Human Adenovirus 14a: A New Epidemic Threat

Gregory C. Gray and Margaret L. Chorazy

Center for Emerging Infectious Diseases, Department of Epidemiology, College of Public Health, University of Iowa, Iowa City

(See the articles by Tate et al. and Lewis et al., on pages 1419–26 and 1427–34, respectively.)

The recent much-publicized report *World at Risk* [1] predicts that we are soon to experience a biological or nuclear weapons attack. This issue of the *Journal* contains 2 reports of outbreaks of a new human adenovirus (Ad) type 14 strain [2, 3], which serves to remind us that we are at least equally likely, if not more likely, to soon experience large-scale morbidity through epidemics of emergent pathogens. As was illustrated by the severe acute respiratory syndrome–associated coronavirus, when a ubiquitous nuisance pathogen suddenly becomes more virulent, its reign of destruction needs little help from rogue nations or terrorist cells. Humankind is quite efficient in spreading such pathogens around.

It is likely that the new Ad14 strain entered Oregon in 2005 and apparently spread throughout the state by 2007 [2, 4]. In their retrospective review of clinical and laboratory data (from 1 November 2006 through 31 July 2007), Lewis et al. [2] demonstrate that the new Ad14 variant quickly became a highly prevalent strain, explaining 60% of Ad infections. Of 40 Ad14-positive patients, 76% required hospitalization, 61% merited supplemental oxygen, 47% received critical care, and 18% died. In a comprehensive contemporary epidemiological investigation in Texas, Tate et al. [3] show a similar rapid transmission of Ad14 with high morbidity. They estimate that, of 1147 otherwise healthy young military trainees with febrile respiratory illness in 2007, 551 (48%) were infected with Ad14. Of these Ad14-infected patients, 23 were hospitalized, 4 required admission to an intensive care unit, and 1 died. These transmission and morbidity statistics are consistent with those from the first report of this emergent Ad14 strain [4], when clusters totaling 140 patients with acute Ad14 respiratory disease were noted in Oregon, Texas, and Washington, with 38% being hospitalized, 17% requiring admission to an intensive care unit, and 9 dying.

The 52 human Ad serotypes [5] cause a broad spectrum of clinical illnesses: pharyngoconjunctival fever, keratoconjunctivitis, pneumonia, hemorrhagic cystitis, gastroenteritis, acute respiratory disease, severe disseminated disease, cardiomyopathy, and encephalitis [6]. Populations commonly at risk for adenoviral illness include new military recruits, young children, and especially those who are immunocompromised.

Ad14 (strain deWit) was first isolated from Dutch military recruits with acute respiratory disease in the 1950s and was associated with a few reported outbreaks of acute respiratory disease in Europe and Asia through the 1960s [7–13]. In the United States, Ad14 was only recently identified in military and civilian populations, has most often been associated with sporadic cases rather than outbreaks, and has not been previously associated with severe clinical illness [14, 15]. However, in 2005, Ad14 suddenly became more prevalent in the United States. In our 2004–2007 US National Surveillance for Emerging Adenovirus Infections program (3026 typed isolates in total) [14], we first detected Ad14 strains during March 2005 in Missouri and Arizona, and by April 2007 we had identified 19 Ad14 isolates from 12 different US laboratories. Similarly, Metzgar et al. [15] reported the abrupt emergence of Ad14 in US military populations in March and April 2006. Through further study, we now recognize that these recent Ad14 isolates are virtually identical to the emergent Ad14 genotype first reported to have caused serious illness among patients in New York, Oregon, Texas, and Washington during 2006–2007 [4]. As was described by both Tate et al. [3] and Lewis et al. [2], the Ad14 isolates detected in these outbreaks were identical by sequence data but were different from the Ad14 deWit strain [7]. On the basis of differences in restriction enzyme digestion patterns, Louie et al. [16] designated the new strain Ad14a. This new strain was observed to be associated with severe clinical illness more of-

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Reprints or correspondence: Dr. Gregory C. Gray, Center for Emerging Infectious Diseases, Dept. of Epidemiology, College of Public Health, University of Iowa, 200 Hawkins Dr., C21K GH, Iowa City, IA 52242 (gregory-gray@uiowa.edu).

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ten than the prototype Ad14 deWit strain [4]. Novel Ad strains have been associated with more severe clinical disease and have seemed to have a competitive advantage in their spread [17–21]. Although the genetic differences between the Ad14 deWit and Ad14a strains may account for the observed higher rate of transmission of Ad14a and its associated more-severe morbidity, one can strongly argue that these observations are confounded by a lack of individual and herd immunity to Ad14 [2, 3, 16]. However, another observer might counter that Ad epidemics are not often seen when other rare Ad strains are detected. Virulence studies using cellular and animal models may be necessary to sort this out.

Fortunately, most Ad14a infections do not cause severe illness. Tate et al. [3] found that, of the trainees with serological evidence of acute Ad14a infection, 51% reported afebrile or mild disease, and 9% reported no respiratory symptoms at all. Even so, Ad14a represents an emerging threat in that it seems to cause more-severe disease in some persons, has been implicated in community-based infections [2], and, in at least 1 facility, has demonstrated a propensity to infect hospital staff [22]. Data from reports on Ad14a suggest that risk factors for severe Ad14a disease may include male sex, older age, smoking, and underlying medical conditions, but more comprehensive study is needed [2, 3]. Available reports further suggest that Ad14a illness is mitigated by preexisting immunity [3, 15]. Tate et al. [3] showed that previous natural infection with Ad7 may protect against severe Ad14a illness requiring hospitalization. This is particularly good news for military trainees, given the loss of Ad4 and Ad7 vaccines in 1999 and their expected return to availability soon [23, 24].

It is difficult to determine the geographical distribution of Ad14a infections, given that Ad surveillance is generally passive. Additionally, relatively few laboratories look for Ad, and even fewer can distinguish Ad14 from other Ad types. Through specific reports of Ad14a and our national surveillance program (for which sampling ended in 2007) [14], we know that Ad14a has been detected in Alaska, Arizona, California, Connecticut, Hawaii, Indiana, Missouri, New York, Oregon, Tennessee, Texas, Washington, and Wisconsin. With its propensity for rapid transmission, it seems likely that Ad14a is now circulating throughout the United States and may have been introduced from another country.

How does our knowledge of Ad14a affect future clinical care and public health? Given its association with more-severe disease, when Ad14a is detected in a medical facility, infection-control professionals may choose to employ patient isolation and special precautions to reduce the risk of nosocomial transmission. For patients with severe infections, clinicians, like those in Oregon [2], may be more aggressive in using antiviral therapy. Confronted with Ad14a outbreaks in crowded long-term-care facilities, public health officials may decide to employ nonpharmaceutical interventions [25]. Finally, should Ad14a prove to be a frequent cause of epidemics, those persons at greatest risk might benefit from the possible cross-protection conferred by Ad7 vaccine (although previous indications have included only military personnel).

Lewis et al. [2] described polymerase chain reaction (PCR)–based methods to detect Ad14. Many other serological [5, 26], PCR-based [27], and DNA sequence–based typing methods [14, 28–30] have been used to distinguish the 52 Ad strains. If Ad14 is detected in the United States, it most likely is the new Ad14a strain. However, restriction enzyme digestion analysis or targeted gene sequencing is necessary to confidently distinguish the Ad14a strain from the Ad14 deWit strain [16].

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