

Neonatal Adenoviral Infection: A Seventeen Year Experience and Review of the Literature

Andrea Ronchi, MD^{1,4}, Christopher Doern, PhD^{2,3}, Evangeline Brock, MT^{2,3}, Lorenza Pagni, MD⁴, and Pablo J. Sánchez, MD¹

Objectives To describe the clinical manifestations and short-term outcomes of adenoviral infections in neonates and review all published cases to better determine impact and treatment outcomes.

Study design Retrospective cohort study of all neonates hospitalized at Children's Medical Center (CMC) and Parkland Memorial Hospital (PMH), Dallas, TX with laboratory-confirmed adenoviral infection from January 1, 1995-December 31, 2012. Neonates were identified by review of the CMC Virology Laboratory's prospective database of all positive adenovirus tests performed in the inpatient and ambulatory settings, and at PMH, of a prospective neonatal database that included all neonatal intensive care unit admissions. Patients also were identified by discharge *International Classification of Disease, 9th edition* codes for adenoviral infection. The medical records were reviewed, and a review of the English literature was performed.

Results During 17 years, 26 neonates had adenoviral infection (25, CMC; 1, PMH). The principle reasons for hospitalization were respiratory signs (88%) and temperature instability (65%). Five (19%) had disseminated disease and 4 (80%) of these infants died. Ribavirin or cidofovir treatment, as well as immune globulin intravenous, did not improve outcomes except in 1 neonate. Literature review (n = 72) combined with our data found that disseminated infection was associated with death (68% vs 21% with localized infection, $P < .001$). In addition, neonates <14 days of age were more likely to have disseminated disease (44% vs 12%, $P = .004$) and death (48% vs 8%; $P < .001$).

Conclusion Adenoviral infection in hospitalized neonates was associated with severe morbidity and mortality, especially when infection was disseminated and involved the respiratory tract. Development of new therapeutic strategies is needed. (*J Pediatr* 2014;164:529-35).

Adenoviruses comprise at least 55 distinct serotypes that are subdivided into seven species (A through G) that have been implicated in human disease.^{1,2} Although adenoviruses can cause infection in people of all ages, more than 80% of infections occur among children younger than 4 years of age. Typically, a self-limited disease mostly involving the respiratory and gastrointestinal tracts of immunocompetent individuals, adenoviruses can cause severe localized and disseminated disease and even death in immunocompromised hosts.^{3,4}

In neonates, adenovirus infections are infrequent, and the few published reports have shown a mortality rate that exceeds 50% for pneumonia⁴ and 85% for disseminated disease.⁵⁻⁸ With improved techniques for viral diagnosis, such as polymerase chain reaction (PCR) testing and emerging antiviral therapies, such as cidofovir, adenoviral infections may be detected more often in neonates and consideration given to antiviral treatment. We sought to describe our experience with adenoviral infections in neonates hospitalized at Children's Medical Center (CMC) and Parkland Memorial Hospital (PMH) in Dallas, TX, and compare data with previously published cases to better understand the impact of adenoviral infections in neonates and to target a patient population for potential trials of therapeutic agents.

Methods

This was a retrospective cohort study of all neonates who were hospitalized at CMC or PMH with laboratory-confirmed adenoviral infection from January 1, 1995-December 31, 2012. Eligible study subjects were identified by review of CMC virology laboratory's prospective database of all positive adenovirus tests performed in

CMC	Children's Medical Center
CSF	Cerebrospinal fluid
DFA	Direct fluorescent antibody
ECMO	Extracorporeal membrane oxygenation
ICD-9	<i>International Classification of Disease, 9th edition</i>
IGIV	Immune globulin intravenous
IV	Intravenous
NICU	Neonatal intensive care unit
PCR	Polymerase chain reaction
PMH	Parkland Memorial Hospital

From the Departments of ¹Pediatrics and ²Pathology, University of Texas Southwestern Medical Center; ³Children's Medical Center, Dallas, TX; and ⁴Neonatal Intensive Care Unit, Department of Clinical Sciences and Community Health, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy

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the inpatient and ambulatory settings, and at PMH, of a prospective neonatal database that included all admissions to the PMH neonatal intensive care unit (NICU). In addition, eligible patients also were identified by discharge *International Classification of Disease, 9th edition* (ICD-9) codes for adenovirus infection (008.62-079.0-049.1-480.0).

All hospitalized neonates whose illness began at ≤ 28 days of age were enrolled. Their medical records were reviewed and pertinent demographic, clinical, and laboratory data were recorded. The study was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center.

Neonates were infants aged 28 days or less. Hypothermia was defined as axillary temperature $\leq 36^{\circ}\text{C}$,⁹ and fever $\geq 38^{\circ}\text{C}$.¹⁰ Respiratory signs suggestive of infection included rhinorrhea, nasal congestion, cough, tachypnea (>60 breaths per minute), retractions or hypoxia (oxygen saturation $<90\%$). The diagnosis of bacterial pneumonia was based on clinical findings and included fever (temperature $>38^{\circ}\text{C}$), tachypnea, abnormal chest radiograph, and receipt of course of antibiotic therapy for ≥ 7 days.¹¹ Tachycardia was ≥ 180 beats per minute and hypotension was blood pressure below the fifth percentile for the age of the neonate at the time of the evaluation and with provision of vasopressor therapy.¹² Hepatitis was defined as elevated serum alanine aminotransferase ≥ 50 U/mL or direct bilirubin ≥ 2 mg/dL with no other etiology identified by the clinical provider. Anemia was a hematocrit $<40\%$ at 0-7 days of age, $<35\%$ at 8-14 days, and <30 at 15-28 days.¹³ Neutropenia was a neutrophil count <1500 cells/mm³, and lymphopenia was <3000 cells/mm³.¹⁴ Thrombocytopenia was $<100\,000/\text{mm}^3$.¹⁵ Coagulopathy was defined as elevated prothrombin time beyond 15.3 seconds, activated partial thromboplastin time >35.2 seconds, fibrinogen <409 mg/dL, or D-dimer >0.5 . Infection was considered localized if there was involvement of only 1 body site or organ, without detection of any clinical or laboratory abnormality of another organ system. Disseminated infection was defined as clinical or laboratory involvement of 2 or more organs, or 1 body site or organ and a positive PCR or culture of blood or cerebrospinal fluid (CSF).

Detection of adenovirus infection was performed by testing relevant clinical specimens since 1995 by direct fluorescent antibody (DFA) test or culture, and since 2008, by PCR (PLx Multi-Code Respiratory Virus Panel [Eragen Biosciences, Inc, Madison, Wisconsin], 2008-2010; xTag Respiratory Vital Panel [Luminex Corporation, Austin, Texas], 2010-2012), performed at CMC or University of Texas Southwestern Virology Laboratory. Quantitative real-time adenovirus PCR (ViraCor Laboratories, Kansas City, Missouri) has been performed on blood and CSF since 2009.

A literature review of neonatal adenovirus infection was performed utilizing [PubMed.gov](http://pubmed.gov) and searching the following key and matching words: adenovirus, adenoviral infection, neonate, viral infection and neonate, cidofovir, and ribavirin. Only English language articles were included in the review of the literature. In addition, the references of previously published articles on adenovirus infections were reviewed.

Statistical Analyses

Data were collected on Excel spreadsheet (Microsoft, Redmond, Washington). Statistical analysis was performed using Sigma Plot 11.0 (SPSS Inc, Chicago, Illinois) and GraphPad Software (GraphPad Corp, San Diego, California). Median and mean with SD and 95% CI of proportions were calculated and used to summarize patient demographics and characteristics. Data were analyzed for relevant trends and associations using Student *t* test, Fisher exact test, or χ^2 test where appropriate and Mann-Whitney test with a *P* value $<.05$ considered to be significant.

Results

During the 17-year study period, 311 children had a positive adenoviral test at CMC, one of whom also was included in the PMH NICU database. No additional neonate was identified from ICD-9 codes. Of the 311 children, 26 (8%) were hospitalized neonates (CMC, 25; PMH, 1) and formed the study population. The majority of the 26 mothers were Hispanic (**Table I**), and none was infected with the human immunodeficiency virus, although infection status of 1 mother was not known. None had a documented adenoviral infection either during pregnancy or at delivery, although 2 had intrapartum fever and another was afebrile but had fatigue, headache, abdominal pain with vomiting, diarrhea, and elevated hepatic enzymes. Their neonates developed signs of infection at ages 7, 17, and 17 days, respectively, and they had no other known sick contacts before admission to CMC. Only the 7-day-old male developed disseminated adenoviral infection, which was diagnosed by positive nasopharyngeal respiratory viral PCR, followed by positive bronchoalveolar lavage DFA and PCR, and manifested by pneumonia and hepatitis with hypothermia, apnea, nasal congestion, tachypnea, cyanosis, poor feeding with emesis, hypotension, neutropenia, hematuria, and hypotonia. The infant had a positive adenoviral blood PCR test (5.6×10^{10} copies/mL) and received acyclovir for possible neonatal herpes infection, followed by cidofovir combined with probenecid for 7 days, as well as 2 doses of immune globulin intravenous (IGIV). The patient required extracorporeal membrane oxygenation (ECMO) and died 16 days later. Autopsy confirmed disseminated adenoviral infection by histopathology and viral culture, and review of the mother's placenta from PMH showed histologic chorioamnionitis.

The 26 neonates (61%, male) had onset of clinical signs of infection at a mean age of 16 ± 8.4 days (range, 3-28) and median duration of hospitalization was 3.5 days (**Table I**). Only 2 (8%) neonates had underlying medical conditions: 1 was premature (34 weeks' gestation) and his toddler sibling had an upper respiratory tract infection while visiting him, and the other had congenital heart disease with coarctation of the aorta and ventricular septal defect. These were the only neonates who acquired the infection while in the hospital. Fifteen (58%) neonates had household contacts (4 of whom were the mothers) with

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