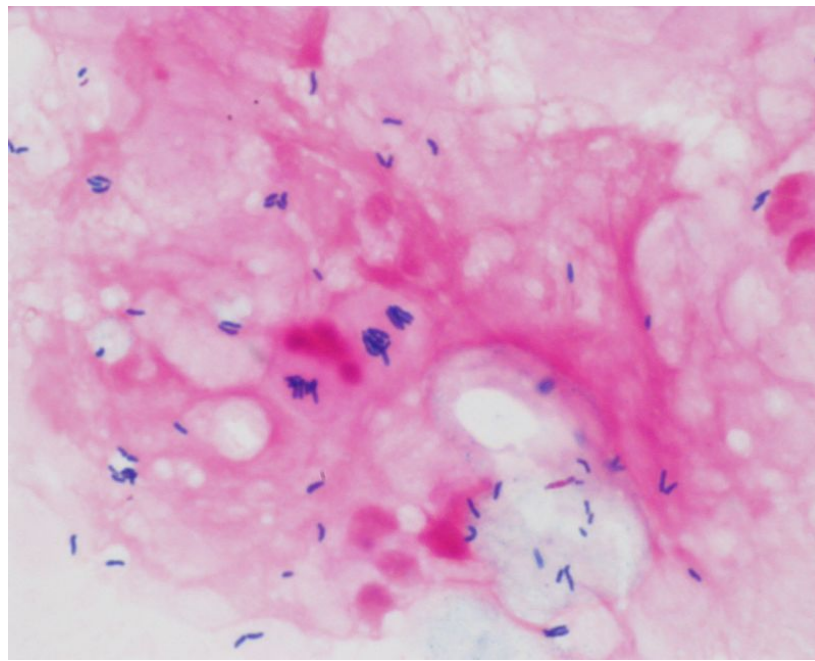


Figure 2. Gram stain of the discharge sample from case 1, original magnification $\times 1000$ Gram-positive rods shaped bacteria in palisade- and 'I, or V' letter-shaped formations were found within polymorphonuclear neutrophil leukocytes.

Case 2: Figures 3 A & B show an ocular surface of a diabetic young man. He had intractable filamentous keratitis after 2 vitrectomies. When he was referred to the author's clinic, a moxifloxacin ophthalmic solution has been prescribed for more than 6 months (from the perioperative stage of the first vitrectomy). After the diagnosis of infectious blepharoconjunctivitis with mucopurulent yellowish discharge, it was determined that the blepharoconjunctivitis may have caused swelling of the eyelid, and the swollen eyelid partially induced intractable filamentous keratitis. Analysis of a smear of the discharge showed a large number of polymorphonuclear leukocytes and Gram-positive rod-shaped bacteria in palisade- and 'I, V, or W' letter-shaped arrangements (Fig. 4). *Corynebacterium* species were identified in the culture of the discharge by using a simple, commercially available identification kit (BBL Crystal, BD, Japan, Tokyo). The author also isolated *Corynebacterium* species on a sheep blood agar plate from the discharge and identified the causative agent as *Corynebacterium macginleyi* on the basis of its biochemical characters tested by API-Coryne (bioMérieux SA, Lyon, France). The minimum inhibitory concentration (MIC) of moxifloxacin and ceftriaxone for the strain (tested by E-test[®], bioMérieux SA, Lyon, France) was $>256\mu\text{g/mL}$ and $2\mu\text{g/mL}$, respectively. Switching moxifloxacin to topical cephmenoxim led to rapid improvement of blepharoconjunctivitis and filamentous keratitis (Fig. 5).

It is currently no exaggeration to say that *Corynebacterium* species are among the major pathogens responsible for chronic conjunctivitis, especially in geriatric patients. These pathogens can also cause infectious keratitis in patients who are immune-compromised [3-5]. All such conditions may be triggered, when the bacterial flora of the ocular surface are disturbed, by opportunistic infections. Endophthalmitis caused by *Corynebacterium* species is

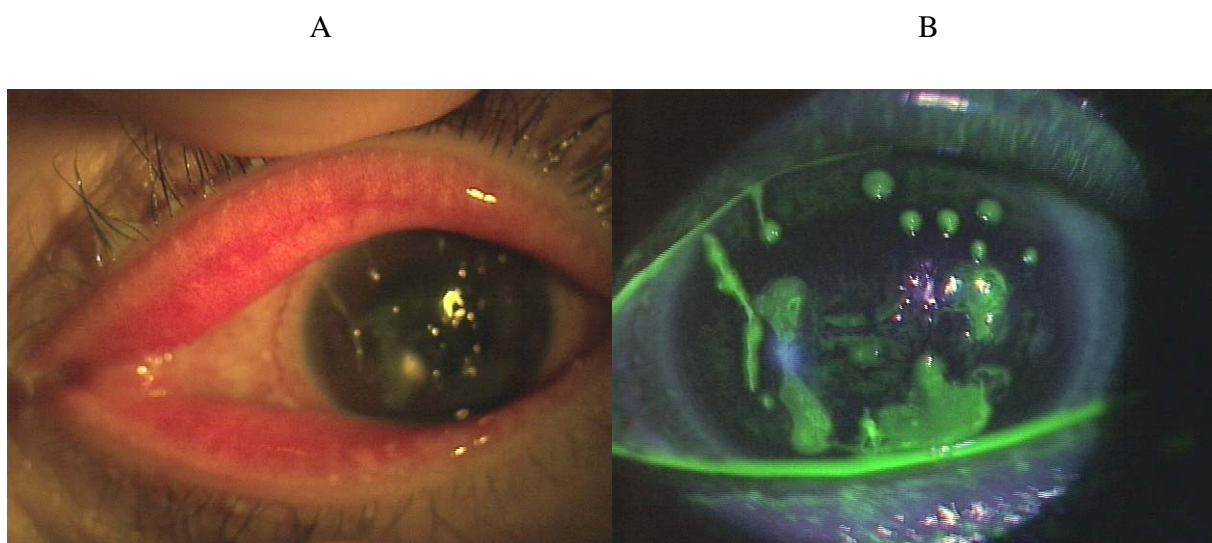


Figure 3. Anterior segments of case 2. Moderate blepharoconjunctivitis, yellowish mucopurulent discharge, and corneal erosion with filamentous keratitis were found.

very rare. Although *C. macginleyi* is the common *Corynebacterium* species to be isolated from the ocular surface [6, 7], it remains unclear whether *C. macginleyi* is the major species responsible for ocular infections because cases caused by other species have been documented as well [5].

4. Diagnostic techniques

According to Koch's postulates, when establishing the specificity of a pathogenic microorganism, the first criterion is the organism must be present in all cases of the disease. Although quantitative analysis of a specific bacterium in samples by using real-time polymerase chain reaction may be useful, this technique is not readily available to practitioners. It is difficult to validate the other criteria of Koch's postulate, always in clinical setting. Thus, most clinical ophthalmologists depend only on first criterion when identifying a pathogen.

The first step when diagnosing and treating *Corynebacterium* infections should be to subject the clinical samples, such as mucopurulent discharge or corneal scrapings, to Gram staining, examine them microscopically, and observe whether Gram-positive rods suggestive of *Corynebacterium* species appear ingested by polymorphonuclear leukocytes (Fig. 2, 4). Finally, the culture results must be accounted.

Although the culture results from discharge and corneal scrapings have clinical significance, we should also recognize the risk of overestimation. As a proof of this, the author has received culture results identifying *Staphylococcus epidermidis* as a pathogen even though plenty of Gram-positive rods are normally found on microscopy in some patients. In some cases,

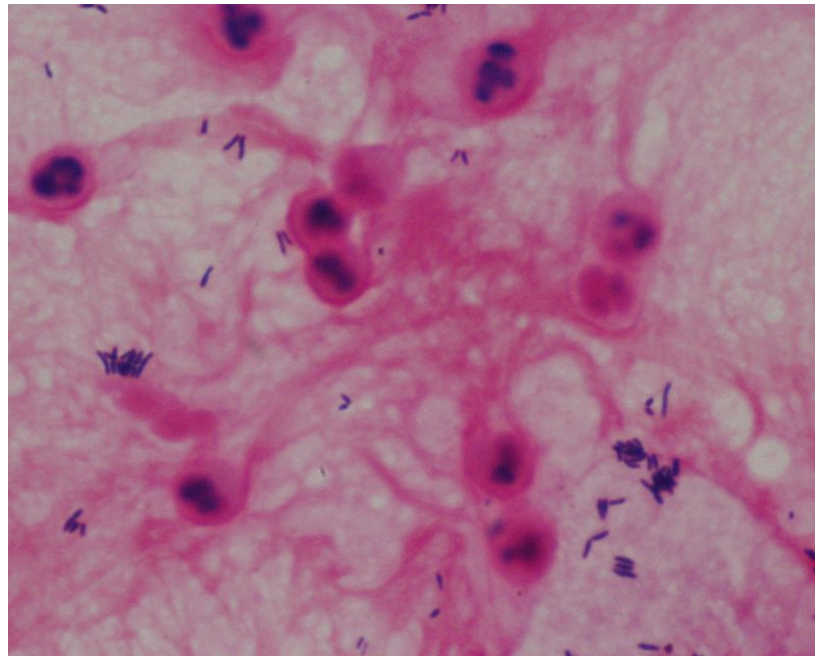


Figure 4. Gram stain of the discharge sample from case 2, original magnification $\times 1000$. A large number of Gram-positive rods are phagocytised by polymorphonuclear neutrophil leukocytes.



Figure 5. Post-medication. The blepharoconjunctivitis and filamentous keratitis are disappeared.

a 'culture negative' result is reported. Figure 6 shows the anterior segments of a bedridden elderly female patient (A) and a panorama Gram stain image of her eye discharge (B). She had a conjunctival hyperaemia with a large amount of yellowish white mucopurulent discharge that lasted for 1 week. The smear prepared from discharge was stained by Gram staining, which showed a large amount of Gram-positive rods suggestive of *Corynebacterium* species. Although she clearly had infectious conjunctivitis and no medication had been administered, the culture result from her discharge was reported as negative. Hence, the smear and microscopic examination of clinical samples contribute significantly to the diagnosis of ocular infections caused by *Corynebacterium* species.



Figure 6. Severe infectious conjunctivitis and a Gram-stained panoramic image of the discharge sample. A: A large quantity of yellowish-white mucopurulent discharge and conjunctival hyperaemia were found. B: A large amount of Gram-positive rods and a few polymorphonuclear leukocytes were found.

Antimicrobial	Max MIC	Min MIC	% Susceptible*
Norfloxacin	256	0.25	25
Ciprofloxacin	32	0.032	25
Levofloxacin	32	0.064	25
Gatifloxacin	32	0.016	40
Moxifloxacin	32	0.016	40
Erythromycin	256	0.016	45
Chloramphenicol	256	2	55
Gentamicin	16	0.064	95
Tobramycin	32	0.064	90
Doxycycline	4	0.064	100
Imipenem	0.08	0.016	100
Ceftriaxon	0.5	0.125	100
Vancomycin	0.5	1	100
Teicoplanin	0.125	1	100

*: The susceptibility test follow the instruction of E-test.

Table 1. MICs of several antimicrobials to 20 bacterial strains. ($\mu\text{g/mL}$)

5. Observation and result

The author found that *Corynebacterium* species isolated from the ocular surfaces of elderly patients in Japan are very sensitive to cephem antibiotics (Table 1, unpublished data). Although they are also sensitive to aminoglycosides, most of the strains are highly resistant to quinolone [7].

6. Conclusion

When faced with the case of an elderly patient with chronic conjunctivitis, the first step should be to collect the discharge and to prepare a Gram stained smear and observation under microscope. Assessment should also determine whether the lacrimal duct is obstructed or not. Documenting a patient's history of antimicrobial use will also contribute to the diagnosis. If the patient has a history of using an antimicrobial ophthalmic solution, and also has Gram-positive rods in palisade, ring or 'N, T, V, W, or Y' letter-shaped arrangement present in their discharge and if these Gram positive rods appear to be ingested by polymorphonuclear leukocytes, then a cephem-based ophthalmic solution should be prescribed first. It is possible that an organism other than a *Corynebacterium* species is the causative pathogen if the cephem antibiotics do not resolve the infection. For *Corynebacterium*-induced keratitis, a systemic carbapenem and glycopeptide may be useful in additions to frequent applications of cephem, aminoglycoside, and glycopeptide eye drops.

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