Chapter 8
Differential Diagnosis Between Influenza and Other Respiratory Viral Infections: What Are the Differential Diagnoses?

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Abstract Respiratory viruses causing seasonal epidemics in the community are called community-acquired respiratory viruses (CARVs). CARVs include RNA viruses such as human rhinovirus, human respiratory syncytial virus, human parainfluenza virus, human coronavirus, human metapneumovirus, human enterovirus, human parechovirus, and DNA viruses such as human adenovirus and human bocavirus. Needless to say, influenza-like illness (ILI) is caused not only by influenza virus but also by other CARVs. Epidemiological studies targeting ILI patients revealed that CARVs other than influenza are universally detected, predominantly the rhinovirus. However, the viral etiology of ILI is affected by many factors such as the study population, season, setting (community or outpatient or inpatient), and regions. Previous studies investigated the utility of fever and cough as clinical diagnosis markers of influenza, nonetheless the sensitivity and specificity were modest. Since CARVs fairly cause respiratory and general symptoms including fever, cough, coryza, sore throat, headache, myalgia, and chills, predicting the causative virus by clinical symptoms is further difficult in most cases, except for diseases presenting with unique features such as laryngotracheobronchitis (croup), herpangina, and hand-foot-and-mouth disease. Consequently, clinical manifestations are not reliable enough for the differential diagnosis between influenza and other CARVs infection, therefore a rapid antigen test or molecular assay is critical to confirm the causative virus.

Keywords Community-acquired respiratory virus · Influenza-like illness Taxonomy · Etiology

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1 Introduction

Respiratory viruses causing seasonal epidemics in the community are called community-acquired respiratory viruses (CARVs). Besides influenza virus, CARVs include human rhinovirus (HRV), human respiratory syncytial virus (RSV), human parainfluenza virus (HPIV), human adenovirus (HAdV), human coronavirus (HCoV), human metapneumovirus (HMPV), human bocavirus (HBoV), human enterovirus (HEV), and human parechovirus (HPeV). CARVs usually cause temporally upper respiratory tract infections in immunocompetent individuals; however, they can also cause severe lower respiratory tract infections (LRTIs) in susceptible individuals such as infants, elders, and immunocompromised patients. Although a vaccine and antiviral treatment have been established only against the influenza virus, knowledge about each CARV is also important from the perspective of clinical practice and infection control. This chapter focuses on CARVs other than influenza virus. Each CARV is briefly overviewed at the beginning, and then clinical aspects, emphasizing on the differential diagnosis between influenza and other respiratory viral infections, are discussed.

2 Brief Summary of CARVs

In this section, basic information for each CARV is briefly described. The taxonomy for CARVs is summarized in Table 8.1.

Table 8.1 Brief description of CARVs taxonomy

Genome	Family	Genus	Species	Envelope
RNA	*Picornaviridae*	*Enterovirus*	Human rhinovirus A, B, C	
			Human enterovirus A, B, C, D	(−)
			Human parechovirus 1, 2, 3, 4, 5, 6	
	Coronaviridae	*Alphacoronavirus*	Human coronavirus NL63, 229E	
		Betacoronavirus	Human coronavirus OC43, HKU1, SARS-CoV-1/2, MERS-CoV	(+)
	Pneumoviridae	*Metapneumovirus*	Human metapneumovirus A, B	
		Orthopneumovirus	Human respiratory syncytial virus A, B	(+)
	Paramyxoviridae	*Respirovirus*	Human parainfluenza virus 1, 3	
		Rubulavirus	Human parainfluenza virus 2, 4	(+)
	Orthomyxoviridae	*Alphainfluenzavirus*	Influenza A virus	
		Betainfluenzavirus	Influenza B virus	(+)
		Gammainfluenzavirus	Influenza C virus	
DNA	*Adenoviridae*	*Mastadenovirus*	Human adenovirus A, B, C, D, E, F, G	(−)
	Parvoviridae	*Bocavirus*	Human bocavirus 1, 2, 3, 4	(−)

2.1 Human Rhinovirus (HRV)

HRV, first reported in 1956 [1], is a single-stranded, positive-sense RNA virus that belongs to the family *Picornaviridae*. The name originally derived from "rhinos" in Greek, meaning "of the nose." HRV consists of more than 160 serotypes and is classified into three genotypes (A, B, and C) [2]. Although previous studies indicated that HRV-C was more virulent than other genotypes, being associated with asthma exacerbation and LRTIs, recent studies showed that specific genotypes are not linked to illness severity [3].

HRV is known as the most common virus causing mild self-limiting upper respiratory tract infections across all age groups; however, HRV can also cause severe LRTIs in immunocompromised patients [4]. Seo et al. reported that the mortality of transplant recipients with HRV present in the lower respiratory tract was as high as the rates of other viral pneumonias caused by RSV, HPIV, and influenza virus [5]. Respiratory viral infections often cause asthma exacerbation and chronic obstructive pulmonary disease (COPD), and HRV is known as the most detected virus in such vulnerable patients [6, 7]. Moreover, experimental inoculation studies revealed that HRV infection induced asthma exacerbations and COPD in human subjects [8–10].

2.2 Human Respiratory Syncytial Virus (RSV)

RSV, reclassified into the family *Pneumoviridae* in 2016 (previously *Paramyxoviridae*), is a single-stranded, negative-sense RNA virus. This virus was firstly isolated from chimpanzees in 1955, and shortly thereafter detected in infants with respiratory symptoms [11]. There are two genotypes (RSV-A and RSV-B) and no difference in virulence was shown in previous studies between genotypes [12, 13]. Approximately 60% of infants under 1-year-old experience a RSV infection and almost all children become infected with this virus at least once by the age of 2 or 3 years old [14]. RSV is the most common virus causing bronchiolitis and pneumonia in infants. A multicenter study targeting 5067 children revealed that RSV was detected in 18% of all children with acute respiratory infections, and that 61% of these patients required hospitalization. Additionally, 2–3% of children younger than 12 months were hospitalized annually due to RSV infections in the United States [15]. RSV also causes LRTIs and exacerbations of underlying diseases in adults, especially in the elderly and in immunocompromised patients [16].

2.3 Human Parainfluenza Virus (HPIV)

HPIV, first isolated from infants with croup in 1956 [17], is a single-stranded, negative-sense RNA virus belonging to the family *Paramyxoviridae*. There are four serotypes (1, 2, 3, and 4); HPIV-1 and HPIV-3 are classified in the genus *Respirovirus*,

while HPIV-2 and HPIV-4 belong to the genus *Rubulavirus*. Clinically, HPIV-1 and HPIV-2 are the leading cause of laryngotracheobronchitis (croup) in children, accounting for 60–75% of croup illnesses [18]. HPIV-3 is the most commonly detected serotype in all age groups and it often causes pneumonia and outbreaks in long-term care facilities [19]. The epidemiology of HPIV-4 infections is not well understood because the detection is relatively difficult and its symptoms often present as subclinical [18].

2.4 Human Adenovirus (HAdV)

HAdV was firstly isolated from surgically resected adenoid tissue of children and initially reported as a "cytopathogenic agent" in 1953 [20]. HAdV is a double-stranded DNA virus categorized into the *Adenoviridae* family. HAdV is further classified into seven species (HAdV-A through HAdV-G) containing 67 immunologically distinct serotypes [21]. HAdV infects the mucosal tissue and each serotype presents with tissue/organ tropism, therefore, HAdV causes a variety of illnesses including respiratory infections, keratoconjunctivitis, and gastroenteritis (Table 8.2). Among these serotypes, 1–5, 7, 21, and 41 are most commonly associated with human disease [22]. Serotypes 4, 7, 14, and 55 were reported to cause severe pneumonia in immunocompetent adults, and of note, the former two (HAdV-4, 7) are known as a common cause of respiratory illness among military recruits in the United States [22–24]. Although temporarily suspended, an oral live nonattenuated vaccine against both HAdV-4 and HAdV-7 is administered to military recruits in the United States [25]. It is also clinically important to consider that gastrointestinal symptoms are sometimes intercurrent in patients (especially in children) having a HAdV respiratory illness [22].

Table 8.2 Disease types and associated serotypes of HAdV

Disease type	Patient population	Common serotypes
Pharyngitis	All age groups	1–7
Pharyngoconjunctival fever	Children	3, 4, 7
Pneumonia	Younger children	1–7
Pneumonia	Adults	3, 4, 7, 14, 21, 55
Epidemic keratoconjunctivitis	All age groups	8, 19, 37, 53, 54, 56
Gastroenteritis	Younger children	40, 41
Hemorrhagic cystitis	HSCT, SOT recipients	3, 7, 11, 21, 34, 35
CNS infections	Children, immunocompromised host	1–3, 6, 7, 12, 32
Myocarditis	Children, adults	1, 2, 5–7, 21
Disseminated disease	Children, immunocompromised host	1–3, 5, 7

CNS central nervous system, *HSCT* hematopoietic stem cell transplant, *SOT* solid organ transplant

2.5 Human Coronavirus (HCoV)

HCoV is a single-stranded, positive-sense RNA virus and belongs to the family *Coronaviridae*. The term of "corona" derives from the crown-like appearance of virions, meaning crown in Latin, by electron microscopy. CoV is further classified into four genera: alpha-, beta-, gamma-, and delta-coronavirus. HCoV was first isolated from the nasal discharge of common cold patients in 1965 [26]. To date, there are seven HCoVs including two alpha-CoVs (HCoV-NL63, HCoV-229E) and five beta-CoVs (HCoV-OC43, HCoV-HKU1, severe acute respiratory syndrome-CoV (SARS-CoV)-1, SARS-CoV-2, and Middle East respiratory syndrome-CoV (MERS-CoV)) [27, 28]. HCoVs were initially considered as a mere pathogen causing common cold-like symptoms; however, emergence of SARS-CoV in 2002 [29], MERS-CoV in 2012 [30], and SARS-CoV-2 in 2019 [28] has reminded us of its significant impact on human public health.

2.6 Human Metapneumovirus (HMPV)

HMPV was first identified from nasopharyngeal samples in children with respiratory symptoms in 2001 [31]. HMPV is a single-stranded, negative-sense RNA virus, and currently reclassified into the family *Pneumoviridae*, which also includes RSV. A seroprevalence study revealed that most children experience HMPV infection at least once by 5 years of age and re-infection occurs throughout the life [32]. HMPV preferentially infects respiratory ciliated epithelial cells and causes a variety of respiratory symptoms. A study investigating the clinical features of HMPV pneumonia in long-term care facilities in Japan showed that HMPV pneumonia patients experienced wheezing more frequently compared to non-pneumonia HMPV infected patients (43% vs. 9%; $p < 0.0001$). Additionally, the authors suggested that proximal bronchial wall thickenings radiating outward from the hilum on chest X-ray is a common finding in HMPV induced pneumonia [33].

2.7 Human Bocavirus (HBoV)

HBoV was first isolated from the respiratory samples of infants as an unknown human parvovirus in 2005 [34]. HBoV is a single-stranded DNA virus belonging to the family *Parvoviridae* and further classified into four subtypes (HBoV-1, -2, -3, and -4). HBoV-1 causes respiratory illness especially in young children, while HBoV-2, -3, and -4 are associated with gastroenteritis [35].

2.8 Human Enterovirus (HEV) and Parechovirus (HPeV)

HEV and HPeV are positive-sense, single-stranded RNA virus and belong to the family *Picornaviridae*. HEV is classified into four species (HEV-A, -B, -C, and -D) and traditional viral names such as coxsackievirus, echovirus, and poliovirus are still retained for individual serotypes [36]. HEV causes a variety of diseases involving not only respiratory organs, but also the skin, eyes, heart, and central nervous system (Table 8.3). Acute flaccid paralysis/myelitis caused by wild-type poliovirus has been eradicated from most countries including Japan. Based on genetic analysis, echovirus 22 and 23 were reclassified into a new genus *Parechovirus* and renamed HPeV-1 and -2, respectively, in 1999. Currently, 16 different parechovirus genotypes are identified and HPeV 1-6 cause infectious diseases in human. Among these genotypes, HPeV-1, -3, and -6 are associated with respiratory infections, and HPeV-3 is known as a cause of sepsis-like illness in neonates [37].

3 Viral Etiology in Patients with Influenza-Like Illness

World Health Organization defines influenza-like illness (ILI) as "an acute respiratory illness with a measured temperature of ≥38 °C and cough; with onset within the past 10 days" [38]. It is well known that CARVs other than influenza can cause ILI. A prospective, multinational, active community surveillance study involving 17 centers in eight countries was conducted from February 2010 to August 2011 [39].

Table 8.3 Disease types and associated serotypes of HEV

Disease type	Patient population	Common species/serotypes
Common cold	All age groups	Not specified
Herpangina	Children (mostly 1–7 years old)	Group A coxsackieviruses
HFMD	Children	Enterovirus 71, coxsackievirus A6, A16
Acute hemorrhagic conjunctivitis	All age groups	Enterovirus 70, coxsackievirus A24
Bronchitis, pneumonia	All age groups	Enterovirus D68
Acute flaccid paralysis/ myelitis	Children	Poliovirus 1, 2, 3, enterovirus A71, D68
Aseptic meningitis	Infants (mostly <1-year-old)	Group B coxsackieviruses, echoviruses
Maculopapular eruptions	Children	Echoviruses
Petechiae/purpuric rash	All age groups	Echovirus 9, coxsackievirus A9
Epidemic Pleurodynia	Adolescents, younger adults	Group B coxsackieviruses
Myopericarditis	Adults	Group B coxsackieviruses

HFMD hand-foot-and-mouth disease

In this study, upper respiratory specimens were collected from 2421 children aged 6 months to 10 years (3717 ILI episodes) and tested by multiplex PCR. As a result, CARVs were detected in 2958 of 3717 episodes (79.6%) and the most commonly detected virus was HRV/HEV (41.5%), followed by influenza (15.8%), HAdV (9.8%), HPIV and RSV (both 9.7%), HCoV (5.6%), HMPV (5.5%), and HBoV (2.0%). The assay used in the study was unable to distinguish between HRV and HEV. Another study enrolling 1023 children with ILI revealed HRV as the most detected virus (49.4%), followed by HPIV-3 (19.5%), HMPV (16.5%), and influenza (5.4%) [40]. Table 8.4 summarizes representative large-scale studies investigating viral etiology in adult patients with ILI [41–47]. Most studies revealed that HRV, as well as influenza virus, were the leading cause of ILI. Needless to say, the viral etiology of ILI varies by many factors such as the study sample (e.g., age, influenza vaccination history), season, setting (e.g., community or outpatient or inpatient), and regions. However, the important thing is that CARVs other than influenza virus are commonly detected even during influenza epidemics [39, 48].

4 Are Specific Symptoms Useful in Distinguishing Between Influenza and Other CARVs?

Before discussing symptoms, the most important factor in clinically diagnosing influenza is whether the patient presenting with ILI visits a clinic during an influenza epidemic. Some studies investigated the utility of fever and cough symptoms to predict the likelihood of influenza [49–51]. Michiels et al. reported that the likelihood of influenza was quite low in patients without fever and cough during influenza non-epidemic periods [49]. On the other hand, the presence of "previous flu-like contacts," cough, "expectoration on the first day of illness," and fever higher than 37.8 °C during an influenza epidemic increased the likelihood of influenza threefold. Ebell et al. reviewed five studies examining the diagnostic accuracy based on the "fever and cough rule" during the influenza season [51]. The sensitivity and specificity of the rule for influenza diagnosis was 30–78% and 55–94%, respectively, and the authors concluded that the rule had a modest accuracy. We should keep in mind that ILI symptoms sometimes lack in some population types such as the elderly, for example. Therefore, clinical diagnosis of influenza should be carefully made by taking a comprehensive decision based on several factors such as the epidemic situation around the region and patient background.

Predicting causative CARV by clinical symptoms is further difficult, except for diseases presenting unique features such as bronchiolitis in children (mostly caused by RSV [52]), laryngotracheobronchitis, known as croup (mostly caused by HPIV [53]), hand-foot-and-mouth disease and herpangina (both caused by HEV). Bellei et al. compared the clinical manifestations (fever, cough, coryza, sore throat, headache myalgia, and chills) of seven CARVs (influenza, HRV, HMPV, HAdV, RSV, HCoV, and HEV) in adult patients with acute respiratory symptoms [46]. Although

Table 8.4 Viral etiology in adult ILI patients

Authors [References]	Country	Period	Number of samples		Percentage of each virus[b]							
			Total	Positives[a] (%)	Flu	HRV	RSV	HAdV	HCoV	HMPV	HPIV	Others
Al-Romaihi et al. [41]	Qatar	2012–2017	43.597	20,278 (47%)	49	18	5	5	9	5	5	3
Tan et al. [42]	Singapore	2009–2012	7.733	3794 (49%)	36	15	NT	17	9	4	3	22
Noh et al. [43]	Korea	2011–2012	1.983	1100 (55%)	77	8	3	0.6	3	6	3	NT
Todd et al. [44]	Vietnam	2013–2015	1.152	651 (57%)	70	9	2	3	2	1	8	4
Falsey et al. [45]	Multinational	2008–2010	556	340 (61%)	35	24	12	0.3	9	9	0.4	NT
Bellei et al. [46]	Brasil	2001–2003	420	274 (65%)	32	38	4	6	7	9	1	3
Louie et al. [47]	USA	2002	266	147 (55%)	35	16	8	0.7	1	3	0.7	9

Flu influenza virus, *HRV* human rhinovirus, *RSV* human respiratory syncytial virus, *HAdV* human adenovirus, *HCoV* human coronavirus, *HMPV* human metapneumovirus, *HPIV* human parainfluenza virus, *NT* not tested

[a]Number of samples positive for at least one virus

[b]Number of positives for each virus/number of positive of any virus

the frequency of fever was relatively higher in patients with influenza (91%) compared to other viruses (51–60%), there was no virus-specific symptom overall. To identify the causative CARVs in patients with respiratory infections, rapid antigen tests using immunochromatography or molecular assays including nucleic acid amplification tests are useful [54].

5 Conclusions

In this chapter, basic information regarding viral and clinical aspects of CARVs other than influenza is briefly summarized. From an epidemiological point, CARVs other than influenza virus are commonly detected even during influenza epidemics, thus a differential diagnosis between influenza and other CARVs infections is important. Additionally, identification of CARVs is sometimes critical especially when managing severe pneumonia patients or in an outbreak setting. Since the usefulness of clinical manifestations for differential diagnosis between influenza and other CARVs infection is limited in most cases, rapid antigen tests or molecular assays are needed to confirm a causative virus.

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