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RESPIRATORY INFECTIONS (F ARNOLD, SECTION EDITOR)

Viral Infections in Children with Community-Acquired Pneumonia

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Abstract Viral pathogens are commonly isolated from children with community-acquired pneumonia (CAP). Viruses like respiratory syncytial virus, human rhinovirus, human metapneumovirus, parainfluenza viruses, and influenza may act as sole pathogens or may predispose to bacterial pneumonia by a variety of mechanisms. New, emerging, or reemerging viral pathogens occasionally cause outbreaks of severe respiratory tract infection in children. The 2009–2010 H1N1 influenza virus pandemic resulted in increased rates of influenza-related hospitalizations and deaths in children. Rapid viral diagnostic tests based on antigen detection or nucleic acid amplification are increasingly available for clinical use and confirm the importance of viral infection in children hospitalized with CAP. Recently published guidelines for the management of CAP in children note that positive viral test results can modify clinical decision making in children with suspected pneumonia by allowing antibacterial therapy to be withheld in the absence of clinical, laboratory, or radiographic findings that suggest bacterial coinfection.

Keywords Community-acquired pneumonia · Bacterial pneumonia · Infant · Child · Adolescent · Viral infection · Viral respiratory tract infection · *Streptococcus pneumoniae* · *Staphylococcus aureus* · Rhinovirus · Influenza · Metapneumovirus · Adenovirus · Bocavirus · Parainfluenza virus · Respiratory syncytial virus · Enterovirus

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Introduction

Community-acquired pneumonia (CAP) is the leading single cause of death among children younger than 5 years old worldwide, with an estimated 1.07 million deaths in 2010 [1] among about 150 million episodes per year [2]. In the U.S., there are about 2.5 to 3.3 million episodes per year [3], with more than 200,000 hospitalizations [4]. Among immunocompetent children, CAP may be caused by a wide variety of microbes, including many viruses, "typical" bacteria (e.g., *Streptococcus pneumoniae*), atypical bacteria (e.g., *Mycoplasma pneumoniae*), *Mycobacterium tuberculosis* and related species, and fungi such as *Histoplasma capsulatum* [5–10, 11••]. Viral infections are involved with 80 % of episodes of CAP in children under 2 years old and 49 % of older children [12].

Viruses may act as sole pathogens in pediatric CAP or predispose to bacterial pneumonia [13–17]. Viral etiologies vary by geography, season, and the age of patients studied, but respiratory syncytial virus (RSV), human rhinovirus (HRV), human bocavirus (HBoV), human metapneumovirus (HMPV), and parainfluenza viruses (PIV) are described consistently as the most common viruses associated with CAP in children. Coinfection with influenza and a bacterial pathogen has been associated with the development of severe disease [18–21]. Severe cases of RSV bronchiolitis requiring mechanical ventilation often have bacterial coinfection [22, 23].

Development of CAP caused by bacterial pathogens that have colonized the upper airway may be facilitated by viral respiratory tract infections that (1) damage ciliated respiratory epithelium and interfere with normally protective mucociliary clearance mechanisms [24], (2) augment adhesion of bacterial pathogens to respiratory epithelial cells [25–27], (3) directly diminish the effectiveness of neutrophils or other components of innate or adaptive immunity

[28], (4) allow overgrowth of bacteria in the nasal passages that increases the likelihood of aspiration into the lower respiratory tract, and/or (5) facilitate translocation of bacteria in the upper airways across mucosal barriers into the bloodstream, with secondary bacteremic seeding of the lung parenchyma [29].

Viral lower respiratory tract infections may generate infiltrates evident on chest radiographs that are difficult to distinguish from those from episodes of CAP due to typical or atypical bacterial agents. This seems especially true for viral etiologies of bronchiolitis in young children. This review focuses on recent studies that provide insights into various aspects of viral infections that are associated with subsequent typical bacterial CAP, including seasonal and pandemic H1N1 influenza, and on recent studies on complications of CAP.

Recent Cohort Studies Assessing Multiple Viruses and CAP

Several recently published studies employing sophisticated molecular diagnostic techniques have added to the growing body of data regarding the impact of viral infections in children with CAP. A prospective study of children hospitalized with radiographically confirmed CAP in one Finnish hospital between January 2006 and April 2007 confirmed that mixed bacterial–viral infections are common [30]. Expectorated or induced sputum samples obtained from 76 children 6 months to 15 years of age were tested for six bacteria by culture and polymerase chain reaction (PCR) testing and for 18 viruses by antigen detection and PCR testing. At least one respiratory pathogen was identified in 74 of 76 patients (97 %). Bacteria were isolated in 91 % of samples, viruses in 72 %, and both in 66 %. The most commonly detected viral pathogens were HRV (30 %), HBoV (18 %), HMPV (14 %), adenovirus (11 %), PIV3 (8 %), coronaviruses (7 %), and RSV (7 %). Seventeen patients (33 %) were positive for two viruses, and 6 patients (8 %) had three viruses.

When bacterial–viral coinfection was identified, *S. pneumoniae*–rhinovirus was the most frequent combination (16 %) [30]. A major limitation of this study was probable contamination of many of the bacterial cultures with naso- or oropharyngeal flora that commonly colonize the nasal passages or oropharynx but sometimes are etiologies of pneumonia (i.e., *S. aureus*, *S. pneumoniae*, *M. catarrhalis*, nontypeable *H. influenzae*).

Investigators in Madrid, Spain studied the etiology of presumed bacterial CAP in children <14 years of age who were hospitalized between September 2004 and July 2010 [31]. CAP was defined as the presence of consolidation and/or pleural effusion on chest radiographs. Nasopharyngeal aspirates were obtained at admission from 1,034 patients and tested for 16 respiratory viruses by RT-PCR. At least one virus was isolated in 649 patients (73.4 %), and 195 (30 %) patients had two or more viruses isolated. RSV was identified most frequently (30.5 %), followed by HRV (19.2 %), HBoV (13.1 %), and adenovirus (AdV; 13.1 %). PIVs, HMPV, and influenza were identified in about 5 % of patients.

Virus detection was higher in infants <18 months of age than in the older children in the study (83 % vs. 67 %). RSV was more common in younger children, while HRV and influenza were more common in older children. Virus-positive patients were more likely than virus-negative patients to present with hypoxia and wheezing. Length of hospital stay, duration of oxygen therapy, and duration of fever did not differ among CAP cases associated with RSV, HRV, HBoV, or HMPV in children <18 months old. Bacterial etiologies of CAP were confirmed by positive blood cultures in only 20 cases, of which 19 (95 %) yielded *S. pneumoniae*. In 14 (70 %), one or more viruses were isolated, including four each with influenza and RSV [31].

Other recent studies have shown similar viral results from children with symptoms of respiratory tract infection. In a six-center study in South Africa during 2009 and 2010, nasopharyngeal or oral specimens from 8,173 patients with severe acute respiratory infection were evaluated with a 10-virus multiplex PCR test [32]. Most of the patients were children with physician-diagnosed lower respiratory tract infection (LRTI), although adults were included as well. Median age was 3 years. A single virus was detected in 40 %, and dual infection in 17 %. HRV was detected in 25 %, RSV 14 %, AdV 13 %, enterovirus 6 %, PIV 6 %, and HMPV 4 %. Influenza A-H3N2, A-H1N1, and B strains were detected in 3 % each. HRV, RSV, and AdV were most commonly involved in coinfections.

Two other recent studies of viral infections in young children from disparate geographic locations, combined with the above results, indicate moderate similarity in epidemiology of viral respiratory tract infections in children around the world. Between February 2010 and February 2011, 295 children <5 years old in southeast Madagascar who had fever, symptoms of acute respiratory infection, and a negative test for malaria were evaluated with a multiplex PCR for 18 viruses and two atypical bacterial agents [33]. HRV was detected in 20 %, HMPV 14 %, coronavirus 12 %, PIV 12 %, RSV 12 %, influenza 9 %, adenovirus 6 %, and HBoV 6 %. *M. pneumoniae* and *C. pneumoniae* were detected in 5 % and 2 %, respectively. Coinfections were noted in 27 %. During the first wave of pandemic influenza in the spring of 2009 in Dallas, Texas, single virus infections were identified in 1,023 symptomatic children: HRV in 49 %, PIV 20 %, HMPV 16 %, and pandemic H1N1 5 % [34].

Isolation of a virus from the respiratory tract does not always prove active infection [30, 31]. Children may shed

viruses for a prolonged period, and viral detection may simply represent asymptomatic persistence. Nevertheless, these studies are consistent with others that have demonstrated a variety of viral etiologies associated with lower respiratory tract infection, often but not always with evidence of concomitant bacterial infection [6, 7, 10, 12, 35].

Seasonal and Pandemic Influenza and CAP

Influenza virus infections have long been associated with secondary bacterial CAP [13, 36]. A recently published retrospective cohort study examined the impact of seasonal influenza virus infection on hospitalized children with complicated pneumonia requiring pleural fluid drainage [37]. Data were obtained from the Pediatric Health Information System (PHIS), a database that contains resource utilization data from 40 free-standing children's hospitals in 27 states and the District of Columbia. Between January 1, 2004 and June 30, 2009, 3,382 children with complicated pneumonia underwent a pleural drainage procedure, and 105 (3.1 %) of these were labeled as having influenza coinfection.

In this cohort, *S. aureus* was the most common bacteria associated with influenza coinfection (n=24), although *S. pneumoniae* was identified almost as often (n=14). In multivariable analysis, influenza coinfection was associated with higher odds of intensive care unit admission and need for mechanical ventilations and vasoactive infusions, as well as a longer hospital stay [37]. These data suggest that viral testing and institution of appropriate isolation precautions are prudent in children hospitalized with complicated CAP and emphasize the need for annual influenza immunization of all children ≥6 months of age.

During the 2009 influenza A H1N1 pandemic, rates of hospitalization due to laboratory-confirmed influenza were substantially higher in the U.S. for children than for the more typical seasonal influenza virus strains that circulated during the preceding 6 years [38, 39]. This was most marked for 5- to 17-year-olds and 18- to 49-year-olds, where the pandemic ratios were five- and sixfold higher, respectively, than the average of preceding seasonal influenza years [38]. Among 2,479 children hospitalized with influenza in 10 regions of the U.S. that were monitored by the Emerging Infections Program of the CDC, 57 % had an underlying medical condition, of which asthma (32 % of cases) was the most common. Pneumonia was present in 813 (33 %), although bacterial coinfection was confirmed in only 49 (2 %). *S. pneumoniae* was present in 21 (43 %) of these, followed by *S. aureus* in 14 (29 %) and *S. pyogenes* in 3 (6 %). Among 24 children who died (1 % of hospitalized cases), 20 (83 %) had underlying medical conditions [38].

Hospitalizations for pneumococcal pneumonia increased 1.6-fold over baseline for children 5 to 19 years old in the U.S., the largest relative increase among any age group, during the second wave of pandemic influenza in the fall of 2009 [40]. In Denver, CO, during the second wave peak in October 2009, there were 12 cases of invasive pneumococcal disease in children 0–19 years old, mostly pneumonia, but only 3 such cases during the peak of the preceding seasonal influenza outbreak in February 2009 [41]. It is not clear whether this increase in case numbers in October versus February, in a stable background population, reflects an increased attack rate of influenza during the pandemic, enhanced facilitation of development of pneumococcal pneumonia by the pandemic versus seasonal strain, or both.

A multicenter study of 1,265 children hospitalized with pandemic H1N1 influenza at 12 Canadian pediatric hospitals (the IMPACT network) found that asthma was more common than among children hospitalized with seasonal influenza A strains during the preceding 5 years (13.8 % vs. 5.5 %, p<.001) [42]. Headache, cough, and gastrointestinal symptoms were more common in the pandemic cohort, as compared with prior years, as well. Radiologically confirmed pneumonia occurred in 57.3 % of hospitalized children with pandemic influenza requiring intensive care, as compared with 34.1 % of those with seasonal influenza A in preceding years (p<.001). No specific coinfection data were provided in this study.

Among 215 children hospitalized for pandemic influenza at multiple Belgian centers, 74 (34 %) had radiographic evidence of pneumonia [43]. Pneumococcal coinfection was confirmed in 3 children by positive blood cultures. In a similar series of 115 children admitted to four Thai hospitals, infiltrates on chest radiographs were present in 89 (77 %) [44]. Among 73 infants <6 months old hospitalized in Texas with laboratory-confirmed pandemic influenza A in 2009, 10 of 67 (15 %) were diagnosed with bacterial coinfection on admission. Bacterial pneumonia was present in 5, and urinary tract infection in 4 [45]. Another infant developed ventilator-associated pneumonia due to *Pseudomonas aeruginosa*.

Emerging or Reemerging Respiratory Viral Infections

Clusters of severe lower respiratory tract infection or CAP may be associated with novel, emerging, or uncommonly seen pathogens. Recent examples include the severe acute respiratory syndrome (SARS) coronavirus outbreak in 2003 [46] and human coronavirus NL63 in 2004 [47]. HBoV was first identified in 2005 [48], but its precise role as a respiratory pathogen remains unconfirmed [35].

In August and September 2010, an increase in pediatric admissions for lower respiratory tract illness was recognized

at a community hospital in rural Arizona [49]. During this time, 43 % of all pediatric admissions were for respiratory illness, as compared with a mean of 17 % during the same time period in the 3 previous years. Eighteen patients had a similar illness characterized by cough and tachypnea or hypoxemia, and new onset wheezing was common. After routine studies conducted by the Arizona Department of Health Services failed to identify a pathogen, seven nasopharyngeal samples were referred to the Centers for Disease Control and Prevention (CDC) for further testing. Specimens from five children tested positive for human enterovirus 68 (HEV68), one of whom also had evidence of pneumococcal infection.

HEV68 was first identified in 1962 in four children with bronchiolitis and pneumonia but, subsequently, has rarely been identified as a cause of acute respiratory tract infection in children [50]. While the spectrum of clinical manifestations caused by HEV68 requires further study, what is known appears similar to other members of the *Picornaviridae* family (e.g., rhinoviruses, enteroviruses). Like other enteroviruses, HEV68 can cause central nervous system disease. Like HRV, EV68 infection may result in mild upper respiratory tract infection [51]. Recent clusters of illness like the one in Arizona confirm that this virus can cause severe, even fatal, pneumonia in children [49].

Some commercially available molecular diagnostic testing systems may not be able to distinguish between HEV68 and HRV. In 2009, a pediatric hospital in Philadelphia identified an unusually large number of children with HRV infection, with 390 children testing positive for HRV between August and October. HRV was recovered from more than twice the proportion of samples than in the same time period during the previous year. A number of the patients were sicker than is typically expected with HRV infection. Twenty-eight of the 66 samples (42 %) referred to the CDC yielded HEV68. More than half of the patients with HEV68 infection were 0–4 years of age. Although none died, 15 (54 %) required admission to the ICU; the median duration of hospitalization was 5 days [49].

During the last half of 2011, a novel swine influenza variant, labeled H3N2v, was identified in children in the U.S. [52•]. Low-level human-to-human transmission may have occurred, although widespread circulation has not been noted as yet. This strain appears closely related to an influenza A variant that circulated in the mid-1990s. A recent seroprevalence study in 2012 in Canada showed that many adolescents and young adults, but not children under 14 years or adults over 44 years old, have antibodies that are cross-reactive with this strain [53]. This emergence suggests that new influenza strains can emerge globally and substantiates the need for ongoing influenza surveillance.

Complications, Outcomes, and Management

From 2000 to 2010, global annual deaths from pneumonia in children less than 5 years old decreased by about 451,000 [1]. This likely has been due to a combination of factors, including advances in health care delivery and availability of supportive care and antimicrobial agents, as well as increased availability of vaccines that can prevent *H. influenzae* type b and many pneumococcal infections. Still, much work is left to be done worldwide in prevention and access to care.

In the U.S., hospitalizations for pneumonia decreased following introduction of a 7-valent conjugate pneumococcal vaccine, but prevalence of pleural empyema complicating pneumonia increased twofold (3.5 to 7.0 cases per 100,000 children) from 1996–1998 to 2005–2007 [54, 55]. *S. aureus*-associated empyema increased 4.1-fold during this time period. Fortunately, outcomes from pleural empyema, with appropriate management, are excellent. Within 12 months of presentation with pleural empyema, there were no clinically significant long-term sequelae in a cohort of 82 children managed at a single center in Toronto between 2008 and 2010 [56].

Analysis of data from 21,213 hospitalizations for non-severe CAP at 29 U.S. children's hospitals participating in PHIS in 2009 showed substantial variations in management among the hospitals [57••]. The median age was 3 years, and 72 % of the children were between 1 and 5 years of age. Median length of stay (LOS) was 2 days, but 25 % of the hospitals had a median LOS of 3 or more days. A shorter LOS correlated with rate of return to the emergency department within 14 days after discharge. The majority of children with CAP at each hospital had chest radiography (interquartile range, 69 %–81 %) and complete blood counts (interquartile range, 52 %–74 %). Blood cultures were obtained in about half (interquartile range, 43 %–64 %). Interquartile ranges for virologic testing and C-reactive protein concentrations were 18 %–40 % and 5 %–18 %, respectively.

Most of the children with CAP during this study period in 2009 received a cephalosporin either alone or in combination with a macrolide, vancomycin, or clindamycin [57••]. The recently published clinical practice guideline for pediatric CAP recommends ampicillin or penicillin G for treatment of children in the U.S. hospitalized with uncomplicated CAP who have been fully immunized and live in areas that lack high-level penicillin resistance among invasive pneumococci [11••]. A low-resource antimicrobial stewardship program using a well-disseminated institutional guideline, coupled with educational outreach by highly visible infectious disease clinicians, has proved successful in increasing ampicillin and decreasing ceftriaxone use for uncomplicated CAP in children [58].

Rapid viral diagnostic tests based on antigen detection or nucleic acid amplification are increasingly available for clinical use for an expanding array of pathogens [32–34, 59]. Multiplex PCR tests increase the proportion of children with CAP for whom a viral infection is identified [7, 10, 60]. One multiplex test for 15 viruses, *M pneumoniae*, and *Bordetella pertussis* that is fully automated and uses a self-contained pouch that can be processed within an hour is currently available in the U.S. [59].

The 2011 pediatric CAP guideline notes that positive viral test results can modify clinical decision making in children with suspected pneumonia by allowing antibacterial therapy to be withheld in the absence of clinical, laboratory, or radiographic findings that suggest bacterial coinfection [11••]. There is growing evidence that the risk of serious bacterial infection is low in children with laboratory-confirmed viral infection [61–64]. This may be true especially for infants and young children who test positive for influenza, RSV, PIV, or AdV and have no other indications for antimicrobial therapy [61–65]. However, positive rapid viral tests are not justification for withholding antimicrobial therapy in infants or children who appear severely ill (e.g., those with respiratory failure) or have other evidence of bacterial coinfection even when rapid viral tests are positive [11••, 17].

The vast majority of children who develop CAP recover fully, even when there are severe bacterial coinfections, provided these are managed appropriately. Abnormalities on pulmonary function testing may persist for months to years after RSV or other viral LRTI in some infants and young children [66–68], but whether symptomatic LRTI is simply a predictor versus etiology of subsequent abnormalities remains unclear. Some viral LRTIs, especially AdV and measles, may be associated with complications such as bronchiolitis obliterans, or bronchiectasis [69–72].

Conclusions

A wide range of viral infections in children can involve the lower respiratory tract and mimic bacterial CAP or facilitate its development. Diagnosis of the bacterial etiology of CAP remains problematic in children, and especially among young children from whom induced sputum cultures of sufficient diagnostic quality are difficult to obtain. Due to the difficulty in distinguishing viral and bacterial etiologies of CAP, especially in young children, antibiotics often are overprescribed for viral LRTI [35]. Recently developed rapid diagnostic tests with short processing times may permit more judicious use of antimicrobial agents in children with apparent CAP.

In the U.S., greater standardization of care for children with CAP is a reasonable expectation that may be facilitated by the 2011 clinical practice guideline [11••]. Criteria for hospital discharge, transition from intravenous to oral therapy, and use of viral and bacterial diagnostic tests in management decisions need further development.

Improved vaccines against influenza and other viral infections should remain a priority, as should increasing global availability of existing vaccines against measles, *Haemophilus influenzae* type b, and pneumococci. Vigilance for emerging viral infections, including new influenza variants, should be maintained. Development of new antiviral agents with novel mechanisms of action is needed. A current example is DAS181, which acts at the level of the host, rather than the microbe, by blockade of influenza virus binding to sialic acid residues on respiratory epithelial cells [73].

In the next few decades, climate change, environmental air pollution in urban areas, and economic or political upheavals that may impact population-level nutritional health, access to health care, and, potentially, seasonality and other epidemiological aspects of some respiratory viruses may become important factors regarding CAP and other infections in children. The potential for new viruses to emerge or become human pathogens may increase, and clusters of unexplained respiratory illness should always be reported to appropriate public health agencies.

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- •• Of major importance

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