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CLINICAL STUDY

Epidemic kerato-conjunctivitis—do outbreaks have to be epidemic?

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Abstract

Purpose **To study:**

- **the epidemiology of an outbreak of adenoviral keratoconjunctivitis in a UK teaching hospital;**
- **disease presentation and its effect on clinical diagnostic efficiency;**
- **patterns of viral transmission between staff and patients;**
- **the effectiveness of infection control procedures in minimising outbreaks.**

Methods **Prospective/retrospective clinical audit and retrospective audit of virological culture results: all viral culture swabs taken during an outbreak of adenoviral keratoconjunctivitis were analysed. The case records of patients whose viral swabs were positive for adenoviral culture were traced. The time for viral cultures to become positive (culture positive time) was calculated. Analysis of the case notes was performed to elucidate (1) the source of infection and (2) the risk factors for acquisition of the infection. Retrospective clinical audit was performed to evaluate the effectiveness of infection control procedures. Adenovirus isolates underwent serotyping.**

Results **During the 3-month period of study, there were 38 confirmed cases of adenoviral keratoconjunctivitis. This represented a 217% increase in the number of new cases per 3-month period. The case notes for five patients were untraceable. Of the remaining 33 patients, 21 (63%) had acquired their infection either directly or indirectly from the eye department and 22 (67%) had presented with unilateral disease. The rate of misdiagnosis was higher (9/22 = 42%) in patients presenting with unilateral disease than those presenting with bilateral disease (2/11 = 18%). Intradepartmental acquisition of infection was associated with invasive procedures, for example use of diagnostic/therapeutic contact lenses. Culture positive times ranged from 3 to 29 days. The introduction of infection control procedures was associated with a dramatic decrease in the incidence of departmentally acquired cases with no new cases after 2 weeks. Multiple serotypes of adenovirus were involved.**

Conclusion **Outbreaks of adenoviral keratoconjunctivitis are a serious public health issue concerning ophthalmic departments. This audit study illustrates several important points: (1) how hospital-acquired infection can account for a significant proportion of the cases seen, (2) how multiple types of adenovirus can be involved in a single outbreak, (3) that severe unilateral disease is associated with a higher rate of misdiagnosis; and (4) how standard viral culture techniques may not be satisfactory in confirming/disproving infection when the diagnosis is in doubt. The potential benefit of infection control procedures in minimising this outbreak could not be proven within this audit.**

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Keywords: epidemic keratoconjunctivitis; audit; infection control procedures

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Introduction

Adenoviral eye infection can manifest itself in many forms ranging from conjunctivitis that is often self-limiting to keratitis, which can be prolonged. Disease severity similarly can be mild to severely disabling. Spread is via droplet or direct contact. The majority of virology departments currently use viral isolation by the culture of conjunctival swab samples to confirm infection, while the uptake of more rapid virological confirmation techniques[1–3, 19–22] has been slow because of the increased cost and expertise required for their implementation.

There is evidence that the adenoviral serotypes involved in eye disease can be transmitted via an inanimate vector,[4] for example, door handles, different types of plastic and tonometer heads. Their importance to eye units stems from the high infectivity and variable incubation period. Asymptomatic infected patients and staff can propagate the virus unknowingly. Similarly, the ophthalmologist can act as vector causing transmission of adenovirus particles from patient to patient.[5,6] Previous reports have shown how outbreaks can rapidly develop,[7,8] potentially resulting in temporary closure of ophthalmic units. Their prompt containment is therefore necessary because of their grave implications on the health of the public and workforce.

In the second week of January 1999, it was noted that there was a dramatic increase in the incidence of adenoviral-related eye disease among the staff and patients of the ophthalmic department of the Royal Hallamshire Hospital, Sheffield, UK, a teaching hospital ophthalmic department. It was noticed quite early that a significant proportion of the patients, who had previously attended for other unrelated reasons, was now reattending with adenoviral eye disease. Infection control procedures were introduced within 2 weeks on the 26th of January in an attempt to minimise the outbreak:

1. Thorough hand washing by all staff after contact with any patient. Although this was encouraged prior to the outbreak, hand washing was only practised half-heartedly by staff.
2. Wearing disposable gloves while examining every patient. The use of gloves was previously dependent on the clinical situation.
3. Thorough cleaning of all examination equipment with Chloramine-T solution after seeing any patient with a red eye. Prior to the outbreak, routine cleaning of the equipment was not performed, with diagnostic/therapeutic contact lenses previously either wiped with 70% isopropyl alcohol only or soaked for a variable period with Chloramine-T. During the outbreak, these lenses were either soaked for 30 min in Chloramine-T or wiped down with Chloramine-T solution.
4. Cleaning the disposable occluders used for testing vision between patients with Chloramine-T and changing to new disposable occluders regularly. Previously, the occluders were shared without cleaning by nurses.
5. Ensuring that the tonometers underwent disinfection by soaking in Chloramine-T for at least 30 min after use. Previously, the duration of disinfection was variable and at times short, especially in the busy eye casualty department where the practice of 'dunking and wiping' was practised.
6. Patients, who were diagnosed to have adenoviral eye disease, either clinically or via virological culture, were encouraged not to return to the eye department to avoid cross spread.
7. Similarly, all infected staff members were advised not to return to work until it was considered that they no longer posed an infection risk.
8. Triaging of suspected cases of adenoviral infection so that they are seen earlier and in isolation from other patients. This was not performed prior to the outbreak.

Methods

A prospective audit was set up to ask several questions:

- How effective was the clinician at diagnosing adenoviral eye disease?
- How many patients had acquired their infection from the eye department?
- What were the risk factors for viral transmission within an eye department?
- How effective were the infection control procedures in the containment of an outbreak?

The virology department was contacted and requested to highlight any virological culture swabs from the eye department that had grown adenovirus during the outbreak. Viral cultures were performed in A549 and Hep2 cells and any cytopathic effect identified as adenovirus by immunofluorescence (Chemicon). Adenoviruses were typed by neutralisation in A549 cells using polyvalent antisera. In addition to the results of viral culture, the results of any other microbiological/radiological investigations that were concurrently requested were also traced, for example, bacterial/chlamydial isolation and corneal scrape results. The case notes of these patients were retrieved and analysed.

Specific points investigated were:

- Clinically, was the eye disease unilateral or bilateral at presentation?
- If there was a delay in making the correct diagnosis of adenoviral eye disease; what were the differential diagnoses made instead?
- What treatment was dispensed for these misdiagnosed cases?
- How long had the culture swabs taken to become positive for adenovirus (culture positive time)?

Patients were classified into three groups depending on how they had acquired their infection:

- group 1: community acquired—via contact with a source who had acquired the infection outside of the eye department;

- group 2a: departmentally acquired–directly infected—that is, infected during a visit to the eye department; and
- group 2b: departmentally acquired–indirectly infected—that is, infected through contact with another person who had acquired infection from the eye department directly.

For example, a patient X could have acquired infection through the community (community acquired— group 1). Patient X visits the eye department and passes on the infection to patient Y (departmentally acquired–directly infected—group 2a). Patient Y returns home and infects his spouse unknowingly (departmentally acquired–indirectly infected—group 2b).

Patients were classified into the three groups based on their history (Figure 1).

Those patients who had attended the eye department for an unrelated reason previously, for example, cataract surgery, laser treatment, but then reattended with adenoviral eye disease were assumed to have acquired their infection directly from the eye department (ie group 2a), provided they denied any history of contact with any person with a red eye in the community.

For the patients who had acquired their infection directly from the eye department (group 2a), possible risk factors for acquiring their infection were looked at.

For example:

- Had any drops been instilled?
- Had applanation tonometry been performed?
- Had a diagnostic/treatment contact lens been applied to the anterior segment?

Finally, for the patients with departmentally acquired eye disease (ie groups 2a and 2b), the date on which they had initially acquired the infection was also calculated. Therefore, the daily frequency of new cases could be plotted over the 3-month period of study.

Results

Source of infection

Over the 3-month period of study, adenoviruses were cultured from 38 viral culture swabs from the ophthalmic

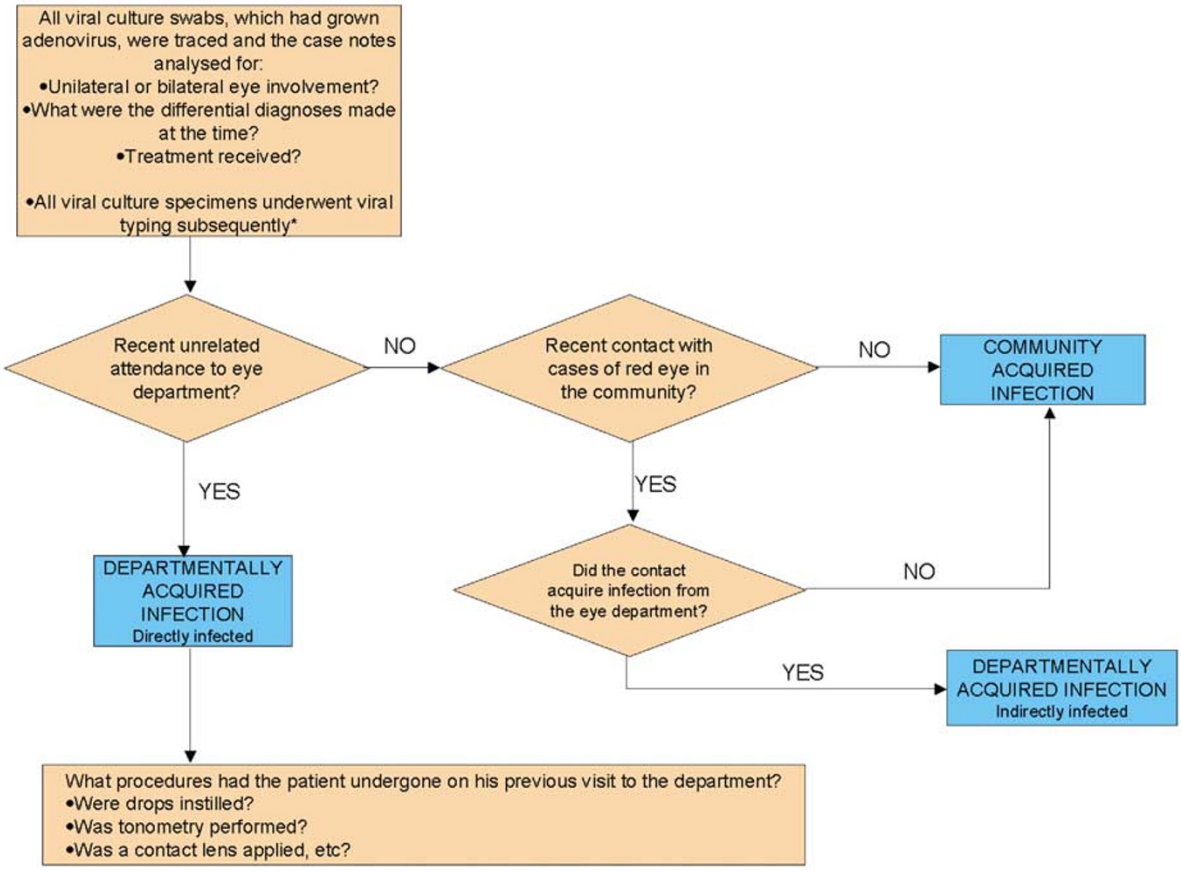

Figure 1 Flow chart illustrating how patients were classified into the various groups of community or departmentally acquired disease based on their clinical presentation.

department. For the 6 months prior to the outbreak, there were on average only four adenoviral positive swabs per month. Similarly, there was an average of four adenoviral positive culture swabs per month for the first quarter of the previous year. This equated to a 217% increase in the number of culture positive swabs for the period of the outbreak. The case notes of the 38 cases with adenoviral positive viral culture swabs were sought, of which five were untraceable. Of the remaining 33 patients, 19 (58%) had acquired the infection directly from the eye department on a previous unrelated visit (group 2a). The remaining 14 patients had acquired their infection from within the community (consisting of groups 1 and 2b).

On further case note analysis of these 19 departmentally acquired cases, four of them were staff members (three doctors and a receptionist). Of the remaining 15 patients, who were members of the public, 11 had acquired their eye infection during a previous unrelated visit to the eye casualty department:

- one patient with acute-angle closure glaucoma;
- one patient with a loose suture in a previous corneal graft;
- three patients seen for removal of foreign body;
- one patient with examination for symptoms of 'flashing lights/floaters';
- one patient with marginal keratitis;
- one patient with dry eye/blepharitis;
- one patient attending with contact lens related problems; and
- one patient with traumatic hyphaema.

(The patient who previously attended with contact lens related problems subsequently presented with a follicular conjunctivitis only. The important differential diagnosis of acanthomoeba infection would require consideration/exclusion had he presented with keratitis.)

Of the remaining four patients who had also acquired their adenoviral disease directly from the ophthalmic department:

- three patients had attended the laser clinic: two for prophylactic Nd : YAG PI for narrow angles, and one for Nd : YAG laser lysis of a vitreous strand in the wound following complicated cataract surgery; and
- one patient attended for a recurrence of herpetic keratouveitis.

Of the total 15 patients who had acquired the infection directly from the ophthalmic department, during their previous visit:

- seven had undergone applanation tonometry (7/15 = 46%);
- five had had a diagnostic/treatment contact lens applied to their eye (5/15 = 33%); and
- all 15 had had some drops instilled into their eye, all of which were of the Minims (Chauvin) single-use type (100%).

Of the remaining 14 patients (14/33 = 42%) who denied attendance to the eye department, two had indirectly acquired their infection from the eye department (group 2b):

- one patient was the partner of an ophthalmologist who was affected; and
- one patient was the relative of a patient who had acquired his infection from the eye department.

In total, therefore, there were 12 community-acquired cases (group 1), 19 departmentally acquired–directly infected cases (group 2a), and two departmentally acquired–indirectly infected cases (group 2b). In total then, 21 out of 33 of the cases were traceable back to the eye department; that is, 63% of all the patients had acquired their eye infection either directly or indirectly from the eye department (groups 2a and 2b combined).

Problems of misdiagnosis and the need for exclusion of differential diagnoses

Further case note analysis showed that 22 out of the 33 (67%) patients presented with clinically unilateral eye disease. Interestingly, all the departmentally infected/directly acquired cases (group 2a) who presented with unilateral adenoviral eye disease also attended for problems in the same eye previously. This suggests that direct contact may play an important role in the transmission of the adenovirus.

A proportion of patients presented with symptoms and signs of such severity, for example, severe periorbital retro-orbital pain, gross chemosis, pseudoproptosis, severe periorbital oedema, that it was essential to exclude a more sinister aetiology. This problem was higher among patients with severe unilateral disease (9/22 = 41%) than among those with bilateral disease (2/11 = 18%). For example, in the unilateral disease group:

- Two patients were given working differential diagnoses of orbital cellulitis/severe adenoviral eye disease because of severe periorbital swelling and retroorbital pain. One patient was misdiagnosed as having orbital cellulitis: adenoviral infection was not suspected until the disease later became bilateral. All were started on high-dose oral antibiotics. One patient underwent CT orbital scanning because of the severe pseudoproptosis. Bacterial blood cultures were negative in all three cases. The correct diagnosis of

adenoviral infection was made only after positive viral isolation using viral culture in all three cases.

- One patient with severe adenoviral keratitis was managed as bacterial keratitis. Corneal scraping was performed and a course of intensive topical ciprofloxacin initiated. Corneal scrape results were negative for bacteria and fungi (he was not a contact lens wearer), but conjunctival swabs were positive for adenovirus after 5 days. The topical ciprofloxacin was immediately stopped and the patient was closely observed. There was spontaneous recovery.
- Two patients were misdiagnosed as having scleritis. Numerous haematological investigations were performed and a short course of systemic prednisolone was started. The correct diagnosis of adenoviral infection was only suspected when the patients returned with bilateral eye involvement.

In the bilateral disease group, for example, one patient, known to have rosacea and rosacea keratitis, attended the eye casualty department after developing severe bilateral keratitis with conjunctivitis. She had been previously seen 2 weeks earlier in the general clinic for a routine appointment, when her condition was stable and she required hypromellose drops only. At her casualty attendance, bacterial and viral conjunctival culture swabs were taken and she was commenced on topical steroid treatment with the diagnosis of 'a flare up of rosacea keratitis' being made by the casualty officer. The correct diagnosis of adenoviral keratoconjunctivitis was made 3 days later based on viral culture results. The topical steroids were stopped and the patient was advised to increase the use of her regular ocular lubricants. Improvement ensued.

Overall, a significant number of patients, with severe symptoms/signs because of adenoviral eye infection, were treated as having a more sinister disease which their presentation mimicked. Of these, there were some frank misdiagnoses; however, the majority were given a list of differential diagnoses which included adenoviral infection. Their management was often governed by the need to investigate and treat a more sinister differential diagnosis. In some cases, the possibility of adenoviral infection was only suspected when previously unilateral eye involvement became bilateral. In all cases, the correct diagnosis of adenoviral infection was only confirmed after the results of the adenoviral culture swabs became positive.

The possibility of dual/multiple pathology among some of these patients, when there could have been multiple pathologies accounting for the clinical picture, is recognised.[9] For example, one patient may have had both bacterial keratitis with secondary adenoviral infection, with the empirical use of intensive topical ciprofloxacin eradicating the bacterial component of their dual pathology. Similarly, a small number of patients underwent continued treatment for a differential diagnosis, while also being treated for adenoviral eye infection, because it was deemed safer to treat these conditions. In most of the patients, however, a diagnosis of adenoviral infection could be confidently made, based on their clinical features and investigations.

Effect of infection control procedures

For the patients who had acquired the infection directly from the eye department, group 2a, one could find out the likely date on which they had acquired the infection. A graph was plotted to show the weekly number of new cases of group 2a patients over the 3-month period of study. The introduction of the infection control procedures was associated with a dramatic decrease in the number of new cases of departmentally acquired infection (Figure 2).

Viral culture times

The time taken for the viral culture swabs to become positive for adenovirus was also calculated for each of the 33 patients (culture positive time). A graph showing the distribution of culture positive times was plotted (Figure 3).

The mean was 9.1 days, with a minimum of 3 days and a maximum of 29 days.

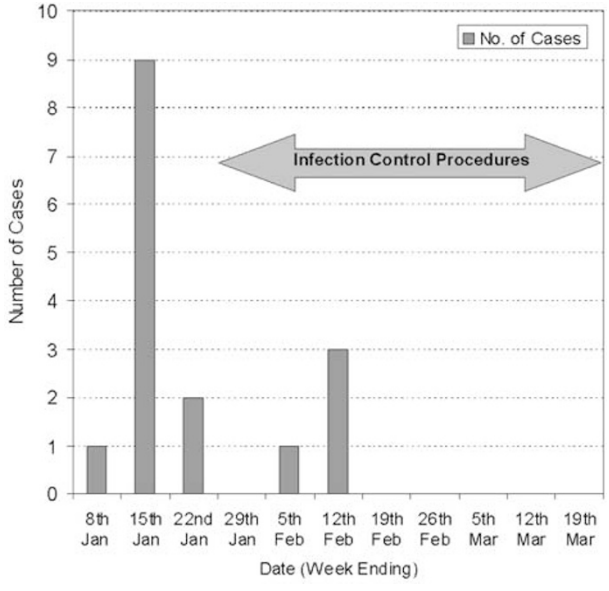

Figure 2 Graph showing the number of new cases per week of departmentally acquired cases. Note the rapid decrease in the frequency of new cases with the introduction of infection control procedures on 26 January 1999.

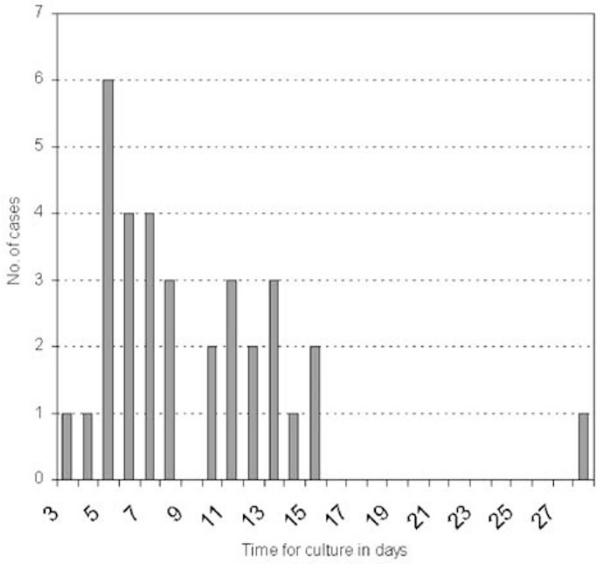

Figure 3 Graph showing the distribution of viral culture times. This is the time required for viral culture swabs to become positive for adenovirus. (Minimum time 3 days, maximum time 29 days, mean viral culture time 9.1 days, and number of patients 32.)

Viral typing

Although not all adenoviruses could be typed in the virus laboratory, regrettably not the 'original' case on the 6th of January, there were one type I, three type II, three type VI, and one type V adenovirus identified in January, demonstrating that this was not a point-source outbreak. In February, there were a further two type I, three type II, one type III, and one type VI adenovirus identified from eye swabs from the clinic.

Discussion

Outbreaks of adenoviral eye infection are a serious health risk and an important risk management problem for all ophthalmic units. In our study, there was a staggering 217% increase in the number of cases seen, with approximately two-thirds of the patients having acquired the infection from the eye department, either directly or indirectly. Not surprisingly, because of the care mix of patients seen, ophthalmic casualty departments carry the greatest risk of rapid spread of infection among patients.

It is disappointing that 5/32 (13.2%) of the notes were untraceable. It is unknown how the inclusion of these patients into this audit would have affected the final figures, for example, for community *vs* departmental acquisition or disease presentation (unilateral *vs* bilateral). Their unfortunate omission somewhat reduces the statistical integrity of this audit, but is unlikely to have a major impact on the conclusions drawn. The reliable archiving of patients' notes in an easily accessible fashion continues to be a problem in busy ophthalmic departments. It is hoped that the current drive for user-friendly electronic patient records will reduce this problem in the future.

It is interesting to note that the outbreak witnessed in our department involved multiple serotypes of adenovirus, suggesting that this was not a single-point outbreak but one with multiple sources.

The role of direct contact appears to be important in the transmission of the virus. All the departmentally acquired cases were associated with some form of invasive procedure, for example, drop instillation, applanation tonometry, etc and this is in keeping with previous studies.[10,11] Indeed, previous studies have examined the role of the ophthalmologist and his tools in adenoviral transmission.[12,13] However, there did not appear to be any single procedure that was associated with an increased likelihood of viral transmission. It is known that corneal epithelial compromise is associated with an increased risk of secondary adenoviral infection.[14] The lack of a control group makes it difficult to make direct conclusions. Likewise, during the period of the outbreak, the majority of patients who were exposed to similar procedures did not acquire the infection. Therefore, there appears to be multiple factors as to why some patients should acquire the infection and others not. There were no obvious risk factors for acquiring viral infection in the group studied, for example, immunosuppression, diabetes, age.

The introduction of infection control procedures was associated with a decrease in the frequency of 'fresh' departmentally acquired cases. Previous observational studies have shown similar results.[15] Again, because of the lack of a comparative control group, one cannot conclude that the control procedures were directly responsible for the outbreak's swift resolution. It is arguable that any adenoviral outbreak is self-limiting and may have followed a similar course regardless of whether or not any active intervention had been introduced. For example, in this audit, there was already a dramatic decrease in the number of departmentally acquired new cases in the week prior to the introduction of infection control procedures. However, previous comparative studies looking into the effectiveness of infection control procedures do support their prompt implementation[16] as soon as the beginning of an outbreak is suspected. Repeating this work would be unnecessary and perhaps unethical.

Severe unilateral eye infection was, at times, extremely difficult to differentiate from more serious eye pathology, for example, orbital cellulitis, scleritis, microbial keratitis.

Indeed, the large variation in clinical presentations encountered may have been due to the different serotypes of adenovirus involved.[17] In our audit, patients who presented with severe unilateral adenoviral disease, for example, severe chemosis, pseudoproptosis, severe periocular pain, had a higher rate of misdiagnosis/differential diagnosis than those presenting with bilateral 'classical' symptoms and signs, for example, mild bilateral conjunctivitis following prodromal symptoms. Consequently, these patients can undergo unnecessary, invasive investigations and hospitalisation, with the correct diagnosis only being made after confirmation from the virology department. These findings support the opinion that the reliability of clinical diagnosis of adenoviral eye infection can be poor.[18]

Ideally, in suspected outbreaks of adenoviral eye disease, there should be a rapid accurate diagnostic test to identify those patients who have adenoviral infection. Their prompt isolation would help minimise the risk of further spread. At present, most UK virology departments use standard viral culture techniques to isolate to detect adenovirus eye infections. Results from this audit suggest that these are not satisfactory as a significant proportion of viral culture swabs do not become positive for at least 10 days. Some affected patients revisited the casualty department repeatedly while awaiting viral culture results and therefore represented a potential infection source. More rapid diagnostic tests, for example, radioimmune dot blot testing and PCR, have been argued for by previous researchers,[19–22] with potential benefits in reducing the degree of spread of the viral transmission. This audit supports their findings.

Conclusion

Overall this audit model has been useful in demonstrating a multipoint outbreak of adenovirus in a UK teaching hospital. It has also demonstrated some of the problems that can hinder the confident diagnosis of infection and alluded to the risk factors for viral transmission. However, there was no previous audit cycle for comparison, which makes it difficult to draw final conclusions on the role of infection control procedures in minimising multiple source outbreaks.

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References

1 Cooper RJ, Yeo AC, Bailey AS, Tullo AB. Adenovirus polymerase chain reaction assay for rapid diagnosis of conjunctivitis. *Invest Ophthalmol Vis Sci* 1999; **40**: 90–95.
2 Elnifro EM, Cooper RJ, Klapper PE, Bailey AS, Tullo AB. Diagnosis of viral and chlamydial keratoconjunctivitis: which laboratory test? *Br J Ophthalmol* 1999; **83**: 622–627.
3 Wood SR, Sharp IR, de Jong JC, Verweij-Uijterwaal MW. Development and preliminary evaluation of an enzyme immunosorbent assay for the detection of adenovirus type 8. *J Med Virol* 1994; **44**(4): 348–352.
4 Kowalski RP, Romanowski EG, Waikhom B, Gordon YJ. The survival of adenovirus in multidose bottles of topical fluorescein. *Am J Ophthalmol* 1998; **126**: 835–836.
5 Azar MJ, Dhaliwal DK, Bower KS, Kowalski RP, Gordon YJ. Possible consequences of shaking hands with your patients with epidemic keratoconjunctivitis. *Am J Ophthalmol* 1996; **126**(6): 711–712.
6 Jernigan JA, Lowry BS, Hayden FG, Kyger SA, Conway BP, Groschel DH *et al*. Adenovirus type 8 epidemic keratoconjunctivitis in an eye clinic: risk factors and control. *J Infect Dis* 1993; **167**(6): 1307–1313.
7 Richmond S, Burman R, Crosdale E, Cropper L, Longson D, Enoch BE *et al*. A large outbreak of keratoconjunctivitis due to adenovirus type 8. *J Hyg* 1984; **93**(2): 285–291.
8 Tullo AB, Higgins PG. An outbreak of adenovirus keratoconjunctivitis in Bristol. *Br J Ophthalmol* 1979; **63**: 621–626.
9 Deutsch FH. Concurrent adenoviral and herpetic ocular infections. *Ann Ophthalmol* 1989; **21**(11): 432–438.
10 Muellar AJ, Klauss V. Main sources of infection in 145 cases of epidemic keratoconjunctivitis. *Ger J Ophthalmol* 1993; **2**(4–5): 224–227.
11 Montessori V, Scharf S, Holland S, Werker DH, Roberts FJ, Bryce E. Epidemic keratoconjunctivitis outbreak at a tertiary referral eye care clinic. *Am J Infect Control* 1998; **26**(4): 399–405.
12 Threlkeld AB, Froggatt III JW, Schein OD, Forman MS. Efficacy of a disinfectant wipe method for the removal of adenovirus 8 from tonometer tips. *Ophthalmology* 1993; **100**: 1841–1845.
13 Buehler JW, Finton RJ, Godman RA, Choi K, Hierholzer JC, Sikes RK *et al*. Epidemic keratoconjunctivitis: report of an outbreak in an ophthalmology practice and recommendations for prevention. *Infect Control* 1984; **5**(8): 390–394.
14 Viswalingam ND. Adenovirus keratoconjunctivitis: an enigma. *Eye* 1993; (Suppl): 5–7.
15 Warren D, Nelson KE, Farrar JA, Hurwitz R, Hierholzer J, Ford E *et al*. A large outbreak of epidemic keratoconjunctivitis: problems in controlling nosocomial spread. *J Infect Dis* 1989; **160**(6): 938–943.
16 Gottsch JD. Surveillance and control of epidemic keratoconjunctivitis. *Trans Am Ophthalmol Soc* 1996; **94**: 539–587.
17 Roba LA, Kowalski RP, Gordon AT, Romanowski EG, Gordon YJ. Adenoviral ocular isolates demonstrate serotype-dependent differences in *in vitro* infectivity titers and clinical course. *Cornea* 1995; **14**(4): 388–393.
18 Fitch CP, Rapoza PA, Owens S, Murillo-Lopez F, Johnson RA, Quinn TC *et al*. Epidemiology and diagnosis of acute

conjunctivitis at an inner-city hospital. *Ophthalmology* 1993;**100**: 530–533.
19 Pring-Akerblom P, Adrian T, Kostler T. PCR-based detection and typing of human adenoviruses in clinical samples. *Res Virol* 1997; **148**(3): 225–231.
20 Jackson R, Morris DJ, Cooper RJ, Bailey AS, Klapper PE, Cleator GM *et al*. Multiplex polymerase chain reaction for adenovirus and herpes simplex virus in eye swabs. *J Virol Methods* 1996; **56**(1): 41–48.
21 Morris DJ, Klapper PE, Killough R, Bailey AS, Nelson J, Tullo AB. Prospective study of adenovirus antigen detection in eye swabs by radioimmune dot-blot. *Eye* 1995; **9**: 629–632.
22 Ankers HE, Klapper PE, Cleator GM, Bailey AS, Tullo AB. The role of a rapid diagnostic testing (adenovirus immune dot-blot) in the control of an outbreak of adenovirus type 8 keratoconjunctivitis. *Eye* 1993; (Part 3 Suppl): 15–17.