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LEARNING OBJECTIVES

After studying the literature presented in this issue, participants should be able to:

- Describe the changing epidemiology of adenovirus type distribution in the United States.
- Assess the impact of the lack of vaccination on the reemergence of adenovirus serotypes and their associated morbidity in US military recruits.

TARGET AUDIENCE

This educational activity is designed for pediatricians, primary care physicians, pediatric and family nurse practitioners, neonatologists, infectious disease specialists, allergists, pulmonologists, immunologists, and other healthcare professionals involved in the care and management of pediatric respiratory patients.

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Some of the drug treatments discussed in this issue may note uses not approved by the Food and Drug Administration. Articles containing such uses will be noted at the end of the article.

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Detecting Prevalence of Adenovirus Types Using the Hexon Gene Sequence Typing Method

Early population-based studies of viral respiratory illness led to the belief that, although common in children, adenovirus infections tended to be relatively mild in nature and self-resolving. In contrast, military populations tended toward more severe adenovirus-based respiratory disease, including pneumonia and encephalitis, with adenovirus types 4, 7, and 21 being the most prevalent. Based on these results, a long-held belief was that adenovirus infection was of little consequence except in military populations.

More recent epidemiologic evidence paints a different picture. In contrast to the limited number of adenovirus types recognized during the early studies, there are now 51 unique known serotypes, many with specific tissue tropisms and wide-ranging clinical manifestations. Furthermore, the emergence of genetic variants with varying geographic distribution and virulence potential has culminated with the association of adenovirus infection with a number of acute and chronic diseases such as chronic airway obstruction and sudden infant perinatal death. In addition, the observation that specific virus types are more likely to respond to certain antiviral therapies

in vitro further underscores the importance of understanding the epidemiology and distribution of adenovirus in the United States.

In an effort to further delineate the prevalence of adenovirus types in the United States, Gray and colleagues utilized the hexon gene sequence typing method to study 2,237 clinical isolate samples obtained from 8 military facilities and 14 civilian medical facilities between 2004 and 2006. Among the 1,608 successfully typed isolates obtained from civilian subjects, the most

prevalent were adenovirus types 3 (34.6%), 2 (24.3%), 1 (17.7%), and 5 (5.3%). Adenovirus types 1 and 2 were more prevalent in children <7 years of age and types 1, 3, and 2 most prevalent in blood, upper respiratory tract, and gastrointestinal tract specimens, respec-

tively. Furthermore, 49.6% of isolates were associated with hospitalization; observations that the authors suggest may reflect the impact of adenovirus infection on morbidity in present-day US medical care facilities. In contrast, distribution of viral types was more limited in the 582 successfully typed military population isolates, with type 4 representing the majority (92.8%), followed by types 3 (2.6%) and

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Disclosures:

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Detecting Prevalence of Adenovirus Types (Continued)

21 (2.4%). Among both populations, there was an increasing trend in the presence of type 21 isolates over the study period. The observation that types 5 and 21 were associated with severe disease was unexpected and warrants further study given their relative rarity in prior studies. Also unexpected was a lack of association of type 7 with severe disease, as was previously predicted. The authors suggest that this finding may reflect a stabilization of circulating adenovirus type 7 in the United States. Results from multivariable risk modeling demonstrated that

age <7 years (odds ratio [OR] 3.2; 95% confidence interval [CI], 1.4-7.4), chronic disease (OR 3.6; 95% CI, 2.6-5.1), having undergone recent transplantation (OR 2.7; 95% CI, 1.3-5.2), and infection with adenovirus type 5 (OR 2.7; 95% CI, 1.5-4.7) or type 21 (OR 7.6; 95% CI, 2.6-22.3) increased the risk of severe disease.

Gray GC, McCarthy T, Lebeck MG, et al. Genotype prevalence and risk factors for severe clinical adenovirus infection, United States 2004-2006. *Clin Infect Dis*. 2007;45(9):1120-1131.

COMMENTARY

JAIME E. FERGIE, MD, Director, Pediatric Infectious Disease, Driscoll Children's Hospital, Corpus Christi, Texas.

The importance of having rapid methods for the determination of adenovirus types was recently highlighted by the emergence of severe respiratory disease caused by adenovirus serotype 14 in different parts of the country. A recent report in the MMWR (November 16, 2007/Vol.56/No.45) described three clusters of 140 patients in Oregon, Washington, and Texas: 53 (38%) were hospitalized, 24 (17%) were admitted to intensive care units, and 9 (5%) died. Cases occurred in military and civilian populations and across different age groups. In this very large study report on epidemiological and clinical features associated with adenovirus infections in the United States, Gray et al discuss a new molecular typing technique. The study was conducted based on a large collaboration between 22 civilian and military medical facilities across the country. This new technique correlated well with serological and other molecular methods for typing human adenovirus. Because most physicians do not send viral cultures from outpatient settings, and most hospital virology laboratories do not type their adenovirus-positive cultures, physicians in clinical practice are not going to see a change in their practices based on this new system. State health departments and the CDC, on the other hand, have great interest in detecting the emergence of new adenovirus types, particularly when they appear to be more pathogenic. It is therefore important for public health reasons that fast and accurate adenovirus typing is developed.

Emergence of Diverse Species B Adenoviruses at US Military Recruit Training Centers

The B (especially B1), C, and E species of human adenovirus are found worldwide and are responsible for outbreaks of respiratory disease and conjunctivitis. A large number of healthy adults lack protective antibodies against the B and E species and, not surprisingly, are more likely to suffer from respiratory disease from these adenovirus types. The species B1 adenovirus, especially serotypes 3 and 7, is responsible for recurring epidemics of febrile acute respiratory disease (ARD) in civilian populations. These serotypes, along with species B1 type 21 and species E type 4, are responsible for ARD epidemics at military recruit training facilities worldwide. Data from US studies demonstrate a significant impact on military trainees in terms of illness from adenovirus infection. US

recruits suffer from 22,000 cases of reported febrile ARD annually, including 15,000 associated with adenovirus infection.

Metzgar and colleagues presented data collected from 2002 to 2006 describing the serotype distributions at 8 training facilities, which form the basis of a US-military-sponsored, population-based ARD surveillance program. This surveillance program was initiated in 1996, coinciding with the loss of vaccine production to adenovirus types 4 and 7, and continued through both the gradual reduction in vaccination from 1997 to 1999 and the subsequent period of no vaccination. In the Metzgar et al study, 1,867 randomly selected clinical ARD samples were typed using antibody neutralization or serotype-specific polymerase chain reaction (PCR).

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Emergence of Diverse Species B (Continued)

The adenovirus species E serotype 4 continued to be a dominant type through 2005, being identified in >95% of the samples collected over the 2002 through 2006 time period. This was followed by the simultaneous emergence of diverse species B serotypes, including the B1 serotypes 3, 7, and 21 as well as the subspecies B2 serotype 14. The B2 serotype 14 virus emerged simultaneously at 5 of the training centers in March and April of 2006. Serotype 14 emerged in coinfections with B1 serotypes and, in 1 case, as part of a triple coinfection with serotypes 4 and 7. Many coinfections containing B1 serotypes were observed, most of which were with the species E serotype 4. The observance of coinfections is important because these environments provide an opportunity for the various adenovirus strains to recombine and potentially generate novel variants. The recognition of coinfection has only

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recently come to light, owing mainly to the advent of new molecular techniques such as PCR typing, which has great sensitivity over the classical immunologic serotyping methods.

These data demonstrate that all the subspecies B1 serotypes previously seen in US training centers have simultaneously reemerged against the background of the species E serotype 4. The emergence of the B2 serotype 14 virus as a significant contributor to ARD is a novel finding. The authors suggest that the simultaneous emergence of several species B serotypes indicates a common external source, most likely the civilian population, and a decrease in the preexisting immunity to the species B virus because of discontinuation of vaccination protocols.

Metzgar D, Osuna M, Kajon AE, et al. Abrupt emergence of diverse species B adenoviruses at US military recruit training centers. *J Infect Dis.* 2007;196(10):1465-1473.

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