Severe Conjunctivitis Due to Multidrug-Resistant *Neisseria gonorrhoeae* and Adenovirus 53 Coinfection in a Traveler Returning From Thailand

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A male traveler returning from Thailand with severe bilateral conjunctivitis was tested for causative pathogens by culture and polymerase chain reaction in late 2010. The culturally grown *Neisseria gonorrhoeae* strain was resistant against penicillin, ciprofloxacin, and tetracycline. The patient was also found to have an eye infection with the unusual and likely recombinant adenovirus type 53. Besides multidrug-resistant gonococcal strains the unusual adenovirus strain is found circulating in Asia and both pathogens may be a risk for travelers.

Although the incidence of gonorrhea has declined in the 1990s, the treatment and control of the disease has been complicated by the appearance and spread of antimicrobial drug resistance in *Neisseria gonorrhoeae*, its causative agent.1 Presently, gonorrhea is the second-most frequently reported communicable disease in the United States, and foreign travel has contributed to the increase of resistance levels against penicillin, doxycyclin, and ciprofloxacin in bacterial isolates from heterosexual males.1 In adult travelers, urogenital infection is not uncommon; however, gonococcal keratoconjunctivitis is rarely seen. Gonococcal eye infections are purulent and may rapidly progress to complications such as corneal ulceration with perforation and, in the worst case, endophthalmitis.2,3 Thus, prompt diagnosis and treatment are crucial. Here, we report the case of a male traveler returning from Thailand with a bilateral eye infection due to a multidrug-resistant gonococcal strain and concomitant adenovirus keratoconjunctivitis of an unusual and likely recombinant type. Adenoviral keratoconjunctivitis is very contagious, nonpurulent, may cause severe itching and pain, and may result in small scars of the cornea with permanent visual impairment.4

**Case Report**

A 27-year-old male traveler was seen as an outpatient in the travel clinic in 2010 with intense conjunctival swelling, purulent secretion from both eyes, and malaise. He had returned home to Germany from a 28-day beach holiday in Ko Samui, Thailand, 5 days earlier. The day before he left Thailand he had noticed a burning and itching sensation of both eyes. Three days later, he was seen by an ophthalmologist in Germany and was referred to the University Eye Hospital for further treatment. At the time of presentation there had been no purulent discharge, but eyelid and caruncula swelling was present and conjunctival chemosis was predominantly seen on the right eye. A point-of-care test on adenovirus antigens from human eye fluid (RPS AdenoPlus, Rapid Pathogen Screening, Sarasota, FL, USA) had been negative. Nonetheless, the clinical diagnosis of a presumptive adenoviral keratoconjunctivitis had been
made and a corneal swab had been sent for specific adenovirus polymerase chain reaction (PCR) testing. The patient was advised to maintain strict eye and hand hygiene and to use topical nonsteroidal and lubrication eye drops. After 1 day a pan-adenovirus real-time PCR test had returned a positive result for an adenoviral conjunctival infection. However, within the next few days, symptoms had deteriorated, purulent discharge had commenced bilaterally, and the patient was seen in the travel clinic for further investigations.

On examination, there was no fever, meningism, or urethral discharge. Laboratory investigations revealed a slightly elevated C-reactive protein level of 4.2 mg/dL (normal <0.5 mg/dL), increased transaminase activities [alanine aminotransferase 119 U/L (normal 0–50) and aspartate aminotransferase 42 U/L (normal 0–33)], and a normal complete blood count.

Gram stain of conjunctival secretions revealed Gram-negative intracellular diplococci (Figure 2), which were confirmed as *N gonorrhoeae* by culture on chocolate agar and biochemical testing. Urinalysis showed leukocyturia (>500 μL⁻¹) and microhematuria (150 red blood cells μL⁻¹). However, urine culture, *Chlamydia trachomatis* PCR testing, or urethral swabs were not performed. A serological screening for syphilis (TPHA and VDRL), human immunodeficiency virus (HIV) testing (HIV-1/2 Ag/Ab Combo-ELISA), and testing for hepatitis C were negative. Test results for hepatitis A showed a positive IgG and negative IgM, reflecting a previous infection or immunization. As the patient did not have immunity to hepatitis B virus (anti-HBs antibodies <10 U/L) he received a postexposure hepatitis B vaccination according to a rapid immunization scheme (days 0, 7, 21, and after 1 year). The patient reported that he had had condom-protected sexual intercourse with a female prostitute a few days before he had left Thailand. Patient history further revealed alcohol consumption, thus possibly explaining the elevated liver enzyme activities. Illegal drug abuse was denied. He was admitted to the hospital and received an initial intravenous antibiotic treatment with ampicillin–sulbactam (2,000 mg/1,000 mg t.i.d.) plus ciprofloxacin (400 mg b.i.d.), and a topical treatment with ofloxacin eye drops (five times per day). Allergy against beta-lactam antibiotics was not reported. After susceptibility testing had shown resistance against ciprofloxacin and decreased susceptibility to penicillin after 2 days of treatment (Table 1), the antibiotic therapy was changed to oral azithromycin (500 mg qd). The clinicians had decided to continue treatment with azithromycin for 6 days until a substantial clinical improvement was achieved and purulent secretions had stopped. An ophthalmological follow-up examination 1 week later showed slight nummular infiltrates of the right cornea, consistent with a keratoconjunctivitis epidemica, and no corneal ulcerations. At this time, repeated urinalysis was normal. Twelve days after admission only slight conjunctival injections were visible, and the outcome was favorable.

Further molecular analysis of the adenovirus strain revealed an adenovirus type 22 sequence in the hexon loop 2 region, adenovirus type 37 in the hexon C4 region, and adenovirus type 8 in the fiber knob region.6,7 This chimeric pattern is characteristic of adenovirus type 53, which probably arose by recombination among adenovirus types 8, 22, and 37.8
additional increase of 11.6% has been demonstrated has increased dramatically since 1994. In 1999, an
Thailand, resistance to ciprofloxacin in *N gonorrhoeae* was positively associated with recent travel.1 In
resistance of gonococcal isolates in the United States, ciprofloxacin and doxycyclin, and intermediate suscep-
tions are, however, no conclusions per se. Moreover, resistance rates to doxycyclin and penicillin reached 95 and 86%, respectively.11 Prompted by the worldwide rise of resistance against these two drugs, fluoroquinolones and cephalosporins were initially recommended for treating gonorrhea in the United States.1 However, because ciprofloxacin resistance has shown a sharp increase in the past decade in Hawaii and later in the continental United States, Thailand, and several other countries, fluoroquinolones are no longer recommended.1,10 Thus, cephalosporins were the only recommended treatment option left in 2007. However, treatment failures resulting from the use of oral cephalosporins for gonorrhea have been reported from Asia,12,13 and decreased susceptibility to cephalosporins is associated with resistance to other microbial agents. Thus, decreased susceptibility in *N gonorrhoeae* is expected to continue to spread.12 Since late 2010, the Centers for Disease Control and Prevention (CDC) have been recommending single-dose azithromycin (1 g) in combination with single-dose injectable cephalosporin regimens such as intramuscular ceftriaxone (250 mg) for uncomplicated gonococcal infections of the cervix, urethra, rectum, and pharynx.12 Single-dose ceftriaxone (1 g) intramuscularly has been recommended for the treatment of gonococcal conjunctivitis in adults,12 as a study among US adults for this ocular infection had previously shown a 100% response to this treatment regimen.14 In this case, the patient was successfully treated with oral azithromycin for a prolonged time as effective therapy, shortly before the CDC recommendations were published, and thus not with intramuscular ceftriaxone. Alternatively, oral azithromycin monotherapy (2 g, single-dose) is regarded as effective against uncomplicated gonococcal infections,12 but not explicitly recommended. The patient was treated with a lower dose of 500 mg qd, but for a prolonged time, as the initial treatment had been seen as ineffective. Retrospectively, this was not an ideal treatment as there are concerns about a possible rapid emergence of resistance against azithromycin in *N gonorrhoeae*. These concerns are already greater with the 1 g dose than with the 2 g dose,12 and therefore, the currently rec-
nealed one dose of 500 mg qd, but for a prolonged time, as the initial treatment had been seen as ineffective.
Retrospectively, this was not an ideal treatment as there are concerns about a possible rapid emergence of resistance against azithromycin in *N gonorrhoeae*. These concerns are already greater with the 1 g dose than with the 2 g dose,12 and therefore, the currently recommended ceftriaxone and azithromycin combination therapy aims at slowing down resistance development in *N gonorrhoeae* against beta-lactams and macrolides. In conclusion, a combination therapy should always be favored for gonococcal infections, or alternatively cef-
triaxone monotherapy intramuscularly for gonococcal conjunctivitis.

**Discussion**

Sexually transmitted gonococcal conjunctivitis in adults is seldom reported, with most cases occurring in under-
developed regions of Africa.3,9 Not only in returning travelers, bilateral gonococcal conjunctivitis is generally a very rare medical problem. The pathognomonic symptoms of the patient and the demonstration of Gram-negative intracellular diplococci allowed the rapid diagnosis of the gonococcal infection, which was confirmed by culture. Gonococcal conjunctivitis is a severe disease frequently complicated by early corneal melting, perforation, and endophthalmitis.23 Unlike other bacteria, gonococci may penetrate intact corneal epithelium and result in corneal ulceration and finally perforation. Clinically, the infection is characterized by a mucopurulent keratoconjunctivitis and eyelid swelling. Early correct diagnosis and treatment are therefore crucial, and concurrent genitourinary manifestations are not mandatory. In this case, the patient had a symptomless leukocyturia and microhematuria, but gonococcal culture was not attempted from the genitourinary tract. The source of infection was most likely the prostitute with whom the patient had practiced sexual intercourse. Handling of the used condom or finger contact to the partner’s genitals followed by contact with the eyes might have been the mode of transmission. Possibly, he may also have had an asymptomatic gonococcal urethritis (which was not further investigated, however) followed by autoinoculation of the eyes. This speculative autoinoculation may have been prompted by itching of the eyes owing to the preceding adenovirus keratoconjunctivitis. These assumptions are, however, no conclusions per se.

The gonococcal isolate was tested resistant against ciprofloxacin and doxycyclin, and intermediate susceptible to penicillin. For heterosexual men, ciprofloxacin resistance of gonococcal isolates in the United States was positively associated with recent travel.1 In Thailand, resistance to ciprofloxacin in *N gonorrhoeae* has increased dramatically since 1994. In 1999, an additional increase of 11.6% has been demonstrated for multiclonal ciprofloxacin-resistant *N gonorrhoeae*.10 More than 90% of genital gonococcal isolates from HIV-positive patients in Bangkok exhibited resistance to ciprofloxacin in a recent survey.11 Therefore, resistance rates to doxycyclin and penicillin reached 95 and 86%, respectively.11 Prompted by the worldwide rise of resistance against these two drugs, fluoroquinolones and cephalosporins were initially recommended for treating gonorrhea in the United States.1 However, because ciprofloxacin resistance has shown a sharp increase in the past decade in Hawaii and later in the continental United States, Thailand, and several other countries, fluoroquinolones are no longer recommended.1,10 Thus, cephalosporins were the only recommended treatment option left in 2007. However, treatment failures resulting from the use of oral cephalosporins for gonorrhea have been reported from Asia,12,13 and decreased susceptibility to cephalosporins is associated with resistance to other microbial agents. Thus, decreased susceptibility in *N gonorrhoeae* is expected to continue to spread.12 Since late 2010, the Centers for Disease Control and Prevention (CDC) have been recommending single-dose azithromycin (1 g) in combination with single-dose injectable cephalosporin regimens such as intramuscular ceftriaxone (250 mg) for uncomplicated gonococcal infections of the cervix, urethra, rectum, and pharynx.12 Single-dose ceftriaxone (1 g) intramuscularly has been recommended for the treatment of gonococcal conjunctivitis in adults,12 as a study among US adults for this ocular infection had previously shown a 100% response to this treatment regimen.14 In this case, the patient was successfully treated with oral azithromycin for a prolonged time as effective therapy, shortly before the CDC recommendations were published, and thus not with intramuscular ceftriaxone. Alternatively, oral azithromycin monotherapy (2 g, single-dose) is regarded as effective against uncomplicated gonococcal infections,12 but not explicitly recommended. The patient was treated with a lower dose of 500 mg qd, but for a prolonged time, as the initial treatment had been seen as ineffective. Retrospectively, this was not an ideal treatment as there are concerns about a possible rapid emergence of resistance against azithromycin in *N gonorrhoeae*. These concerns are already greater with the 1 g dose than with the 2 g dose,12 and therefore, the currently recommended ceftriaxone and azithromycin combination therapy aims at slowing down resistance development in *N gonorrhoeae* against beta-lactams and macrolides. In conclusion, a combination therapy should always be favored for gonococcal infections, or alternatively cef-
triaxone monotherapy intramuscularly for gonococcal conjunctivitis.

Interestingly, the patient had an ophthalmologic adenovirus coinfection, and the adenoviral symptoms preceded those of the gonococcal infection. One case of a coinfection with adenoviruses has been reported so far.15 Epidemic viral keratoconjunctivitis occurs in outbreaks worldwide and in all age groups with

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**Table 1** Results of antimicrobial susceptibility testing of *Neisseria gonorrhoeae* isolated from patient’s eye

<table>
<thead>
<tr>
<th>Substance</th>
<th>Interpretation (CLSI, M100-S22, 2012)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>I</td>
</tr>
<tr>
<td>Ampicillin/sulbactam</td>
<td>–</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>S</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>R</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>R</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>I</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>I</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>I</td>
</tr>
</tbody>
</table>

There are no interpretative standards for ampicillin/sulbactam, cotrimoxazole, gentamicin, and azithromycin. MICs were determined by E-test. MIC = minimal inhibitory concentration; S = susceptible; I = intermediate susceptible; R = resistant; CLSI = Clinical Laboratory and Standards Institute.
a seasonal peak in spring and early summer and is highly contagious. In Asia, however, it is endemic and mainly affects children. The disease is caused by several serotypes of adenoviruses, mainly 8, 19, and 37, and the recently discovered adenovirus types 53 and 54. Adenovirus type 53, which was detected in our patient, has initially been described in outbreaks of keratoconjunctivitis in Germany and Japan. Subsequently, adenovirus type 53 was found to be endemic in Japan, Detection of adenovirus type 53 in this patient who was infected in Thailand suggests circulation of adenovirus type 53 in East Asia, also outside of Japan. The point-of-care test (sensitivity 90% and specificity 96%, as per manufacturer’s information) failed to detect the unusual adenovirus type 53 in our case. Clinically, adenoviral keratoconjunctivitis presents with acute onset of eyelid swelling, conjunctival injection and chemosis, swelling of the caruncula, and sometimes with lymphadenopathy. In severe cases, subconjunctival hemorrhages and pseudomembranes develop. Patients describe acute onset of watering, discomfort, and severe photophobia. Symptoms usually start unilaterally and after a few days (incubation time up to 12 days) the second eye is affected. After the acute phase, visual impairment can occur owing to subepithelial corneal infiltrates lasting for months.

In conclusion, patients with suspected gonococcal eye infection should undergo rapid diagnosis and treatment as complications can occur within a short time. Because of the widespread and increasing resistance of Neisseria gonorrhoeae to different antibiotics, culture and susceptibility testing should generally be performed in all gonococcal infections, especially in bacterial isolates recovered from travelers. As shown in this case, a concomitant and/or preceding viral eye infection can be present and initially mask a bacterial infection. Itching caused by other eye infections may be a predisposing factor for ocular autoinoculation of gonococci. Detailed medical history should therefore be obtained in travelers with suspected keratoconjunctivitis including a history of sexual contacts.

Declaration of Interests
The authors state that they have no conflicts of interest.

References