CONCISE COMMUNICATION

Detection and Prevalence of Adenoviral Conjunctivitis among Hospital Employees Using Real-Time Polymerase Chain Reaction as an Infection Prevention Tool

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Hospital employees with suspected adenoviral conjunctivitis underwent evaluation and testing with real-time polymerase chain reaction. Viral conjunctivitis was suspected in 307 (59%) of 518 employees with eye complaints; adenovirus was detected in 4% (22 of 518). Four employees had genotypes consistent with epidemic keratoconjunctivitis. This algorithm minimizes productivity loss compared with clinical diagnosis.

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Adenoviral eye infection is a public health concern; certain strains can cause epidemic keratoconjunctivitis (EKC) that is highly infectious. Infection can be self-limited with short-term significance or cause prolonged ocular morbidity. Outbreaks in hospitals and eye clinics result in substantial morbidity and lost productivity.[1-7] In response to healthcare-associated EKC outbreaks,[1-7] one of which nearly shut down a large eye institute,[7] a "red eye room," where persons with potentially infectious conjunctivitis could be triaged and isolated, was established in 1990 in the Wilmer Eye Institute emergency department, Department of Ophthalmology, at Johns Hopkins Hospital (JHH).[8] This was part of an infection prevention program consisting of ophthalmic instrument decontamination, hand hygiene, use of single-dose eye drops, and employee furloughs. The program required restructuring when institutional changes led to the permanent closure of Wilmer emergency department and the red eye room at the end of January 2008. A multidisciplinary team comprising an ophthalmologist with expertise in corneal and external eye disease and stakeholders in infection prevention, employee health, and clinical virology devised a new practice algorithm for preventing healthcare-associated transmission of adenoviral eye disease. Here we report this new practice algorithm and novel information on adenoviral conjunctivitis in healthcare workers, including prevalence and infecting serotypes.

METHODS

Key components of the new red eye employee practice algorithm are shown in Figure 1. It consists of initial evaluation by nurse practitioners (NPs) in the occupational health clinic and rapid diagnostic testing by real-time polymerase chain reaction (PCR) in individuals with signs and symptoms consistent with adenoviral conjunctivitis. Employees telephone the occupational health clinic for health concerns that arise during work hours and that may impact their work, and they are evaluated the same day. Appointments are required for red eye evaluation to limit the possibility of healthcare-associated transmission within the occupational health clinic.

A corneal specialist taught NPs in the occupational health clinic to recognize signs and symptoms of probable viral conjunctivitis and how to collect swab specimens of the inferior conjunctival fornix. Screening criteria included duration of symptoms, presence of viral prodrome, discharge or tearing, and unilateral onset. The NPs also reviewed how to recognize conditions such as suspected corneal abrasion and subconjunctival hemorrhage, and they were instructed to swab only when viral conjunctivitis was suspected. The conjunctival swab (polyester, Dacron, or rayon with plastic or aluminum shafts) was placed in M4 medium and promptly sent at room temperature for PCR analysis, which was performed daily. Employees with suspected viral conjunctivitis were examined, swabbed, and discharged home within 30 minutes. Employees were notified of PCR results and furlough status by 8 PM if specimens were received in the laboratory by 3 PM. A 2-week furlough was invoked if adenovirus was detected by PCR; the employee was reexamined to ensure that no redness or drainage was present before release back to work. For epidemiologic purposes, direct sequencing of specimens found to contain adenovirus DNA was performed retrospectively to determine whether employees were infected with viral strains that have been reported to be associated with EKC (8, 19, and 37).[9-15] The Department of Ophthalmology provided consultation for evaluation of any employee whose case the NPs deemed to be an emergency or for whom they were unsure of the red eye diagnosis.

Total nucleic acid was isolated from conjunctival specimens (processed volume, 400 μL) using automated instrumentation (BioRobot M48, using Virus Mini Protocol software, version 1.1, and MagAttract Virus Mini M48 reagents [Qiagen]). Adenovirus DNA was detected by real-time PCR.[16] The assay has an analytical sensitivity of 300 copies/mL and detects at least 16 adenovirus serotypes, including strains from 6 of 7 adenovirus serogroups (A–F). Serotype was determined by nested PCR of the hexon gene hypervariable regions 1–6[17] using previously extracted total nucleic acid followed by bidirectional Sanger sequencing using AdhexF2/AdhexR2 as sequencing primers. The ability to identify serotypes associated with ocular disease (8, 19, and 37) and other serotypes that commonly cause ocular disease (3, 7, and 11) was confirmed in-house using acquired strains (ATCC).

RESULTS

From November 22, 2011, to July 31, 2013, 518 (18%) of 2,902 initial employee occupational health visits were attributable to unique, eye-related complaints. The number of em-

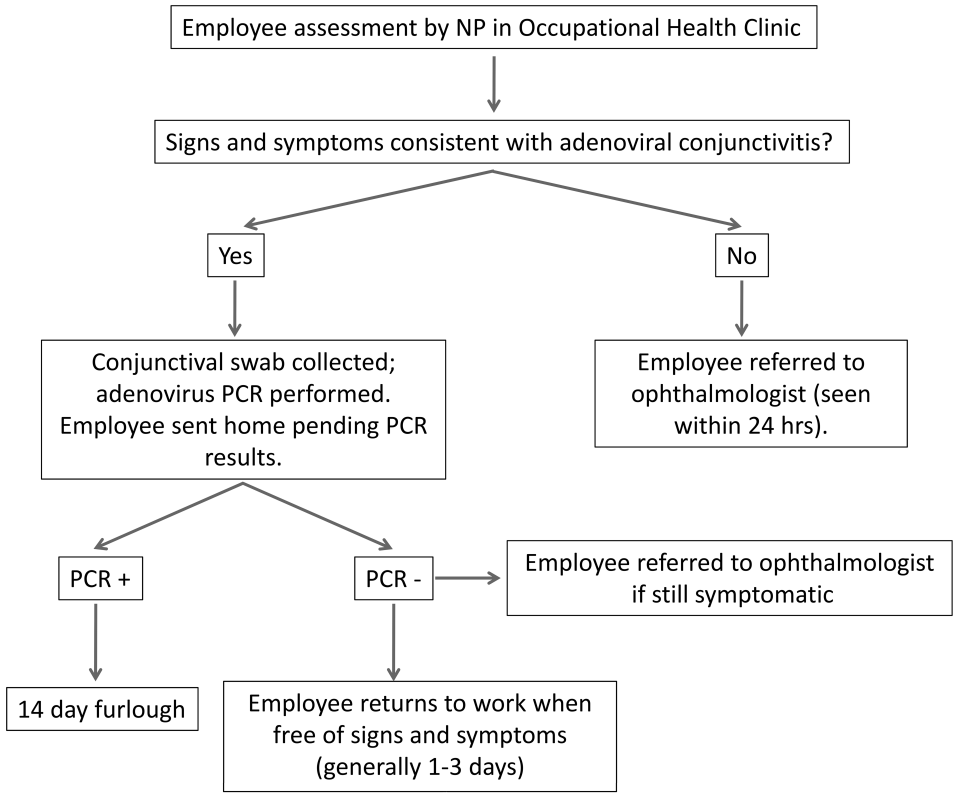

FIGURE 1. Schema of red eye employee triage system at Johns Hopkins Hospital. NP, nurse practitioner; PCR, polymerase chain reaction.

ployees seen for eye concerns ranged from 6 to 36 per month (Figure 2). Most employees complained of red eyes. Of the 518 employees with eye concerns, 307 (59%) underwent conjunctival swabbing and adenovirus PCR testing. Twenty-two employees (7% of suspected adenoviral cases, or 4% of all employees with eye concerns) had real-time PCR results positive for adenovirus. Seventeen samples could be amplified by the nested conventional PCR for serotype determination by Sanger sequencing. Four samples contained serotypes associated with EKC, including type 8 ($n = 2$), 19 ($n = 1$), and 37 ($n = 1$). Other serotypes found were 3 ($n = 4$), 56 ($n = 4$), 1 ($n = 2$), 4 ($n = 2$), and 7 ($n = 1$).

More than half of the employees (293 [57%] of 518) had conditions that were determined to be noninfectious after eye examination; allergic conjunctivitis was most common. The other diagnoses after consultation at Wilmer or private ophthalmologists included corneal or conjunctival foreign body, pingueculum, episcleritis, scleritis, corneal abrasion, contact lens overuse, iritis, dacryocystitis, and preseptal cellulitis.

To compare the prevalence of laboratory-diagnosed adenoviral conjunctivitis among healthcare employees with eye concerns to that among general ophthalmology patients, Wilmer General Eye Service visits consistent with conjunctivitis were analyzed. In the 2-year period before red eye room closure (January 2006 through January 2008), there were 9,609 patient visits with unique diagnoses (ie, follow-up visits for the same diagnosis for the same patient were excluded). An *International Classification of Diseases, Ninth Revision* (ICD-9), code consistent with adenoviral conjunctivitis was attached to 986 visits. The vast majority of diagnoses were made clinically; the ICD-9 codes included 372.00, 372.03, 372.71, 379.93, 077.1, 077.3, 077.4, and 077.8. Therefore, the prevalence of clinically diagnosed adenoviral conjunctivitis in the General Eye Service was 10% (986 of 9,609 cases).

DISCUSSION

The new triage algorithm for red eye evaluation at our hospital has been successful in its goal to isolate and furlough employees with adenoviral conjunctivitis rapidly, thus preventing spread of ocular disease among patients and other employees. The causes of red eye in hospital employees are now recorded systematically (rather than as a simple description of red eye), and the prevalence of adenoviral infection can be monitored readily. To our knowledge, there has been no other report of a similar triage system for adenoviral conjunctivitis, nor has there been any report of its prevalence among hospital employees.

This algorithm has several potential benefits. First, the initial evaluation of healthcare workers at a single site by a select group of trained care providers maximizes the likelihood of adherence to EKC prevention policies. Before this algorithm, numerous different clinicians evaluated employees, adenovirus cultures were infrequently obtained, and adenoviral

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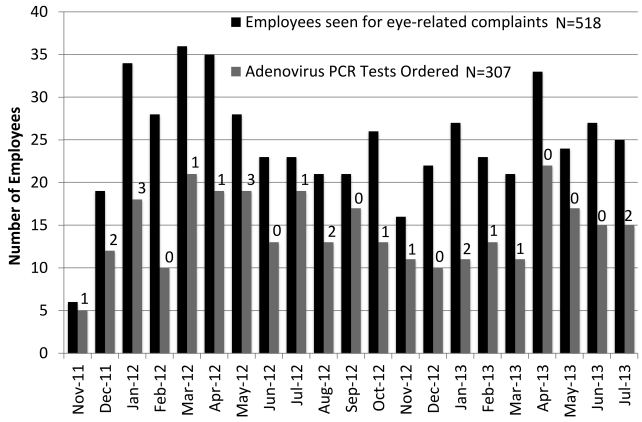

FIGURE 2. Employees seen for eye concerns, adenovirus polymerase chain reaction (PCR) tests ordered, and positive adenovirus PCR results during the first 22 months of algorithm use. Numbers above the Adenovirus PCR Tests Ordered columns indicate the number of positive adenovirus PCR results. A total of 518 employees with eye concerns were seen, and 307 employees had conjunctival specimens sent for adenovirus PCR by an occupational health nurse practitioner. A total of 22 employees had positive adenovirus PCR results.

conjunctivitis was often clinically diagnosed. Second, given that clinical diagnosis of this disease is imperfect, adjunctive use of PCR testing for employees with suspected adenoviral conjunctivitis facilitates judicious use of furlough for infection prevention.

Determination of adenovirus prevalence and delineation of serotypes associated with red eye among healthcare employees were major aims once the practice algorithm was implemented. Prevalence of adenoviral conjunctivitis among hospital personnel (4%) was less than half that seen among General Eye Service patients (10%) in whom the infection was clinically diagnosed. Potential explanations for this difference include varying prevalence of adenoviral conjunctivitis between the general public and hospital employees or the comparatively lower specificity of clinical diagnosis compared with PCR testing. It is likely that not all of the clinically diagnosed cases in the General Eye Service were truly adenoviral.

Molecular serotyping showed that approximately 20% of the employees found to have adenoviral conjunctivitis were infected with an EKC-associated strain, which raises the question of whether the algorithm should include serotype determination to tailor furlough duration. For example, employees with EKC-associated serotypes could be assigned a 2-week work furlough, whereas those with other serotypes could be furloughed for a shorter duration until resolution of clinical symptoms; clinical clearance by occupational health NPs would be required before returning to work in either situation. The 2-week furlough commonly recommended for patients with presumed or definite adenoviral conjunctivitis may have arisen in part from a report of a large outbreak of EKC in an ophthalmology department in which adenovirus was isolated from conjunctival surfaces up to 2 weeks after the onset of clinical illness.[7] Detection of adenovirus by culture or PCR, however, does not imply that the eye is infectious, and adenoviral conjunctivitis can span from mild disease to EKC. Although patients with other infectious conjunctivitides (eg, enteroviral) are furloughed for only a few days, adenoviral conjunctivitis is more common, and potential complications are more severe. The cost of PCR for 307 employees with suspected adenoviral conjunctivitis was 5% of the possible cost of furloughing them for 2 weeks on the basis of clinical diagnosis alone. It is possible, however, that the 2-week furlough is excessive. A more flexible policy, invoking shorter or longer furlough on the basis of community molecular epidemiologic data of circulating adenovirus serotypes, may be more appropriate and deserves additional investigation.

One challenge of this practice algorithm is the lack of a US Food and Drug Administration–cleared nucleic acid amplification assay for use in the detection of adenoviruses in conjunctival specimens. Centers seeking to adopt a similar algorithm are therefore tasked with implementing laboratory-developed tests that use noncommercial primers or adapting tests that have been cleared for use with nasopharyngeal samples. Our data suggest that adenovirus DNA detection is more accurate than diagnosis of adenoviral conjunctivitis on the basis of clinical criteria and provide a rationale for the development and regulatory approval of commercial adenovirus nucleic acid detection tests for use in conjunctival specimens, in particular in large institutional settings.

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