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Serious and Lethal Respiratory Tract Infections of Viral Etiology in Children

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Viruses may lead to serious and lethal pulmonary infections in immunocompetent and immunocompromised children. Series of children with acute respiratory distress syndrome and series of children requiring extracorporeal membrane oxygenation, as well as reported series of nosocomial viral illness, offer an insight into the extent of serious viral disease documented in the medical literature. Series of children with specific viral respiratory illness also will be reviewed, as will the means of diagnosis in these groups of patients.

Viral pneumonia is a well-recognized disease in immunocompetent[1-4] and immunocompromised[5-8] pediatric patients. The frequent mode of transmission is by droplet spread, aerosol, or direct contact after a close encounter with an infected individual. Most viruses cause pneumonia by spread from the upper to lower respiratory tract, except for cytomegalovirus (CMV), which is spread locally, and herpesviruses, which are spread hematogenously.[9] Respiratory syncytial virus (RSV), parainfluenza virus, and influenza viruses A and B are the chief etiologic agents in pediatric viral pneumonias.[10,11]

Overview of Serious Lethal Infections

Table 1 shows the frequency and relative severity of the various viruses that cause pneumonia.[12]

The purpose of this article is to review the literature regarding severe and lethal respiratory tract infections of viral etiologies in children. A review of pediatric series of adult respiratory distress syndrome (ARDS) and extracorporeal membrane oxygenation (ECMO) and an understanding of the viral etiologies of nosocomial infections in pediatric patients are places to start.

The Extent of Serious and Lethal Viral Disease

Adult Respiratory Distress Syndrome

In 1991, Timmons et al[13] described 44 children with adult respiratory distress syndrome (ARDS). In this series, an overall mortality rate of 75 percent was reported, with 1 of the 3 children with viral infection (all RSV) surviving. In a later series of 60 children with ARDS reported by Davis et al,[2] the overall mortality rate was 62 percent. These patients represented 2.7 percent of the admissions to their pediatric intensive care unit (PICU), 8 percent of the total days in the unit, and 33 percent of the PICU deaths during this 2-year study period. The authors reported that, for the group as a whole, the alveolar-arterial oxygenation tension difference ($P_{(A-a)}O_2$) was the best early predictor of death. In determining mortality by etiology, the authors found that sepsis (n = 22, 37% of patients), including two cases with viremia, was the most common cause. The 12 patients with ARDS secondary to a viral pneumonia represented 9 percent of the total of 135 patients admitted to their PICU with the diagnosis of viral pneumonia during this same period. The mortality rate in the children with a viral etiology for ARDS was 58 percent as compared with less than 1 percent of those with viral pneumonia that did not progress to ARDS. The viruses isolated in patients with ARDS included RSV, influenza, CMV, and measles; the frequency of each reflected its relative frequency in the 135 patients admitted with viral pneumonia.

Viral Pneumonia Treated With ECMO

Because viral infections are recognized as the most common indication for pediatric ECMO, Meyer and Warner[3] reviewed the pediatric Extracorporeal Life Support Organization (ELSO) registry through December 1994 to report differences in outcomes of different viral etiologies. The viruses reported are listed in Table 2, which shows RSV as the most common. Of the overall survival rate of 57 percent, the lowest survival rates were in patients who had adenoviral and herpes simplex virus infections (25% and 31%, respectively). Patients with RSV and CMV had the highest survival rate (67%). Of note, complications of ECMO were more common with specific viruses (Table 3). (See additional information regarding ECMO in the RSV section later.)

Nosocomial Disease

Nosocomial viral disease often is a significant cause in serious and fatal viral pneumonias, particularly in children who are

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Table 1. Etiologic Agents in Nonbacterial Pneumonia

Etiologic Agents	Frequency*			Usual Degree of Severity†			Mode of Access to Lung
	0-3 mo	4 mo-5 yr	6-16 yr	0-3 mo	4 mo-5 yr	6-16 yr	
Virus							
Respiratory syncytial virus	+++	++++	+	++	++	−	Respiratory
Parainfluenza viruses							
Type 1	+	++	+	++	++	+	Respiratory
Type 2	+	+	+	++	++	+	Respiratory
Type 3	++	+++	++	++	++	+	Respiratory
Influenza viruses							
Type A	++	+++	+++	++	++	+	Respiratory
Type B	++	++	+	++	++	+	Respiratory
Adenoviruses‡	+	++	++	+++	++	+	Respiratory
Rhinoviruses§	+	+	+	−	++	+	Respiratory
Enteroviruses¶	+	+	+	++	++	+	Respiratory (hematogenous)
Coronaviruses	−	+	+	−	++	+	Respiratory
Measles virus	+	++	++	+++	++	++	Respiratory (hematogenous)
Rubella virus	+	−	−	++	−	−	Hematogenous
HIV	+	++	+	++	++	++	Hematogenous
Varicella-zoster virus	+	+	+	+++	+++	+++	Hematogenous (respiratory)
Cytomegalovirus	+++	+	+	++	+++	+++	Hematogenous (respiratory)
Epstein-Barr virus	−	+	++	−	++	+	Hematogenous (respiratory)
Herpes simplex virus	++	+	+	++++	+++	+++	Hematogenous (respiratory)

*++++, most frequent; +++, frequent; ++, infrequent; +, rare; −, no reported cases.
†++++, often fatal; +++, severe; ++, usually hospitalized; +, home management; −, no reported cases.
‡Types 1, 2, 3, 4, 5, 7, 14, and 21.
§90 or more types known.
¶Coxsackieviruses A9, A16, B1, B4, and B5; echoviruses 9, 11, 19, 20, and 22.
Adapted with permission.[12]

admitted because of underlying decreased immunocompetence (eg, after solid organ or bone marrow transplant, malignancies, Crohn disease) or in children with increased risk of pulmonary disease from acute (eg, measles) or chronic (eg, bronchopulmonary dysplasia, congential heart disease) illness. Viral etiologies of nosocomial lower respiratory infections in pediatric patients are reported to be up to 20 percent[13] and frequently are spread by pediatric hospital personnel.[14] Nosocomial adenoviral infection in patients admitted with measles disease may lead to death.[15] (See Adenovirus section below for additional information.) In a series of 95 children hospitalized with parainfluenza virus infections, noscomial infection occurred in 5 patients with bronchopulmonary dysplasia, 3 of whom died of progressive respiratory failure.[16] RSV has been shown by Hall and colleagues[17-19] to be a frequent source of nosocomial infections in the pediatric population, with a reported 100 percent infection rate for infants hospitalized longer than 4 weeks during a community outbreak.[18] In addition, nosocomial RSV infection has been associated with increased mortality in premature infants and in children with bronchopulmonary dysplasia or congenital heart disease.[20,21]

Table 2. Demographics of Patients With Culture-Proven Viral Pneumonia Treated With ECLS

	n	Age (mo)	Weight (kg)	Male/Female (n)
RSV	81	3.6 ± 0.4 (3.0)	3.72 ± 0.19	43/38
HSV	13	1.2 ± 1.0 (0.13)	3.35 ± 0.39	5/8
Adenovirus	12	4.4 ± 1.9 (0.6)	5.02 ± 1.00	9/3
CMV	9	6.9 ± 2.9 (2.5)	5.90 ± 0.99†	5/4
Other	12	15.4 ± 5.8 (5.5)*	8.14 ± 1.41*	7/5

NOTE. The group termed "other" consists of patients with varicella, influenza, parainfluenza, and enterovirus. Data are means ± SEM. Numbers in parentheses are medians.
Abbreviation: ECLS, extracoporeal life support.
*$P < .05$ versus all other groups.
†$P < .05$ versus RSV and HSV groups.
Adapted with permission.[3]

Specific Viral Etiologies

Respiratory Syncytial Virus

Despite the use of prophylactic[22-24] and therapeutic medical strategies,[25-28] RSV remains a significant cause of serious and fatal respiratory infections. In addition to being a significant cause of illness in children with underlying chronic illnesses, in an early series Krasinki[29] reported 3 of 7 pediatric patients dying, with 1 of the 7 surviving with chronic long disease. Moler et al[30] reported the RSV experience of the ELSO registry database as of June 1992. To that date, 53 pediatric patients with RSV infection had been placed on ECMO through the registry. Of 8 who had preexisting chronic lung or congenital heart disease, 6 survived. Of the total group, 27 of 53 (51%) survived. A backward stepwise logistic regression model of survival found nonsurvival to be associated with four factors: male gender, longer duration of mechanical ventilation before ECMO, peak inspiratory pressure, and a lower ratio of P_aO_2/F_iO_2.

Table 3. Complications During Extracorporeal Life Support

	RSV	*HSV*	*Adenovirus*	*CMV*	*Other*
Bleeding, n (%)					
Intracranial					
Infarct/bleeding	9 (12)	3 (23)	3 (25)	1 (12)	3 (25)
Gastrointestinal bleeding	2 (3)	1 (8)	1 (8)	1 (12)	1 (8)
Surgical site bleeding	20 (27)	1 (8)	1 (8)	1 (12)	4 (33)
Other bleeding	9 (12)	4 (31)*	3 (25)	1 (12)	2 (17)
Neurological, n (%)					
Brain death	1 (1)	0	0	0	1 (8)
Seizures	10 (13)	4 (31)	4 (33)	2 (25)	2 (17)
Other neorological	2 (3)	4 (31)*	1 (8)	2 (25)*	0
Cardiopulmonary, n (%)					
Required CPR	1 (1)	0	3 (25)*	1 (12)	2 (17)
Required inotropes	20 (26)	10 (76)†	4 (33)	4 (50)	4 (36)
Hypertension	9 (12)	2 (15)	1 (8)	3 (38)	3 (25)
Pneumothorax	9 (12)	2 (15)	0	1 (12)	0
Renal, n (%)					
Cr >1.5 mg/dL	7 (9)	1 (8)	3 (25)	1 (12)	0
Cr >3.0 mg/dL	1 (1)	0	0	0	0
Required dialysis	25 (33)	5 (38)	8 (67)	1 (12)	4 (33)

NOTE. The group termed "other" consists of patients with varicella, influenza, parainfluenza, and enterovirus. Figures are rounded to the nearest integer.
*$P < .05$ versus RSV group.
†$P < .05$ versus adenovirus group.
Adapted with permission.[3]

Parainfluenza Virus

As stated above, nosocomial parainfluenza virus infections have been reported in patients with bronchopulmonary dysplasia, with three of five dying of progressive respiratory failure.[16] Delage et al[31] reported parainfluenza type 3 causing death after giant-cell pneumonia in two patients with severe combined immunodeficiency syndrome.

Influenza

The majority of influenza infections in children are self-limiting, without complications or sequelae, and have a reported mortality of 0.02 to 0.05 percent.[32-35] Glenzen,[36] however, builds an argument that influenza deaths have not been apparent in excess mortality calculations for influenza epidemics. He notes that one explanation may be the reciprocal fluctuations in the intensity of epidemics caused by the group of viruses most likely to produce life-threatening respiratory infections in children (eg, RSV, influenza A and B, and parainfluenza 1 and 3) and that the risk of lower respiratory illness in young children remains relatively constant from one year to another. Deaths attributable to such illness would be detectable only under exceptional circumstances of a particular virulent and explosive influenza epidemic.

Cytomegalovirus

CMV will be discussed in the sections below regarding Children Undergoing Thoracic Surgery and Bronchoalveolar Lavage.

Measles

In 1990, Navarro et al[37] reported a clinicopathologic series of 71 children younger than 5 years (68% younger than 2 years) who died of acute lower respiratory tract infections in the Philippines. Measles was identified in 35 (49.9%) of these children. Of the 11 children in the series who died of isolated pneumonia without complicating or associated disease, 6 had a viral etiology. Similarly, in the 2 patients who had evidence of cardiac failure associated with pneumonia, both had measles. In this series, the odds ratio of a child with a bacterial acute lower respiratory tract infection dying with uncomplicated infection was significantly less than that for a child with a viral acute lower respiratory tract infection (Table 4). A number of children manifested evidence of a disseminated viral infection that could not be distinguished from bacterial sepsis on clinical grounds (Table 5).

Swift et al[38] reported a series of 19 children who were admitted to a California PICU between June 1989 and June 1990 with the diagnosis of measles and who required mechanical ventilation for respiratory failure. Respiratory failure was caused by upper airway obstruction in 10 of the children (53%)

Table 4. Prevalence, Odds Ratios, and 95% Confidence Intervals of Specific Pathophysiology of Death Among Children With Bacterial or Viral ALRI

	No. With Indicated ALRI			
Cause of Death	*Bacterial (n = 19)*	*Viral (n = 16)*	*Odds ratio*	*95% Confidence Interval*
Pneumonia alone	1	6	0.09	0.01, 0.88
Pneumonia with sepsis	14	4	8.4	1.83, 38.57
Cardiac failure	1	2	0.39	0.03, 4.74
Nosocomial infection	3	3	0.81	0.14, 4.72

Abbreviation: ALRI, acute lower respiratory tract infection.
Adapted with permission.[37]

Table 5. Cause of Death of Children, According to Demonstrated Pathogen

	Pathogen				
Cause of Death	*Viral*	*Bacterial*	*Mixed*	*Undetermined*	*Total*
Pneumonia	6	1	3	1	11
Pneumonia with sepsis	4	14	19	5	42
Pneumonia with cardiac failure	2	1	2	1	6
Pneumonia with hypovolemia	1	0	1	1	3
Nosocomial infection	3	3	1	2	9
Total	16	19	26	10	71

Adapted with permission.[37]

and by pneumonitis with refractory hypoxemia in 9 (47%). The patients with tracheitis all survived, whereas those children with pneumonitis and refractory hypoxemia, defined as an oxygenation index ([mean airway pressure] $\times$ [$F_iO_2/P_{a\ O_2}$] $\times$ 100) of greater than 40 for 4 hours, had a 56 percent mortality (5 of 9 children). The total group mortality was 26 percent (5 of 19). These authors reported that "most of the children came from lower socioeconomic backgrounds and lacked proper immunizations." Of note, in the 10 patients who had tracheitis, 70 percent had *Staphylococcus aureus* isolated from tracheal cultures. Two of these 7 had signs and symptoms of toxic shock syndrome, with toxic shock toxin-1 (TTST-1) later isolated from each patient.

During this same period, Ross et al,[39] also in California, and Fortenberry et al[40] in Houston reported two series of patients (n = 82 and n = 27, respectively) with laryngotracheobronchitis (LTB) as a complication of two urban measles epidemics. Their series are remarkably similar: the California series reported an incidence of 18.6 percent of LTB in their review of their patients meeting the Centers for Disease Control and Prevention (CDC) criteria for measles, and the Houston series reported an incidence of 22 percent. The respective mean ages of the children with LTB secondary to measles were 14.7 months and 12 months. The respective percentages of the children admitted to the ICU were 12 percent and 17.3 percent, and the respective percentages of the children requiring endotracheal intubation were 22 percent and 9 percent.

In 1995, Abramson et al[41] reported severe complications of measles in children requiring admission to an ICU in Israel. During two measles epidemics between January 1990 and May 1992, 500 cases of measles were reported in the Negev region; of these, 237 children were hospitalized. Of those hospitalized, 15 patients, aged 24 days to 6 years (24 $\pm$ 14 months [mean $\pm$ SD]), required admission to the PICU. All 15 had pneumonia with severe respiratory failure requiring mechanical ventilation, 12 (80%) had severe hypoxemia (P_aO_2/F_iO_2 ratio, 76 $\pm$ 42), and 8 (53%) had severe hypercarbia (P_aCO_2 68.4 $\pm$ 9.8). All patients had interstitial infiltrate on chest radiograph, and 14 of the 15 children had additional areas of localized consolidation. In the 7 children with massive bilateral consolidations, a clinical syndrome consistent with ARDS developed.

Adenovirus

Schonland et al[42] reviewed autopsy findings in 107 children who died with pneumonia in South Africa. Of these, 15 children (14%) had adenoviral infections, as diagnosed by histopathologic and ultrastructural features of the lungs. In 11 of these children (73%), the adenoviral infection followed a measles infection, the pathogenicity appearing to be increased when the adenoviral infection supervened on a damaged respiratory tract. Similar findings of association with fatal adenovirus infection have been reported by Chany et al[43] and Nahmias et al.[44] Adenovirus type 7[44-47] and type 3[48,49] have been reported frequently as etiologic agents in serious and fatal lung disease in infants and children. Singh-Naz et al[49] reported a 30 percent attack rate (types 2 and 3) in a nosocomial outbreak in a pediatric chronic care facility. Of the 10 patients with underlying bronchopulmonary dysplasia, 3 had progressive pulmonary failure and 2 children died (both type 3). Fatal adenoviral respiratory disease in neonates has been reported with type 7[14,50] and with type 21/H21 + 25.[14] Abzug and Levin[15] in a review of the literature of neonatal adenoviral infections through 1991 reported 11 of 13 patients with fatal infections, death occurring 4 to 19 days after onset of illness. The authors commented on the preponderance of vaginal deliveries (n = 11, 85%) and prolonged rupture of membranes in 31%, suggesting a possible ascending infection or an infection acquired from the birth canal during delivery.

Varicella-Zoster

Serious varicella infections and deaths usually are associated with encephalitis[51]; however, serious and fatal pneumonia can develop, most often in immunocompromised children.[52,53]

Children Undergoing Thoracic Surgery

A useful classification of children undergoing thoracic surgery is into groups of immunocompromised and immunocompetent hosts, for which the viral etiologies differ (Table 6).[54] The use of immunosuppressive medications in children undergoing heart, lung, or heart-lung transplantation affects cellular immunity,

Table 6. Major Viruses Producing Respiratory Infections in Patients Undergoing Cardiothoracic Surgery

Immunocompromised Host	*Immunocompetent Host*
Cytomegalovirus	Respiratory syncytial virus
Virus	Influenza
Epstein-Barr virus (PTLD)	Parainfluenza
Herpes simplex virus	Adenovirus
Varicella zoster virus	

Abbreviation: PTLD, posttransplant lymphoproliferative disease.
Adapted with permission.[54]

increasing the risk of these children developing an infection with one of the herpes viruses. On the other hand, in the immunocompetent patient who has viral pneumonia in the perioperative thoracic surgery period, the etiology is more likely to be a community-acquired or nosocomial virus. The viral agent may have been acquired and be incubating preoperatively, with the clinical manifestations of pneumonia only developing postoperatively, or the virus may be a true nosocomial infection. However, in the latter case, the specific etiologies parallel the viruses isolated in the community.[55]

MacDonald et al[21] reported increased mortality in infants undergoing congenital heart surgery during RSV outbreaks in the community. Bork et al[7] reported a series of 128 infants who underwent cardiac transplantation, of whom 19 (15%) had CMV infections. Most of these children had symptoms within the first 2 to 3 months posttransplant. Fifteen patients had RSV infection, with infants younger than 6 months having a higher risk. Bridges et al[8] reported a series of pediatric patients undergoing lung or heart-lung transplantation. Sixteen patients underwent 19 transplants. Virus was identified in the transplanted lung on 29 occasions, with a frequency of 0.13 events per patient-month of follow-up. RSV was found 9 times in 8 patients. In 8 patients, the RSV infection was associated with relatively mild illness. However, in 1 patient, the RSV infection was associated with mortality, with RSV isolated from a tracheal aspirate in a patient dying of overwhelming *Pseudomonas* sepsis. Conversely, adenovirus was identified in 8 of 16 (50%) patients and was significantly associated with respiratory failure, leading to death or graft loss, and with a histologic diagnosis of obliterative bronchiolitis. Two cases of CMV were associated with significant respiratory disease; 1 patient recovered after receiving ganciclovir. In the second child, while receiving ganciclovir, CMV was identified concurrently with an adenoviral infection. This child required a second lung transplantation after severe respiratory failure. Both cases of parainfluenza disease also were associated with significant respiratory disease: one was associated with an RSV infection, and the other case led to obliterative bronchiolitis after an adenoviral infection. Other identified viruses, Epstein-Barr virus, herpes simplex virus, and influenza B were not associated with clinical respiratory illness.

Diagnostic Technology

Bronchoalveolar Lavage

Bronchoalveolar lavage (BAL) is a useful technique to diagnose etiologies of lower respiratory tract infections in immunocompetent children,[4] in children with cancer,[5] and in children with pulmonary complications of bone marrow transplantation.[6] Rock[4] reported a series of 25 consecutive immunocompetent but significantly ill children with unexplained infiltrates on chest radiograph in whom 27 BAL procedures were performed. The diagnosis was made in 8 patients (30% yield), with 4 (50%) having a viral origin (2 RSV, 1 CMV, and 1 parainfluenza virus type 3). Stokes et al[5] reported a series of 60 consecutive flexible bronchoscopies performed in 48 pediatric cancer patients. These procedures included bronchial washings, brushings, and biopsies, in addition to BAL. CMV was isolated in 1 of the 40 children who received bronchial brushings (the only positive yield in this group). In the children who received a BAL (n = 50) there were 14 positive results. Of these 14, only 3 yielded a viral etiology, all CMV. In a series of 27 children who received BAL to evaluate 29 episodes of serious pulmonary complications after bone marrow transplantation, McCubbin et al[6] reported 15 positive results. Of these, 5 were positive for CMV, 2 for RSV, and 1 child had RSV plus parainfluenza virus isolated. Although the authors do not give data as to mortality by etiology, only 7 of 27 children (26%) were alive 90 days after BAL.

Polymerase Chain Reaction

Using polymerase chain (PCR) to amplify sequences of viruses known to cause viral infections in fixed-lung tissue of children dying of viral pneumonia, Akhtar et al[56] showed that PCR offers a rapid and sensitive method for the detection of viral genome from lung tissue. In a recent follow-up, the same group reported the successful use of tracheal aspirates as a substrate for the PCR to show viral genome in childhood pneumonia and myocarditis. Of significance were seven cases of myocarditis (Epstein-Barr virus) for which the viral genome amplified in cardiac biopsy specimens (Epstein-Barr virus) also was found in the tracheal aspirate.[57] The ease of obtaining tracheal samples, with less morbidity than with BAL or open-lung biopsy, renders this method a particularly exciting new tool for diagnosing children with severe and clinically unstable viral respiratory illness.

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