Adenoviral Infections in Children: The Impact of Rapid Diagnosis

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ABSTRACT. *Background.* **Adenovirus (ADV) infections were difficult to diagnose in the past, and many infections were unrecognized. Direct fluorescent assay (DFA) for the rapid diagnosis of ADV infection, as part of a viral respiratory panel, became available at Primary Children's Medical Center (Salt Lake City, UT) in December 2000.**

Objective. **To describe children with ADV infection diagnosed by DFA and viral culture and document the impact of rapid ADV testing on patient care.**

Methods. **DFA testing for respiratory viruses including ADV was performed on nasal wash specimens with parallel viral culture. Chart review was performed for all ADV-positive patients identified from microbiology records between December 2000 and May 2002.**

Results. **Of 1901 patients positive for respiratory viruses, 143 (7.5%) were ADV-positive by DFA or culture. The mean age of ADV-positive children was 23 months; 90% were ≤60 months old. Eighty percent were previously healthy, and 56% required admission with a mean length of stay of 3.4 days. The most common diagnoses included fever (31%), bronchiolitis (24%), and pneumonia (14%). Other conditions included suspected Kawasaki disease (KD) and hepatitis. Forty-six percent of ADV-positive children were given antibiotics at presentation, but only 2 (1.4%) had documented bacterial infection (one had *Escherichia coli* urinary tract infection and one had *Moraxella catarrhalis* bacteremia). Thirty-six percent of children had a change in management based on positive ADV DFA. In children with suspected KD ($n = 5$), 100% had positive ADV DFA, and immune globulin was withheld in 4. One immunocompetent patient with fulminant liver failure received cidofovir treatment after a positive ADV DFA and recovered before liver transplant.**

Conclusions. **ADV is a common infection in young children and often results in admission and unnecessary antibiotic therapy. Identifying ADV as the cause of illness can favorably impact care and in some instances may be life-saving. DFA testing for ADV should be considered for infants and children requiring admission for fever, respiratory illness, suspected KD, and hepatitis.** *Pediatrics* **2004;113:e51–e56. URL: http://www.pediatrics.org/cgi/content/full/113/1/e51; *adenovirus, rapid diagnosis, Kawasaki disease.***

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Received for publication Jul 14, 2003; accepted Sep 18, 2003.

Portions of these data were presented at the Pediatric Academic Societies Annual Meeting, May 3, 2003, Seattle, WA.

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ABBREVIATIONS. ADV, adenovirus; PCMC, Primary Children's Medical Center; DFA, direct fluorescent assay; ED, emergency department; RSV, respiratory syncytial virus; KD, Kawasaki disease; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; IVIG, intravenous immune globulin.

Adenovirus (ADV) is a well-known cause of respiratory illness in children.[1–4] It may produce upper or lower respiratory infection including bronchiolitis and pneumonia.[5] In addition, ADV infection is frequently associated with entities such as pharyngoconjunctival fever and epidemic conjunctivitis that are often diagnosed based on clinical examination alone.[6] Although most infections are self-limited, ADV can be associated with severe or lethal infection in both immunocompromised and healthy individuals.[7–10]

In clinical practice, ADV may be underdiagnosed. Isolation of ADV from cell culture is quite sensitive, but results take several days, limiting clinical utility.[6] At Primary Children's Medical Center (PCMC), in Salt Lake City, UT, rapid testing for ADV became available in December 2000 as part of a 7-valent viral respiratory direct fluorescent assay (DFA) panel (SimulFluor Respiratory Screen, Light Diagnostics, Temecula, CA). This test provides results in several hours. The purpose of our study was to describe the spectrum of illness in children with ADV infection and investigate the impact of rapid ADV testing on patient care. We hypothesized that ADV infections would be relatively common and that a positive DFA result would impact patient care.

METHODS

Approval to conduct this research was obtained from the University of Utah Institutional Review Board.

Setting

The study was conducted at PCMC, a 232-bed children's hospital that serves as a community hospital for Salt Lake County, UT, and as a tertiary referral center for the intermountain west. The emergency department (ED) evaluates 33 000 children per year, and there are ~10 000 admissions to the hospital each year. PCMC cares for the majority of chronically ill children in the state; this population may be overrepresented in the data but is likely similar to the populations cared for in other children's hospitals.

Viral Testing

No protocols were in place during the study period that would dictate which children had DFA testing. Testing for respiratory viruses was performed at the discretion of the attending physician. In general, DFA testing was routinely requested for infants <90 days old with fever and for infants and children with acute respiratory illness who presented to the PCMC ED. The patient charge for DFA testing was $32.

TABLE 1. Sensitivity, Specificity, and Positive and Negative Predictive Value of the DFA Assay at PCMC Based on 1188 Specimens

Component	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Completete DFA	86.7	93.8	87.9	93.1
ADV	62.5	100	100	93.8
Influenza A	80	98.6	85	99.6
Influenza B	67.4	100	100	98
Parainfluenza 1, 2, or 3	88.5	99.7	96.4	98.9
RSV	93.8	95.6	87	98

The clinical microbiology technicians at PCMC performed testing for respiratory viruses in a 2-step process. Each nasal wash sample collected between December 12, 2000 and September 10, 2001 was prepared by cytospin and tested by using the SimulFluor Respiratory Screen (Chemicon International, Temecula, CA) followed by SimulFluor FluA/FluB and SimulFluor Para 1,2,3/Adeno stains if the screen was positive. The DFA panel identifies respiratory syncytial virus (RSV), influenza viruses A and B, parainfluenza viruses 1, 2, and 3, and ADV. The test was performed 3 to 5 times daily depending on the season. After DFA testing, viral respiratory culture using 4 shell vials with 72-hour and 10-day exit stains was performed on all specimens. Beginning September 11, 2001, viral culture was offered only for DFA-negative specimens and for those positive for parainfluenza virus to document serotype. Using viral culture positivity as the gold standard, we analyzed the sensitivity, specificity, and negative and positive predictive values for the DFA test based on 1188 specimens obtained in the first period of the study.

Review of Medical Records

To review the characteristics of ADV infection in children, we queried the microbiology records for patients who tested positive by DFA or culture for ADV between December 12, 2000 and May 23, 2002. The records were reviewed, and data abstracted included demographic and clinical information for children with ADV infection and the impact of rapid viral testing on patient care.

RESULTS

Viral Testing

During the 17-month study period, viral testing was performed on 4568 nasal wash specimens; 1901 (42%) were positive for respiratory viruses. Test performance results for rapid DFA testing are shown in Table 1. Of the 1901 patients with positive specimens, 143 (7.5%) were identified with ADV. The DFA test was positive for >1 virus in 5/143 children (3%); all had coinfections with ADV and RSV. In all cases we counted them as ADV-infected; 3 children had bronchiolitis, 1 had fever, and 1 had dehydration.

Of the ADV-positive patients, 89 (62%) were identified by DFA, and viral culture identified the remainder. In a subset of 17 patients with severe or life-threatening disease, the DFA was positive in 88% ($P = .03$ compared with 62% of all patients with ADV infection). The mean time to DFA results was 4 hours, and the mean time to positive viral culture was 9 days (range: 4–16 days)

Epidemiology and Patient Characteristics

ADV infections were identified during nearly all study months (Fig. 1). The frequency peaked between January and March 2002. Demographic characteristics of ADV-infected patients are shown in Table 2. The mean age of the ADV-positive patients was 23 months, and 90% were ≤60 months old. Twenty percent of patients had chronic illnesses including history of prematurity; cerebral palsy; congenital heart disease; genetic conditions including cystic fibrosis, CHARGE, and DiGeorge syndromes; and malignancy. Of patients with ADV infection,

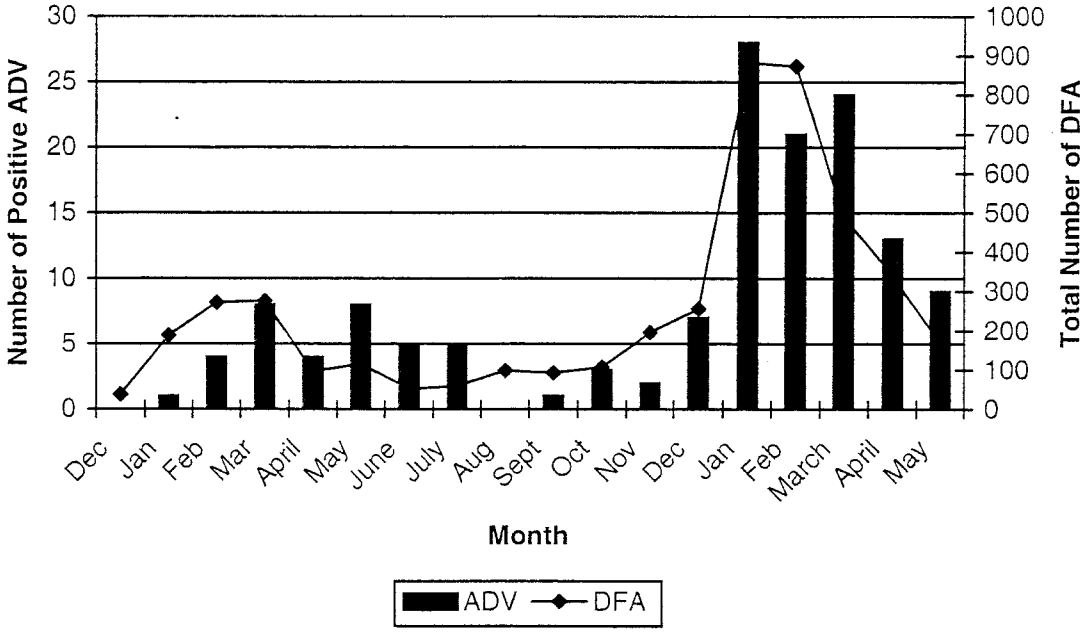

Fig 1. Seasonal distribution of ADV-positive DFA samples compared with total DFA samples.

TABLE 2. Demographic and Clinical Information for ADV-Positive Infants and Children

Variable	*N* (%)
Mean age	23 mo (18 d–21 y)
Male	80 (56)
Previously healthy	114 (80)
Required hospitalization	80 (56)
ED admitting diagnosis (%)	
Fever	44 (31)
Bronchiolitis	34 (24)
Pneumonia	20 (14)
Respiratory distress	9 (6)
Sinusitis, otitis media	8 (6)
Vomiting/diarrhea/dehydration	7 (5)
Suspected KD	5 (3.5)
Reactive airways	3 (2)
Arrythmia	3 (2)
Seizure	2 (1)
Meningitis	2 (1)
Hepatitis	1 (<1)
Other	5 (3.5)

56% required hospitalization with a mean length of stay of 3.4 days. Children with chronic conditions required admission more frequently than those without underlying illness (83% vs 50%; $P = .028$).

Clinical Features of ADV Infection (Table 2)

Fever and Respiratory Illness

Fever was present in 80% of the 143 patients and was the admitting diagnosis in 31%. Seventy-seven patients had fever documented in the hospital with a mean temperature of 39.6°C. Fever duration at the time of discharge from the hospital ranged from 0 to 21 days with a mean duration of 2.7 days. Other clinical signs, such as conjunctivitis and rash, commonly associated with ADV infection were infrequent in our patient population. Conjunctivitis was present in 25 patients (17%), and rash was noted in 10 patients (7%).

The majority of patients presented with respiratory conditions. The most common diagnoses were bronchiolitis (24%) and pneumonia (14%). A chest radiograph was performed for 82 patients (57%). Abnormalities were diagnosed in 51 patients (62%), including perihilar infiltrates or atelectasis in 30 (36%) and a focal infiltrate consistent with pneumonia in 21 (26%). More than one-quarter (27%) of children had a new oxygen requirement. The duration of oxygen requirement among patients without a previous need ranged from 1 to 11 days with a mean of 4 days. Of patients with a new oxygen requirement, 14 (36%) were discharged with home oxygen. Four patients (2.8%) required endotracheal intubation and mechanical ventilation for respiratory failure associated with ADV infection. One of the 4 had an underlying condition of prematurity; the remainder had been previously healthy. The duration of mechanical ventilation ranged from 1 to 7 days.

Other Conditions

Suspected Kawasaki Disease

Five patients with documented ADV infection presented to the hospital with suspicion of Kawasaki disease (KD) (Table 3). Their mean age was 51 months. Two fulfilled all clinical criteria for the diagnosis of KD. All had elevated inflammatory markers; 3 had an erythrocyte sedimentation rate (ESR) of >60 mm/hour and a C-reactive protein (CRP) of >4 mg/dL. However, platelet counts were normal in 4 children and only modestly elevated in 1 child. All 5 children had positive DFA results, and intravenous immune globulin (IVIG) was withheld in 4. The child who received IVIG did not have the DFA test until after the infusion of IVIG was initiated. This same patient had a normal echocardiogram and was discharged from the hospital immediately after the positive ADV result was obtained.

Hepatitis

One immunocompetent patient presented with fulminant hepatic failure, pancreatitis, and encephalopathy. The patient also had a new oxygen requirement, and basilar pneumonia was evident on chest radiograph. Prothrombin time and ammonia were elevated; transaminases peaked at >5000 IU. An evaluation for liver transplantation was initiated. A nasal wash specimen obtained on the first day of hospitalization was DFA-positive for ADV. Diagnostic testing for hepatitis A, B, and C, and Epstein-Barr virus, cytomegalovirus, and herpesviruses was negative. The patient was treated with cidofovir, responded to this treatment, and recovered without transplantation.

TABLE 3. Clinical and Laboratory Findings of Children With Suspected KD

Patient (age in mo)	Clinical	Laboratory	DFA	IVIG	Echocardiogram
1 (42)	Fever (6 d), conjunctivitis, cracked lips, strawberry tongue	ESR: 60 CRP: 12.9 Platelets: 330 000/mm^3	Positive	No	Not done
2 (48)	Fever (5 d), conjunctivitis, swollen hands and feet, lymphadenopathy, rash	ESR: 28 CRP: 7.6 Platelets: 240 000/mm^3	Positive	No	Not done
3 (81)	Fever (8 d), conjunctivitis, swollen hands and feet, lymphadenopathy, rash, cracked lips	ESR: 66 CRP: 4.1 Platelets: 468 000/mm^3	Positive	Yes	Normal
4 (28)	Fever (6 d), conjunctivitis, cracked lips, strawberry tongue, rash	ESR: 60 Platelets: 295 000/mm^3	Positive	No	Not done
5 (55)	Fever (6 d), conjunctivitis, lymphadenopathy	ESR: 16 Platelets: 218 000/mm^3	Positive	No	Not done

Patient Management

Because of the presence of fever, many of the ADV-positive patients were evaluated for infection with bacterial cultures of blood, urine, and cerebral spinal fluid. Seventy-three (51%) patients had at least 1 bacterial culture. Two children (1.4%) had a culture-confirmed bacterial infection. The dual infections included an *Escherichia coli* urinary tract infection in an 11-month-old and bacteremia with *Moraxella catarrhalis* in a 22-month-old.

Antibiotics were commonly given to patients with ADV infection. At presentation to the ED, 33% of the patients were receiving oral antibiotics for their illness. After evaluation in the ED, 46% received antibiotics, with intravenous antibiotics used most frequently.

The positive ADV DFA resulted in documented changes in clinical care for 51 patients (36%). The most common changes in management were the discontinuation of antibiotics and/or discharge of the patient from the hospital ($n = 39$). A positive DFA also changed management in 4 of the 5 children with suspected KD. Finally, in the patient with fulminant hepatitis, the positive ADV result may have been life-saving, because antiviral therapy was initiated based on a positive DFA.

DISCUSSION

In this study, ADV infection was documented in 7.5% of children with a positive DFA test for respiratory viruses. This is similar to earlier studies that have documented ADV as a cause of ~7% to 8% of pediatric respiratory infections.[4,11] The mean age of patients in our study was 23 months, and 90% of patients were ≤60 months old. This is consistent with previous studies that reported very few cases of school-aged children requiring hospital evaluation for ADV.[2] As expected, the seasonal distribution showed a wintertime peak, but illness occurred year-round.[4,12,13] Although the majority of ADV infections resulted in respiratory illness, nearly 20% of the children had nonrespiratory diagnoses. Unique findings in this study include documentation of the serious nature of ADV infections in previously healthy children and the impact early diagnosis can have on patient management.

To be useful clinically, viral diagnostic testing must be sensitive, timely, affordable, able to detect a range of pathogens, and influence clinical decision-making. The DFA test used in this study begins to meet these requirements. Although the sensitivity of the DFA for ADV was not optimal (63%) despite using nasal washes, there are still many benefits to recommending this type of testing. In our laboratory, the results were very timely, with positive results available, on average, 4 hours after testing. Moreover, ADV testing is part of a panel that includes other common pediatric pathogens, and the sensitivities for RSV, influenza A and B, and parainfluenza are greater than that of ADV (Table 1).[14] The test is inexpensive and reproducible. We have been able to show that ADV testing as well as the complete DFA panel influence the decision to administer antibiotics and improve antibiotic stewardship in the hospital setting.[15] Although based on modest numbers, the DFA was positive in 88% of patients with severe or life-threatening disease, suggesting that it is more sensitive among those most likely to benefit by early diagnosis and antiviral therapy. Testing multiple specimens might improve the test sensitivity, but we have not formally evaluated this approach. In the future, the polymerase chain reaction may offer a more sensitive alternative to DFA testing.[16,17]

Half of the previously healthy children with ADV infection and 83% of those with underlying conditions required hospitalization. The primary reason for admission was respiratory distress or hypoxia. Over a quarter of the children had a new oxygen requirement. This finding, along with the occasional severe illness seen in normal hosts[10] as well as life-threatening disease in the immunocompromised[18,19] highlights the clinical importance of ADV disease in children.

One significant finding in our study was that 5 children were admitted with suspected KD. All had prolonged fever and conjunctivitis; 4 of 5 had rash and elevated CRP and/or ESR, 3 had mucous membrane changes and 3 had lymphadenopathy, and 2 had swelling of the hands and feet. Thus ADV infection can be a convincing imitator of KD. Others have documented that ADV infection, in contrast to what is seen in other viral illnesses, typically elevates ESR and CRP.[20,21] Barone et al[20] compared 7 children with ADV infection initially suspected of having KD with 36 children with KD. They found substantial overlap between the 2 groups, but exudative conjunctivitis was more common in ADV infection, and perineal rash or peeling and higher platelet counts helped to identify KD.[20]

Isolated reports have noted individuals believed to have both KD and ADV,[22,23] and some have hypothesized that DNA viruses may be triggers of KD.[24] However, at this time ADV is not believed to be the cause of KD, and it is one of the viruses that should be excluded before the diagnosis of KD is made.[25]

It seems prudent to test all patients suspected of having KD for ADV infection. During the study period 41 children were diagnosed with KD at our institution, but not all had testing for ADV. If we include the patients described in this article, children with ADV disease accounted for at least 10% of those with suspected KD. Positive DFA results for ADV could help to exclude KD, especially in immunocompetent children. This could avoid unnecessary, expensive, and potentially harmful treatment for KD.[26–29] In addition, the prospective study of ADV infection in children with suspected KD could help clarify important issues such as how often ADV and KD occur together, whether asymptomatic shedding of ADV occurs in children with KD, and which serotypes of ADV mimic KD.

Fulminant hepatitis is a known complication of ADV infection in preterm infants, children with disseminated disease, and in the immunocompromised[7,18,30–32] and has a high mortality rate. One patient in this study had fulminant ADV hepatitis. The availability of a rapid test for ADV allowed for

initiation of antiviral therapy with cidofovir on day 1 of hospitalization. Despite advanced liver failure, the patient recovered without liver transplantation, although the role of cidofovir is unclear. The availability of antiviral agents with activity against ADV increases the importance of rapidly establishing the diagnosis of ADV, especially in children with life-threatening disease.[19,33,34]

We could clearly document a change in management for 50 additional patients (36%) based on the diagnosis of ADV despite the retrospective nature of the study. The most common change in management we observed was the discontinuation of antibiotics as a result of the diagnosis of ADV. Other changes included hospital discharge and, as discussed previously, the withholding of IVIG in patients with suspected KD. Possibly, ADV DFA testing had a greater impact than could be documented by this study. Frequently patients were discharged from the ED shortly after the nasal wash sample was obtained with the expectation that the primary care physician would use the results in the outpatient setting.

This study has several limitations. First, all the ADV testing was performed in a hospital setting and may overestimate the serious nature of ADV infections in children. Second, ADV testing was performed primarily in children with respiratory symptoms. Children with ADV disease, especially gastrointestinal disease, may have been missed. Third, ADV infections may have been missed in the second year of the study if children had positive DFA testing for another respiratory virus and no back-up culture was performed. Fourth, typing of ADV isolates was not performed, so we cannot comment on clinical entities associated with individual ADV types. Fifth, long-term follow-up of children with suspected KD who did not receive IVIG therapy was not performed. Finally, we were limited by our lack of access to outpatient records for patients discharged from the ED before the diagnosis of ADV.

Despite these limitations, our data lead to several conclusions. First, ADV infection remains a common cause of pediatric illness. Although most infections are self-limited, ADV can cause serious infection in previously healthy children and often results in hospitalization. ADV can mimic bacterial infection and KD. DFA testing is a reasonably sensitive and timely way to detect ADV infection. Identifying ADV infection can affect care favorably and in some cases may be life-saving. Consequently, DFA testing for ADV—or other rapid, sensitive tests—should be strongly considered for infants and children requiring admission for fever, respiratory illness, suspected KD, and hepatitis.

ACKNOWLEDGMENT

Dr Byington was supported by the Robert Wood Johnson Generalist Physician Faculty Scholar Program.

REFERENCES

1. Pacini DL, Collier AM, Henderson FW. Adenovirus infections and respiratory illnesses in children in group day care. *J Infect Dis*. 1987;156:920–927
2. Loda FA, Clyde WA Jr, Glezen WP, Senior RJ, Sheaffer CI, Denny FW Jr. Studies on the role of viruses, bacteria, and *M. pneumoniae* as causes of lower respiratory tract infections in children. *J Pediatr*. 1968;72:161–176
3. Larranaga C, Kajon A, Villagra E, Avendano LF. Adenovirus surveillance on children hospitalized for acute lower respiratory infections in Chile (1988–1996). *J Med Virol*. 2000;60:342–346
4. Edwards KM, Thompson J, Paolini J, Wright PF. Adenovirus infections in young children. *Pediatrics*. 1985;76:420–424
5. Hong JY, Lee HJ, Piedra PA, et al. Lower respiratory tract infections due to adenovirus in hospitalized Korean children: epidemiology, clinical features, and prognosis. *Clin Infect Dis*. 2001;32:1423–1429
6. Demmler G. Adenoviruses. In: Long S, Pickering L, Prober C, eds. *Principles and Practice of Pediatric Infectious Diseases*. Vol. 1. Philadelphia, PA: Churchill Livingstone; 2003:1076–1080
7. Munoz FM, Piedra PA, Demmler GJ. Disseminated adenovirus disease in immunocompromised and immunocompetent children. *Clin Infect Dis*. 1998;27:1194–1200
8. Pichler MN, Reichenbach J, Schmidt H, Herrmann G, Zielen S. Severe adenovirus bronchiolitis in children. *Acta Paediatr*. 2000;89:1387–1389
9. Civilian outbreak of adenovirus acute respiratory disease—South Dakota, 1997. *MMWR Morb Mortal Wkly Rep*. 1998;47:567–570
10. Two fatal cases of adenovirus-related illness in previously healthy young adults—Illinois, 2000. *MMWR Morb Mortal Wkly Rep*. 2001;50:553–555
11. Brandt CD, Kim HW, Vargosko AJ, et al. Infections in 18,000 infants and children in a controlled study of respiratory tract disease. I. Adenovirus pathogenicity in relation to serologic type and illness syndrome. *Am J Epidemiol*. 1969;90:484–500
12. Maletzky AJ, Cooney MK, Luce R, Kenny GE, Grayston JT. Epidemiology of viral and mycoplasmal agents associated with childhood lower respiratory illness in a civilian population. *J Pediatr*. 1971;78:407–414
13. Glezen WP, Loda FA, Clyde WA Jr, et al. Epidemiologic patterns of acute lower respiratory disease of children in a pediatric group practice. *J Pediatr*. 1971;78:397–406
14. Respiratory Virus Activity Summary. Available at: http://www.ped.med.utah.edu/GeneralInfo/InfDis_files/ID.htm. Accessed September 11, 2003
15. Byington CL, Castillo H, Gerber K, et al. The effect of rapid respiratory viral diagnostic testing on antibiotic use in a children's hospital. *Arch Pediatr Adolesc Med*. 2002;156:1230–1234
16. Osiowy C. Direct detection of respiratory syncytial virus, parainfluenza virus, and adenovirus in clinical respiratory specimens by a multiplex reverse transcription-PCR assay. *J Clin Microbiol*. 1998;36:3149–3154
17. Avellon A, Perez P, Aguilar JC, Lejarazu R, Echevarria JE. Rapid and sensitive diagnosis of human adenovirus infections by a generic polymerase chain reaction. *J Virol Methods*. 2001;92:113–120
18. Krilov LR, Rubin LG, Frogel M, et al. Disseminated adenovirus infection with hepatic necrosis in patients with human immunodeficiency virus infection and other immunodeficiency states. *Rev Infect Dis*. 1990;12:303–307
19. Legrand F, Berrebi D, Houhou N, et al. Early diagnosis of adenovirus infection and treatment with cidofovir after bone marrow transplantation in children. *Bone Marrow Transplant*. 2001;27:621–626
20. Barone SR, Pontrelli LR, Krilov LR. The differentiation of classic Kawasaki disease, atypical Kawasaki disease, and acute adenoviral infection: use of clinical features and a rapid direct fluorescent antigen test. *Arch Pediatr Adolesc Med*. 2000;154:453–456
21. Appenzeller C, Ammann RA, Duppenthaler A, Gorgievski-Hrisoho M, Aebi C. Serum C-reactive protein in children with adenovirus infection. *Swiss Med Wkly*. 2002;132:345–350
22. Embil JA, McFarlane ES, Murphy DM, Krause VW, Stewart HB. Adenovirus type 2 isolated from a patient with fatal Kawasaki disease. *Can Med Assoc J*. 1985;132:1400
23. Okano M, Thiele GM, Sakiyama Y, Matsumoto S, Purtilo DT. Adenovirus infection in patients with Kawasaki disease. *J Med Virol*. 1990;32:53–57
24. Shingadia D, Bose A, Booy R. Could a herpesvirus be the cause of Kawasaki disease? *Lancet Infect Dis*. 2002;2:310–313
25. Dajani AS, Taubert KA, Gerber MA, et al. Diagnosis and therapy of Kawasaki disease in children. *Circulation*. 1993;87:1776–1780
26. Bresee JS, Mast EE, Coleman PJ, et al. Hepatitis C virus infection associated with administration of intravenous immune globulin. A cohort study. *JAMA*. 1996;276:1563–1567
27. Berger A, Scharrer I, Doerr HW, Hess G, Weber B. Infection with hepatitis G virus in immunoglobulin recipients. *Lancet*. 1997;349:207
28. Lefrere JJ, Ravera N, Corbi C, Mariotti M, Loiseau P. Infection with hepatitis G virus in immunoglobulin recipients. *Lancet*. 1997;349:206

29. American Academy of Pediatrics, Committee on Infectious Diseases. Aspirin and Reye syndrome. *Pediatrics*. 1982;69:810–812
30. Kim YJ, Schmidt NJ, Mirkovic RR. Isolation of an intermediate type of adenovirus from a child with fulminant hepatitis. *J Infect Dis*. 1985;152:844
31. Wang WH, Wang HL. Fulminant adenovirus hepatitis following bone marrow transplantation. A case report and brief review of the literature. *Arch Pathol Lab Med*. 2003;127:e246–e248
32. Michaels MG, Green M, Wald ER, Starzl TE. Adenovirus infection in pediatric liver transplant recipients. *J Infect Dis*. 1992;165:170–174
33. Carter BA, Karpen SJ, Quiros-Tejeira RE, et al. Intravenous Cidofovir therapy for disseminated adenovirus in a pediatric liver transplant recipient. *Transplantation*. 2002;74:1050–1052
34. Gavin PJ, Katz BZ. Intravenous ribavirin treatment for severe adenovirus disease in immunocompromised children. *Pediatrics*. 2002;110(1). Available at: http://www.pediatrics.org/cgi/content/full/110/1/e9

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Pediatrics 2004;113;e51
DOI: 10.1542/peds.113.1.e51

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