

# Conjunctivitis Caused by a Strain of *Neisseria gonorrhoeae* That Was Less Susceptible to Ceftriaxone

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## Abstract

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A 20-year-old man presented with bilateral ocular discharge and conjunctival injection. An ocular culture revealed *Neisseria gonorrhoeae* with decreased susceptibility to multiple drugs, including ceftriaxone. The patient was successfully treated with doxycycline (100 mg), which was administered orally, twice a day, for 7 days.

**Key words:** conjunctivitis, ceftriaxone-less susceptible, *Neisseria gonorrhoeae*

(Intern Med 56: 1443-1445, 2017)

(DOI: 10.2169/internalmedicine.56.7656)

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## Introduction

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*Neisseria gonorrhoeae* is a common causative pathogen of sexually transmitted infections (STIs). When infected, patients develop symptoms of urethritis, cervicitis, and conjunctivitis. Antimicrobial-resistant *N. gonorrhoeae* represent a serious problem. Ceftriaxone-resistant *N. gonorrhoeae* was first reported in Kyoto City in 2011 (1). The treatment of ceftriaxone-resistant *N. gonorrhoeae* is a challenging problem worldwide. We herein report a case of conjunctivitis that was caused by *N. gonorrhoeae* with reduced susceptibility to ceftriaxone that was eventually treated with doxycycline.

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## Case Report

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A 20-year-old man presented with bilateral conjunctival injection and ocular discharge at a private ophthalmologist clinic. He did not show any improvement; thus, the following week he visited the Department of Ophthalmology in our hospital. A culture of the ocular discharge was obtained, and he was prescribed 1.5% levofloxacin and 0.3% ofloxacin. He returned the next day and his treatment was changed to colistin sodium methanesulfonate, and 0.5% cefmenoxime hydrochloride. He was referred to a urologist due to suspected chlamydial conjunctivitis. The patient did

not have bacteriuria or pyuria. A urine sample was tested for gonorrhea and chlamydia using the cobas 4800 CT/NG test. The test results were positive for gonorrhea and negative for chlamydia. The patient returned one week later. The ocular discharge culture was positive for *N. gonorrhoeae*, and a susceptibility test using the disc diffusion method indicated multi-drug resistance, including resistance to ceftriaxone (Table 1). At this point, he was referred to the Department of Infectious Disease. He presented to us with conjunctival injection and discharge, but reported a slight improvement since his first visit to the hospital. He reported that he had not had sexual intercourse in the past 6 months and that he was not a man who has sex with men (MSM). He developed a gonococcal infection one year previously, which had been treated by a private physician. He did not remember any of the details of the treatment of the previous infection. We prescribed doxycycline (100 mg), which was taken orally, twice a day, for 7 days. A pharyngeal culture revealed *N. gonorrhoeae* with similar susceptibility results to the ocular discharge culture (Table 2). He tested negative for other STIs, including syphilis and human immunodeficiency virus (HIV), hepatitis B virus, hepatitis C virus infection. One week later, another urine sample was subjected to a cobas 4800 CT/NG test to detect *N. gonorrhoeae*. This time, the result was negative. His symptoms resolved within 2 weeks.

We also tested the susceptibility of the bacteria to mino-

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Received for publication May 2, 2016; Accepted for publication October 4, 2016

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**Table 1. Susceptibility Results of Ocular Discharge.**

Drug	Susceptibility	Inhibition circle diameters (mm)
PenicillinG	R	14
Ceftriaxone	R	28
Cefixime	R	18
Spectinomycin	S	20
Tetracycline	R	18
Ciprofloxacin	R	8

**Table 2. Susceptibility Results of Pharyngeal Culture.**

Drug	Susceptibility	Inhibition circle diameters (mm)
PenicillinG	R	17
Ceftriaxone	R	30
Cefixime	R	27
Spectinomycin	S	26
Tetracycline	R	27
Ciprofloxacin	R	8

cycline and azithromycin using the disc susceptibility test. The inhibition circle diameters were 35 mm and 33 mm, respectively.

We sent the pharyngeal *N. gonorrhoeae* specimen from this patient to the National Institute of Infectious Diseases of Japan for susceptibility testing and a resistant gene analysis. Unfortunately, the isolate did not remain viable for testing. We therefore attempted to take genomic DNA from dead cells and performed a polymerase chain reaction (PCR) for the *penA* gene; the amplified product was sequenced as previously described (2). The obtained sequences were identical to the *penA X* gene (2).

## Discussion

The patient whose *N. gonorrhoeae* infection displayed decreased susceptibility to ceftriaxone, presented with conjunctivitis without any other symptoms. We successfully treated the patient with doxycycline (100 mg), which was administered orally, twice a day for 7 days.

Ceftriaxone-resistant *N. gonorrhoeae* was first reported in Kyoto, Japan in 2011 (1). In 2013, *N. gonorrhoeae* with decreased susceptibility to ceftriaxone was reported in India (3) and China (4). In Japan, a nationwide surveillance report stated that no ceftriaxone-resistant *Neisseria* strains were detected; however 10.7% of the strains were considered to be less susceptible to ceftriaxone (5). A new strain of *N. gonorrhoeae* with decreased susceptibility to ceftriaxone was reported in Japan in 2016 (6). Ceftriaxone-resistant *N. gonorrhoeae* isolates have been reported from France (7), Australia (8), and Spain (9). Moreover, in 2016, new ceftriaxone-resistant *N. gonorrhoeae* isolates were reported in Japan (10). Multi-drug resistant *N. gonorrhoeae* is an important issue throughout the world.

We treated this case of gonococcal conjunctivitis with doxycycline. The Japanese STI guidelines recommend ceftriaxone, or spectinomycin for the treatment of gonococcal conjunctivitis (11). The Center for Disease Control and Prevention (CDC) guidelines recommend combined treatment with ceftriaxone and azithromycin (12). Similarly a recent review recommended combined treatment with ceftriaxone and azithromycin or cefixime and azithromycin (13). However, the prevalence of azithromycin-resistant *N. gonorrhoeae* has been reported to be high in Fukuoka, Japan (14). The report showed that 22.6% of *N. gonorrhoeae* strains

were azithromycin-resistant. Thus, ceftriaxone and azithromycin combination therapy may no longer be useful for treating gonococcal infections. To treat *N. gonorrhoeae* infections, we should perform culture and susceptibility testing for each case. In a case report from Ehime Prefecture in Japan, two patients with conjunctivitis caused by a strain of *N. gonorrhoeae* that displayed decreased susceptibility to cephalosporin were reportedly treated with minocycline (15).

Although the strain was resistant to tetracycline, tetracycline-resistant strains may be susceptible to doxycycline (16). Particular efflux pumps confer resistance to tetracycline but not to doxycycline (17). The resistance mechanism of the strain to tetracycline might involve to this type of efflux pump.

The patient in this case report presented with conjunctivitis without any other symptoms. Gonococcal conjunctivitis in adults is considered to be caused by autoinoculation (18). We suspect that the treatment for his previous gonococcal infection failed. We hypothesize that his symptoms resolved spontaneously, and that *N. gonorrhoeae* then colonized his pharynx. Thereafter, *N. gonorrhoeae* infected his eyes via autoinoculation.

Our case report is associated with several limitations. Firstly, we are unaware of any details of his previous gonococcal infection, such as the treatment or culture results. Secondly, we did not conduct accurate susceptibility tests. Our susceptibility test was based on the "Performance Standards for Antimicrobial Susceptibility Testing: Twenty-Third Information Supplement (19)." We assessed the susceptibility of this strain using the disc diffusion method, but we did not know the minimum inhibitory concentration of each antimicrobial drug. Hence, we could not define the isolate as "ceftriaxone-resistant." Although we tested the susceptibility of the isolate to minocycline and azithromycin using the disc susceptibility test, the interpretative criteria for these drugs are not defined in this standard (19). Thus, we could not clearly state whether the strain was susceptible to these drugs. Although we attempted to analyze the isolate at the National Institute of Infectious Diseases, Japan, the isolates were not viable for further testing. *N. gonorrhoeae* is difficult to store; thus, isolates should be sent for susceptibility testing as soon as possible. The *penA X* gene was only detected by sequencing following PCR amplification using dead cells. The *penA* gene encodes the penicillin binding protein 2. The *penA X* gene is reported to be associated with

a reduced susceptibility to cephalosporins, including ceftriaxone, in Japan (20). Thirdly, it is unclear whether this infectious episode was caused by the same organism as the patient's previous infection, which had occurred one year previously. One possibility is that the patient remained asymptomatic while *N. gonorrhoeae* colonization occurred over a 6-month period. The patient reported that he had not had sexual intercourse in the past 6 months, but we could not confirm this. Asymptomatic *N. gonorrhoeae* infections have been reported in HIV-infected men, and/or MSM (21-23). According to these studies, asymptomatic gonococcal infection is more common than originally thought.

In conclusion, we successfully used doxycycline to treat gonococcal conjunctivitis with decreased susceptibility to multiple drugs. Multi-drug resistant *N. gonorrhoeae* is an important issue and this should be considered when treating gonococcal infection. Culturing and susceptibility testing is essential, prior to the initiation of treatment.

**The authors state that they have no Conflict of Interest (COI).**

#### Acknowledgement

The Laboratory work was performed at the SRL Kansai Laboratory.

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