• Clinical Research •

# Microbiological spectrum and antibiotic susceptibility analysis of secretion from 308 cases of chronic dacryocystitis in north China

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## Abstract

● **AIM:** To determine the microbiological agents and antibiotic susceptibility of chronic dacryocystitis in recent years to guide effective treatment strategies.

● **METHODS:** A total of 308 adult patients with chronic dacryocystitis were enrolled from January 2020 to September 2022 in Beijing Tongren Hospital. The 229 pus specimens were taken from the conjunctival sac, while 79 specimens were taken from the opened lacrimal sac during transnasal dacryocystorhinostomy (DCR) surgery. All the samples were sent for microbiological smear and culture and drug susceptibility tests.

● **RESULTS:** The 202 specimens showed microbial growth, with a positive rate of 65.6%. The 313 strains of bacteria were isolated, including 272 aerobic or facultative anaerobes, accounting for 86.9%, and 41 anaerobic bacteria, accounting for 13.1%. The most common strains were *Staphylococcus epidermidis*, *Corynebacterium macginleyi*, and *Staphylococcus aureus*. Six strains of fungi were isolated. The 14 strains (18.9%) of *Staphylococcus* were found to be multidrug resistant. It showed a wide variety of gram-negative bacteria, up to 23 species. Specimens obtained during DCR surgery had a positive rate of 70.9%, which was higher than those obtained from the conjunctival sac (63.8%), with a statistically significant difference. More microbiological species were found in intraoperative specimens, and consisted largely of pathogenic bacteria or conditional pathogens. All the 6 strains of fungi were obtained from intraoperative specimens. All bacteria were sensitive to vancomycin, while a large number of bacteria were resistant to erythromycin. The commonly used ocular antibiotics levofloxacin, moxifloxacin and tobramycin were generally sensitive to most of the bacteria.

● **CONCLUSION:** Gram-positive cocci, gram-positive bacilli, and gram-negative bacilli are the predominant pathogens for chronic dacryocystitis. Specimens taken during DCR surgery can obtain more accurate microbiological results.

● **KEYWORDS:** microbiological spectrum; antibiotic susceptibility; chronic dacryocystitis; dacryocystorhinostomy
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## INTRODUCTION

Chronic dacryocystitis is a common disease in ophthalmology. It is mainly caused by the stenosis or obstruction of the nasolacrimal duct, which leads to tearing and the reproduction of bacteria in the lacrimal sac. Patients not only have the symptoms of epiphora and purulent discharge, but also may cause secondary keratitis, endophthalmitis, and orbital cellulitis due to persistent secretion[1-2]. With the extensive application of broad-spectrum antibiotics and the change of environment, the microflora of chronic dacryocystitis is constantly changing[3]. In the late 20th century, the majority of bacteria isolated in both acute and chronic dacryocystitis were gram-positive, with over 60% of the pathogens identified as gram-positive[4-5]. However, in recent years, an increasing number of gram-negative organisms and methicillin-resistant *Staphylococcus aureus* (MRSA) have been isolated in lacrimal sac infections[6-8]. Moreover, higher rate of polymicrobial infection have been identified in microbiological cultures of dacryocystitis[1,9]. In order to understand the microbiology and antibiotic susceptibility of chronic dacryocystitis in recent years, we collected and analyzed the microbial culture and drug susceptibility results of lacrimal sac secretion of patients with chronic dacryocystitis who were admitted to the lacrimal duct disease unit of the Department of Ophthalmic Plastic Surgery, Beijing Tongren Hospital, Capital Medical University from January 2020 to September 2022.

## PARTICIPANTS AND METHODS

**Ethical Approval** The Medical Ethics Committee of the Beijing Tongren Hospital approved the study protocol (approval number: TRLAWEC2024-S166), fulfilling the requirements published in the Declaration of Helsinki. For patients whose microbial culture results were collected, informed consent was waived by the Institutional Review Boards.

**General Information** A total of 308 patients with chronic dacryocystitis, including 83 males and 225 females, aged from 21 to 87 years old, were enrolled from January 2020 to September 2022 in Beijing Tongren Hospital. All the samples were lacrimal sac secretions. All the patients presented with epiphora and pus, and purulent secretions from the lacrimal sac area spilled from the lacrimal punctum. The 229 specimens taken from outpatient, and 79 specimens taken from the opened lacrimal sac during transnasal dacryocystorhinostomy (DCR) surgery[10].

**Methods** Clean the area around the lacrimal punctum with sterile saline, press the lacrimal sac area, the secret ion can overflow from the lacrimal punctum, and then pick up the secret ion with sterile cotton swab. The method of sampling during transnasal DCR: after opening the lacrimal sac during the operation, the lacrimal sac secretion overflow was seen, and the secretion was sucked into the lacrimal sac cavity with a 10 mL sterile empty needle head for examination. All the samples were sent to the microbiology Laboratory of Beijing Tongren Hospital for microbiological smear and culture. All strains were identified using conventional methods in accordance with national clinical testing procedures, and drug susceptibility tests were conducted in strict accordance with the broth microdilution method and disk diffusion test. Drug susceptibility results were determined using Clinical and Laboratory Standards Institute (CLSI) standard or European Committee for Antimicrobial Susceptibility Testing (EUCAST) fold point.

**Statistical Analysis** SPSS statistical software, V.26.0, was used for statistical analysis. A $t$ test was used to compare and analyze differences between numerical variables of normal distribution between groups. Inter-group count data were analyzed by Chi-square test. Logistic regression analysis was used to screen independent factors influencing bacterial culture rates, composition ratio of bacterial strains and drug susceptibility. $P<0.05$ was considered statistically significant.

## RESULTS

A total of 202 of 308 specimens showed microbial growth, as shown in Table 1, with a positive rate of 65.6%. The 313 strains of bacteria were isolated from 202 positive specimens, including 272 aerobic or facultative anaerobes, accounting for 86.9%, and 41 anaerobic bacteria, accounting for 13.1%. The most common strains were 49 strains of *Staphylococcus epidermidis*, 31 strains of *Corynebacterium macginleyi*, 19 strains of *Staphylococcus aureus*, 14 strains of *Propionibacterium acnes*, and 11 strains of *Eikenella corrodens*. Six strains of fungi were isolated, including 3 strains of *Candida parapsilosis,* 1 strain of *Wickerhamomyces anomalus*, 1 strain of *Fusarium solani*, and 1 strain of *Aspergillus flavus*. Among the positive samples, 123 samples had 1 species of bacteria isolated, 79 samples had 2 or more species of bacteria isolated, and a maximum of 5 different species of bacteria were isolated from a single sample.

Among the 272 aerobic or facultative anaerobic bacterial strains, there are 132 gram-positive cocci, 10 gram-negative cocci, 49 gram-positive bacilli, and 80 gram-negative bacilli. Gram-positive cocci are mainly *Staphylococcus* and *Streptococcus*. It is worth noting that a total of 14 strains (18.9%) of *Staphylococcus* were found to be multidrug-resistant: 20.4% (10 strains) of *Staphylococcus epidermidis* were methicillin-resistant *Staphylococcus epidermidis* (MRSE), 15.8% (3 strains) of *Staphylococcus aureus* were MRSA, and 50.0% (1 strain) of *Staphylococcus haemolyticus* were methicillin-resistant *Staphylococcus haemolyticus*. There are as many as 23 types of gram-negative bacilli having been isolated. The common ones are 14 strains of *Haemophilus*, 11 strains of *Eikenella*, and 8 strains of *Aggregatibacter*.

**Drug Susceptibility Test Results of Main Bacteria**

***Staphylococcus*** The drug susceptibility results are shown in Table 2. The resistance rate of *Staphylococcus* to penicillin is as high as 91.3%, followed by erythromycin, with a resistance rate of 73.9%. No vancomycin resistant strains were detected, and the susceptibility rates to linezolid, tigecycline, and rifampicin were 100%. The susceptibility rates of common ophthalmic antibiotics levofloxacin and moxifloxacin were 56.5% and 60.8%, respectively.

***Streptococcus*** The drug susceptibility results are shown in Table 3. *Streptococcus* has a high resistance rate to clindamycin and erythromycin, respectively 82.4% and 73.1%. The susceptibility rate to vancomycin and moxifloxacin is 100%, and the susceptibility to levofloxacin, ceftriaxone, and linezolid is also high.

**Gram-negative bacilli** The drug susceptibility results are shown in Table 4. The susceptibility of gram-negative bacilli to ampicillin, moxifloxacin, and cefoxitin is relatively low, with 48.5%, 51.5%, and 62.5%, respectively. The susceptibility to other types of antibiotics is above 70%. The commonly

**Table 1 The distribution of strains in 202 positive samples**

| Genus | Species | No. of cases |
|---|---|---|
| Gram-positive cocci | | |
| *Streptococcus* | *Streptococcus anginosus* | 6 |
| | *Streptococcus constellatus* | 10 |
| | *Streptococcus pneumoniae* | 8 |
| | *Streptococcus intermadius* | 3 |
| | *Streptococcus oralis* | 5 |
| | *Streptococcus agalactiae* | 1 |
| | *Streptococcus mitis* | 4 |
| *Staphylococcus* | *Staphylococcus epidermidis* | 49 |
| | MRSE | 10 |
| | *Staphylococcus aureus* | 19 |
| | MRSA | 3 |
| | *Staphylococcus haemolyticus* | 2 |
| | MRSH | 1 |
| | *Staphylococcus capitis* | 3 |
| | *Staphylococcus warneri* | 1 |
| *Micrococcus* | *Micrococcus luteus* | 1 |
| *Enterococcus* | *Enterococcus faecalis* | 3 |
| *Gemella* | *Gemella mobillorum* | 3 |
| Gram-negative cocci | | |
| *Moraxella* | *Moraxella catarrhalis* | 1 |
| | *Moraxella osloensis* | 1 |
| *Neisseria* | *Neisseria microflava* | 3 |
| | *Neisseria* (undetermined strain) | 5 |
| Gram-positive bacillus | | |
| *Corynebacterium* | *Corynebacterium macginleyi* | 31 |
| | *Corynebacterium pseudodiphtheriticum* | 2 |
| | *Corynebacterium striatum* | 2 |
| | *Corynebacterium nonfermentans* | 2 |
| | *Corynebacterium crowded* | 2 |
| | *Corynebacterium propinquum* | 2 |
| | *Corynebacterium mastitis* | 1 |
| *Lactobacillus* | *Lactobacillus casei* | 1 |
| | *Lactobacillus inerta* | 1 |
| *Dermabacter* | *Dermabacter hominus* | 1 |
| *Bacillus* | *Bacillus cereus* | 1 |
| | *Gram-positive Bacillus* | 1 |
| *Rothia* | *Rothia myxococcus* | 1 |
| | *Rothia* (undetermined strain) | 1 |
| Gram-negative bacillus | | |
| *Aggregatibacter* | *Aggregatibacter segnis* | 4 |
| | *Aggregatibacter aphrophilus* | 3 |
| | *Aggregatibacter* (undetermined strain) | 1 |
| *Morganella* | *Morganella morganii* | 2 |
| *Pseudomonas* | *Pseudomonas aeruginosa* | 4 |
| *Klebsiella* | *Klebsiella pneumoniae* | 5 |
| | *Klebsiella oxytoca* | 1 |
| *Flavimonas* | *Flavimonas oryzihabitans* | 1 |
| *Capnocytophaga* | *Capnocytophaga gingivalis* | 1 |
| | *Capnocytophaga ochracea* | 1 |
| *Enterobacter* | *Enterobacter cloacae* | 1 |
| | *Enterobacter buganda* | 2 |
| *Stenotrophomonas* | *Stenotrophomonas maltophilia* | 7 |
| *Acinetobacter* | *Acinetobacter Joni* | 1 |
| | *Acinetobacter Watson* | 1 |
| | *Acinetobacter nosocomial* | 1 |
| *Eikenella* | *Eikenella corrodens* | 11 |
| *Citrobacter* | *Citrobacter freundii* | 3 |
| | *Citrobacter koseri* | 1 |
| *Haemophilus* | *Haemophilus influenzae* | 6 |
| | *Hemophilus parainfluenzae* | 8 |
| *Pantoea* | *Pantoea agglomerans* | 1 |
| *Serratia* | *Serratia marcescens* | 4 |
| *Escherichia* | *Escherichia coli* | 2 |
| *Tsukamura* | *Tsukamura* (undetermined strain) | 1 |
| *Achromobacter* | *Achromobacter xyloxide* | 1 |
| *Brevundimonas* | *Brevendimonas vesicularis* | 1 |
| | *Brevendimonas* (undetermined strain) | 1 |
| *Providencia* | *Providencia rettgeri* | 1 |
| *Wolinella* | *Wolinella* (undetermined strain) | 1 |
| *Pasteurella* | *Pasteurella multocida* | 1 |
| *Ochrobactrum* | *Ochrobactrum anthropi* | 1 |
| *Elizabethkingia* | *Elizabethkingia meningosepticum* | 1 |
| *Anaerobion* | | |
| *Propionibacterium* | *Propionibacterium acnes* | 14 |
| | *Propionibacterium acidipropionici* | 1 |
| *Prevotella* | *Prevotella intermedia* | 4 |
| | *Prevotella loescheii* | 1 |
| | *Prevotella* (undetermined strain) | 3 |
| *Fusobacterium* | *Fusobacterium nucleatum* | 4 |
| | *Fusobacterium periodonticum* | 2 |
| | *Fusobacterium naviforme* | 2 |
| | *Fusobacterium* (undetermined strain) | 1 |
| *Actinomyces* | *Actinomyces odontolyticus* | 1 |
| | *Actinomyces gregori* | 1 |
| | *Actinomyces* (undetermined strain) | 1 |
| *Leptothrix* | *Leptothrix gutteri* | 2 |
| *Peptoniphilus* | *Peptonophilus indolis* | 1 |
| *Micromonas* | *Micromonas minuta* | 1 |
| *Anaerococcus* | *Anaerobicococcus tetragenus* | 1 |
| | *Anaerococcus* (undetermined strain) | 1 |
| Fungus | | |
| *Candida* | *Candida parapsilosis* | 3 |
| *Wickerhamomyces* | *Wickerhamomyces anomalus* | 1 |
| *Fusarium* | *Fusarium solani* | 1 |
| *Aspergillus* | *Aspergillus flavus* | 1 |

MRSE: Methicillin-resistant *Staphylococcus epidermidis*; MRSA: Methicillin-resistant *Staphylococcus aureus*; MRSH: Methicillin resistant *Staphylococcus haemolyticus*.

**Table 2 Antibiotic susceptibility results for *Staphylococcus***

| Antibiotics | Resistance rate | Intermediary rate | Susceptibility rate |
|---|---|---|---|
| Erythrocin | 73.9 | 0 | 26.1 |
| Levofloxacin | 37.0 | 6.5 | 56.5 |
| Linezolid | 0 | 0 | 100.0 |
| Penicillin | 91.3 | 0 | 8.7 |
| Vancomycin | 0 | 0 | 100.0 |
| Clindamycin | 50.0 | 0 | 50.0 |
| Moxifloxacin | 23.9 | 15.2 | 60.8 |
| Selectrin | 40.9 | 0 | 59.1 |
| Tigecycline | 0 | 0 | 100.0 |
| Oxacillin | 48.8 | 0 | 51.1 |
| Gentamicin | 27.3 | 6.8 | 65.9 |
| Ciprofloxacin | 34.9 | 9.3 | 55.8 |
| Quinupristin/dalfopristin syncercid | 0 | 0 | 100.0 |
| Tetracycline | 7.9 | 0 | 92.1 |
| Rifampicin | 0 | 0 | 100.0 |
| Macrodantin | 0 | 0 | 100.0 |

used ophthalmic antibiotics tobramycin and levofloxacin are generally sensitive to gram-negative bacilli.

**Comparison of Outpatient and Intraoperative Sampling** Of all patients, 229 specimens were obtained from outpatient patients with pus overflowing out of *puncta lacrimalia* (146 positive specimens), and 79 specimens were obtained directly from the opened lacrimal sac during DCR surgery (56 positive specimens). The positive rate of outpatient sampling was 63.8%, while the positive rate of intraoperative sampling was 70.9%, with a statistically significant difference. Figure 1 presents the proportion of isolated bacterial species in positive specimens. Among outpatient sampling positive specimens, 65.8% showed isolation of a single bacterial species, while among intraoperative sampling positive specimens, 50% showed isolation of a single bacterial species. The proportion of specimens with two or more bacterial species isolated during intraoperative sampling was higher than that of outpatient sampling. The positivity rate of outpatient sampling was lower than that of intraoperative sampling, and a considerable portion of bacterial species isolated from outpatient positive specimens were common skin or conjunctival bacteria, such as *Staphylococcus epidermidis* and *Corynebacterium macginleyi*, while the types of bacterial species isolated from intraoperative positive specimens were more diverse, with pathogenic or opportunistic pathogens being predominant. The six fungal strains obtained were all from intraoperative specimens.

## DISCUSSION

In previous literature, the positive culture rate of chronic dacryocystitis secretions ranged from 38.2% to 96%[11-26], with the majority around 80%. In this study, the positive culture rate of chronic dacryocystitis purulent specimens collected from Beijing Tongren Hospital between January 2020 and September 2022 was 65.6%. Compared to most literature reports, the positivity rate was lower. Although the positivity rate of intraoperative direct sampling of the lacrimal sac was higher than that of outpatient direct sampling, it was only 70.9%. The lower positivity rate is mainly attributed to previous treatment in other hospitals and long-term local antibiotic use before coming to our hospital. Obtaining specimens for culture before antibiotic use can yield higher positivity rates.

Among all positive specimens, the top three genera were *Staphylococcus, Corynebacterium*, and *Streptococcus*. However, since *Staphylococcus epidermidis*, *Corynebacterium macginleyi*, and *Streptococcus oralis* are common skin and conjunctival bacteria, they cannot accurately represent the microbial growth in chronic dacryocystitis. During our statistical analysis, a considerable proportion of outpatient sampling grew *Staphylococcus epidermidis*, *Corynebacterium macginleyi*, and other common skin and conjunctival bacteria. In contrast, specimens obtained by direct sampling of the lacrimal sac during DCR surgery had a greater variety of isolated microorganisms, mainly pathogenic or opportunistic pathogens, with a smaller proportion of common skin and conjunctival colonized bacteria. Mixed infections with two or more bacterial species accounted for half of the positive specimens. This suggests that outpatient sampling may suffer from inadequate sampling or contamination by skin and conjunctival surface colonized bacteria, while direct sampling of purulent fluid from the opened lacrimal sac during

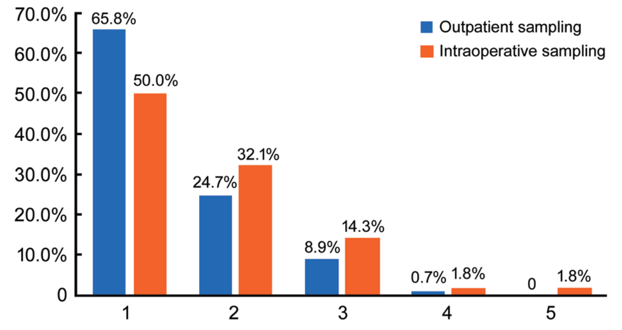


**Figure 1 The number of strains isolated from positive samples.**

**Table 3 Antibiotic susceptibility results for *Streptococcus***

| Antibiotics | Resistance rate | Intermediary rate | Susceptibility rate | No criteria |
|---|---|---|---|---|
| Erythrocin | 73.1 | 9.6 | 17.3 | |
| Levofloxacin | 0 | 5.4 | 86.5 | 8.1 |
| Linezolid | 2.1 | 0.0 | 97.9 | |
| Penicillin | 3.9 | 3.9 | 68.6 | 23.5 |
| Vancomycin | 0 | 0 | 100.0 | |
| Clindamycin | 82.4 | 2.0 | 15.7 | |
| Ceftriaxone | 0 | 8.6 | 91.4 | |
| Moxifloxacin | 0 | 0 | 100.0 | |
| Trimethoprim/sulfamethoxazole | 73.3 | 6.7 | 20.0 | |

**Table 4 Antibiotic susceptibility results for gram-negative bacilli**

| Antibiotics | Resistance rate | Intermediary rate | Susceptibility rate | No criteria |
|---|---|---|---|---|
| Tobramycin | 12.5 | 4.2 | 83.3 | |
| Levofloxacin | 8.9 | 11.1 | 80.0 | |
| Ceftriaxone | 1.8 | 3.6 | 94.5 | |
| Piperacillin-tazobactam | 5.9 | 2.9 | 91.2 | |
| Cefoxitin | 25.0 | 12.5 | 62.5 | |
| Imipenem | 4.5 | 6.1 | 89.4 | |
| Meropenem | 7.1 | 0.0 | 92.9 | |
| Moxifloxacin | 27.3 | 12.1 | 51.5 | 9.1 |
| Ampicillin | 36.4 | 12.1 | 48.5 | 3.0 |
| Aztreonam | 16.0 | 10.0 | 74.0 | |
| Selectrin | 25.0 | 1.9 | 73.1 | |
| Amikacin | 2.5 | 0.0 | 97.5 | |
| Cefepime | 5.1 | 2.6 | 92.3 | |
| Ceftazidime | 10.0 | 0.0 | 90.0 | |
| Cefuroxime | 22.2 | 0.0 | 77.8 | |
| Ertapenem | 0.0 | 4.3 | 95.7 | |
| Tigecycline | 0.0 | 0.0 | 100.0 | |
| Gentamicin | 5.3 | 0.0 | 94.7 | |
| Ciprofloxacin | 20.8 | 4.2 | 75.0 | |
| Trimethoprim/sulfamethoxazole | 0.0 | 0.0 | 83.3 | 16.7 |
| Amoxicillin-clavulanic acid | 10.0 | 10.0 | 80.0 | |
| Minocycline | 11.1 | 11.1 | 77.8 | |

DCR surgery can provide more accurate microbiological results and better reflect the microbial profile of chronic dacryocystitis. Therefore, when performing DCR surgery, it is recommended that surgeons collect purulent fluid from the lacrimal sac after its opening to obtain more accurate culture results. Additionally, many patients have comorbidities such as cataracts, glaucoma, and diabetic retinopathy, requiring surgeries. Microbial culture and susceptibility results of the lacrimal sac can provide valuable diagnostic and therapeutic guidance for subsequent ocular surgeries.

In this study, we isolated a wide variety of gram-negative rods, with 23 genera and 33 species. This is significantly more diverse than previous literature reports, which identified 6–13 genera of gram-negative rods[10,13-17,19-20,22-24]. We also found several bacterial species that were previously unreported in dacryocystitis secretions, such as *Elizabethkingia meningosepticum*, *Morganella morganii*, and *Providencia rettgeri*. These are highly virulent pathogens or opportunistic pathogens that can cause corneal infections[27-28], and in severe cases, lead to lung infections, sepsis, meningitis, and other life-threatening consequences[29-33]. Species such as *Pasteurella multocida* and *Morganella morganii* are commonly found in both humans and animals, including pets, suggesting that long-term close contact with pets is also a contributing factor to lacrimal sac infections. The increasing diversity of gram-negative rods indicates that the types of pathogens in chronic dacryocystitis are continuously expanding and changing, despite the widespread use of topical antibiotics in ophthalmology.

Similar to previous reports, gram-positive cocci bacteria account for a significant proportion in the culture results of the secretion samples[13-14,16-17,21,23,25-26], with *Staphylococcus* and *Streptococcus* being the predominant genera. Among the 88 strains of *Staphylococcus* obtained, we identified a total of 14 methicillin-resistant *Staphylococcus* strains, accounting for 15.9% of the *Staphylococcus*, indicating a serious drug resistance issue. This is attributed to the long-term use of antibiotic eye drops by patients prior to their visit to our hospital, highlighting that prolonged antibiotic use in chronic infections can increase the resistance of pathogens. Therefore, hospitals at all levels should strengthen infection control measures and promote standardized use of antimicrobial drugs. Additionally, bacterial culture and antibiotic susceptibility testing should be performed prior to antibiotic administration whenever possible.

Regarding the antibiotic susceptibility results, we found that various pathogens exhibited a relatively high resistance rate to erythromycin, while demonstrating higher susceptibility to levofloxacin. This suggests that erythromycin eye ointment is nearly ineffective in controlling inflammation associated with chronic dacryocystitis, whereas levofloxacin can still be used as a first-line topical treatment for ocular conditions. Tobramycin, a commonly used topical antibiotic in ophthalmology, is rarely included in drug susceptibility tests for various bacterial species. Furthermore, several antibiotics having drug susceptibility tests do not have ophthalmic topical agents, such as penicillin, cephalosporins, vancomycin, and so on. Whether the drug susceptibility test of chronic dacryocystitis pus should make the corresponding drug susceptibility selection from the type of antibiotic eye drugs peculiar to ophthalmology. This question requires interdisciplinary discussions and communication between ophthalmology, laboratory medicine, and pharmacy.

In summary, chronic dacryocystitis is a prolonged chronic process characterized by recurrent episodes and repeated treatments, which also contributes to the development of drug resistance among the pathogens involved. The causative bacteria and their resistance patterns in patients with chronic dacryocystitis should be given sufficient attention in clinical practice. It is recommended to perform bacterial culture and drug susceptibility testing before initiating antibiotic treatment in order to timely identify the latest pathogenic bacteria and changes in drug susceptibility, thus facilitating the rational use of antibiotics and combining them with lacrimal drainage surgery to achieve optimal therapeutic outcomes.

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**Authors' Contributions:** He YQ: conceptualization, methodology, investigation, data curation, visualization and writing original draft. Tian XB: Methodology, investigation and data curation. Zhang Y: Methodology, investigation and data curation. Sun H: Writing-review, editing and supervision. All authors reviewed the final manuscript.

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