Viral Infections of the Respiratory Tract

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Shailendra Prasad, Elizabeth Lownik, and Jason Ricco

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S. Prasad (✉) • E. Lownik • J. Ricco
Department of Family Medicine and Community Health, North Memorial Family Medicine Residency, University of Minnesota, Minneapolis, MN, USA
e-mail: pras0054@umn.edu; lown0011@umn.edu; ricco004@umn.edu

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General Principles

Definition/Background

Viral infections of the respiratory tract are common events in all age groups and are the leading cause of mortality in children under 5 years of age in developing countries [1]. These infections cause significant economic burden, with estimated direct and indirect medical costs in the US exceeding $70 billion annually [2, 3]. Children under the age of 5 have an average incidence rate of four to six viral respiratory infections/year and the rate gradually decreases to one to two/year in most adults [4].

Epidemiology

Respiratory viruses spread mainly through direct contact with infected individuals, predominantly through respiratory droplets. While respiratory infections tend to be present throughout the year in warmer areas, in temperate climates these are seen most often in the winter months (see Fig. 1) [5] Although some of the new and emergent infections may arise from an animal host, the majority of the respiratory viral infections are spread from other humans. Most of the illnesses are introduced to families by young, school-age children or other caregivers with secondary infections occurring following these initial cases.

Pathophysiology

Respiratory infections caused by viruses are transmitted primarily by droplets. These viruses can attach to the upper or lower respiratory tract and induce an IgA-mediated immune response in the mucous secretions of the respiratory tract and an IgG-mediated response in serum. Respiratory viral infections generally induce adaptive immune responses that should be protective. However, repeated respiratory infections are due to the large numbers of serotypes of each virus, or antigenic variations in viruses such as the influenza virus, and their ability to induce similar, non-specific clinical signs.

The clinical presentation of respiratory viruses can vary, however their clinical symptoms are

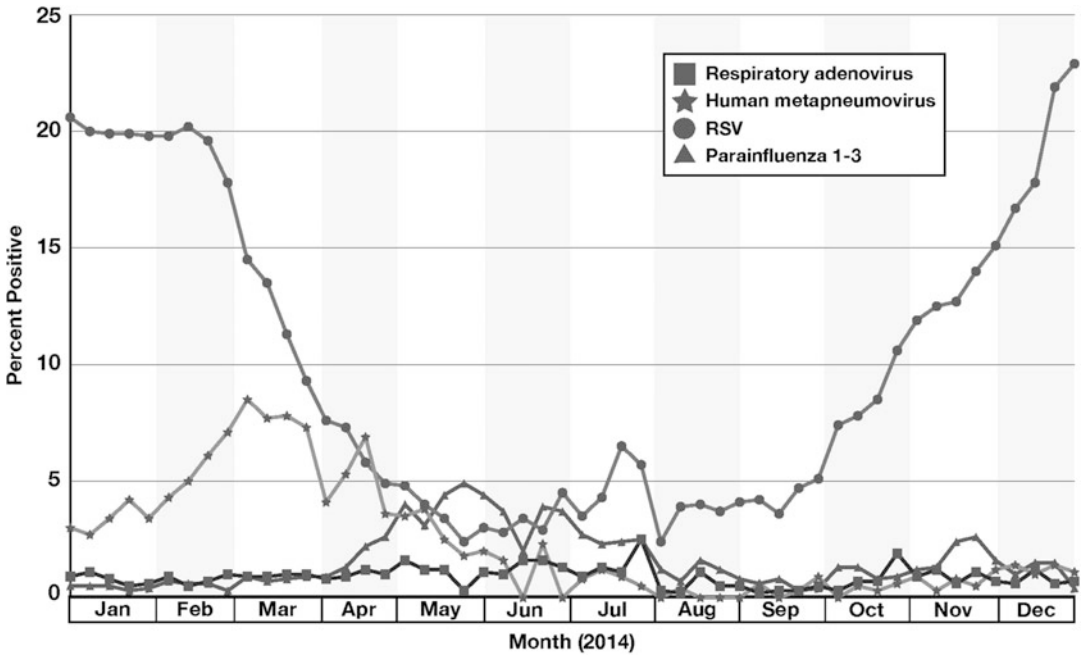

Fig. 1 Weekly laboratory test data of respiratory viruses in the USA, 2014 (Data from CDC National Respiratory and Enteric Virus Surveillance System. http://www.cdc.gov/surveillance/nrevss/)

Table 1 Clinical presentations and causes of viral respiratory syndromes [4, 6–8]

Clinical condition	Common causes	Occasional causes	Infrequent causes
Common cold	Rhinovirus Coronavirus	RSV Influenza Parainfluenza	Metapneumoviruses Enteroviruses Adenovirus
Laryngitis	Parainfluenza Rhinovirus	Influenza	Adenovirus
Acute bronchitis	Influenza Adenovirus RSV	Parainfluenza Coronavirus Rhinovirus	Enterovirus Metapneumovirus
Influenza like illness[a]	Influenza A	Influenza B	Enterovirus Adenovirus
Croup	Parainfluenza	Influenza RSV	
Pneumonia	RSV Influenza	Adenovirus	Rhinovirus Coronavirus Herpes Simplex virus
Pharyngotonsillitis	Adenovirus Herpes Simplex Virus	Enterovirus Influenza B	
Bronchiolitis	RSV	Human metapneumovirus Influenza Parainfluenza	Bocavirus Coronavirus Adenovirus

[a]Influenza includes – fever, cough, myalgia and malaise

often very similar. Table 1 describes common clinical presentations and the viruses that cause these [4, 6–8].

Laboratory Testing

Respiratory viruses may be identified using viral cultures or by rapid tests identify antibodies to the virus [9]. Viral cultures are reserved primarily for research purposes given the time for culture growth, the cost, and often their relatively low sensitivity. Clinical diagnosis of respiratory viral infections remains the standard in clinical practice. Rapid tests are being used more frequently in the clinical setting to identify influenza and RSV infections and initiate targeted treatments, however rapid virus detection does not reduce antibiotic use or cost [10].

Laboratory tests are increasingly being used to differentiate viral from bacterial infections, since early use of antibiotics may be advantageous in the latter. C reactive protein (CRP) and procalcitonin levels in blood are two of the tests used. While procalcitonin-guided treatment algorithms have been shown to decrease antibiotic use [11], CRP is neither specific nor sensitive enough to differentiate a bacterial respiratory infection from one that is caused by a virus [12].

Common Cold

Definition/Background

The common cold, an acute infection of the upper respiratory tract that is usually self-limited, is the most frequent human infection [13, 14]. There are over *one billion* colds every year in the United States, and it is estimated that the common cold results in 20 million days of absence from work and 22 million days of absence from school each year [14, 15]. Typical common cold symptoms consist of nasal congestion and discharge, sore throat, cough, sneezing, and sometimes headache, with symptoms usually lasting less than 10 days in duration. These symptoms are fairly nonspecific and can easily be confused with allergies or early symptoms of more serious diseases. However, taking a detailed history, particularly identifying sick contacts, is usually helpful in distinguishing the common cold from other illnesses.

Causes

Although numerous viruses have been identified as etiologies of the common cold (see table of viral prevalence by illness presentation), rhinoviruses are by far the most common viruses detected across all age groups in the setting of common cold symptoms, accounting for 30–50 % of all cases [4, 14, 16]. Coronaviruses account for 10–15 % of cold cases, and influenza viruses are detected 10–15 % of the time. Given that cold viruses such as respiratory syncytial virus also are responsible for many flu-like illnesses, there is significant overlap in viral etiologies of the common cold and flu syndromes [4, 14].

Clinical Manifestations

Rhinovirus infections typically begin with a sore throat, soon followed by nasal congestion, rhinorrhea, cough, and sneezing. As the illness progresses, sore throat symptoms tend to resolve quickly, and the initially watery rhinorrhea becomes increasingly purulent. Fever is uncommon among adults with colds, but is more frequent in children with viral respiratory infections. Common cold symptoms peak in severity within 2–3 days of onset, and have a mean duration of 7–10 days [14].

Diagnosis

The diagnosis of the common cold is primarily based on clinical symptoms alone, and is often correctly made by adult patients themselves. Diagnosis in children and infants can be more difficult, especially in the early course of a febrile illness. Streptococcal pharyngitis can resemble early common cold symptoms, but the nasal congestion and drainage usually seen in common cold are atypical in streptococcal pharyngitis [14, 16]. Given the wide range of overlap in symptoms caused by different respiratory viruses, influenza included, it is often impossible to identify a specific viral etiology for cold symptoms in a particular patient. Although rapid detection of viral pathogens with real-time polymerase chain reaction can increase diagnostic accuracy, it has not been shown to reduce antibiotic use or costs, and therefore is of limited use in everyday clinical practice [10].

Treatment

The approach to treatment for the common cold focuses on symptomatic relief as well as prevention. Antibiotics are ineffective and inappropriate treatment for the common cold and should be avoided in adults and children [17, 18]. Over the counter cough and cold medications should be avoided in all children younger than 4 years due to the potential for harm and lack of benefit. Products shown to improve cold symptoms in children include vapor rub, zinc sulfate, *Pelargonium sidoides* extract, and buckwheat honey, although the quality of the evidence varies. Ineffective treatments for children include both inhaled and oral corticosteroids and *Echinacea*. Among adults, decongestants, antihistamine/decongestant combinations, and intranasal ipratropium have been shown to improve cold symptoms [17, 18]. Additionally, non-steroidal anti-inflammatory drugs have been shown to relieve discomfort due to colds but not to improve respiratory symptoms [19]. When taken within 24 h of symptom onset, zinc has been shown to reduce the duration of common cold symptoms in healthy adults [20]. *Echinacea* plant preparations have not proven effective in treating common colds among adults [21]. In supplementation trials, regular use of vitamin C did not decrease the incidence of common colds, but did have a positive effect on symptom duration and severity. Therapeutic trials of vitamin C during a cold have not shown a significant effect on common cold symptom reduction, but it may be worth considering in individual cases given its favorable safety profile and low cost [22].

Laryngitis

Definition/Background

Inflammation of the larynx can be caused by a variety of conditions, including: viral or bacterial infection, acid reflux, voice misuse and overuse,

toxic inhalation or ingestion, postnasal drainage, or coughing from any cause. Acute laryngitis, defined as inflammation of the larynx or vocal cords lasting less than 3 weeks, is one of the most common disorders of the larynx. Symptoms include lowering of the normal pitch of the voice or hoarseness, usually lasting from 3 to 8 days. Other symptoms of an upper respiratory infection are common along with laryngitis, and the condition has been linked to changes in the weather [23].

Treatment

Although acute laryngitis is usually caused by a viral infection, there are no useful clinical criteria to distinguish between viral and bacterial causes such as *Moraxella catarrhalis*, *Haemophilus influenzae*, or *Streptococcus pneumoniae.* Viral laryngitis is likely caused by the same viruses as the common cold (i.e., rhinovirus, coronavirus). Treatment is largely supportive, and includes voice rest, corticosteroids, and proton pump inhibitors [24]. Antibiotics are often prescribed for acute laryngitis. However, a recent systematic review concluded that antibiotics are of no benefit in the treatment of acute laryngitis [23].

Influenza

Definition/Background

Influenza is an acute respiratory illness caused by the influenza virus. In temperate climates, seasonal epidemics of influenza occur annually during the winter months, while in tropical climates influenza cases occur intermittently throughout the year [24]. Worldwide, three to five million people develop influenza each year and approximately 250,000–500,000 die of influenza-related illness [25]. The Epidemiology and Prevention Branch in the Influenza Division at the Centers for Disease Control and Prevention (CDC) tracks and reports influenza activity in the United States in a weekly report throughout the influenza season [26]. In the USA, influenza can peak in the colder weather months with most peaks occurring in February (see Fig. 2) [28]. Influenza results in significant economic costs as well as morbidity and mortality. Between 1976 and 2007 in the USA, estimated deaths attributable to influenza ranged from 3,000 to 49,000 per year, with the majority of deaths occurring in those aged >65 years [28].

Causes

The influenza virus is a single stranded RNA virus from the Orthomyxoviridae family that comes in three subtypes: A, B, and C. Human influenza virus types A and B cause the epidemics of human disease, while influenza virus type C causes a mild respiratory illness similar to the common cold [29]. The influenza A virus is further classified by the type of surface hemagglutinin (H) and neuraminidase (N) antigens that are expressed [30]. The appearance of new combinations of the H and N antigens results in "antigenic shifts" that have the potential to cause pandemics of human illness due to a lack of pre-existing immunity [29]. Within the last decade, two new strains of influenza A have emerged and resulted in pandemics- the H1N1 strain in Mexico in 2009 and the H7N9 strain in China in 2013 [31].

Prevention

Vaccination is the preferred public health method for prevention of influenza. Both inactivated influenza vaccine (IIV) and live attenuated influenza vaccine (LAIV) are available each season and are created from the circulating influenza A and B virus isolates that are anticipated to circulate in the following season according to recommendations of the World Health Organization [32]. Current recommendations call for annual influenza vaccination for all individuals greater than 6 months of age. The LAIV is recommended over the IIV for children ages 2–8 when immediately available if the child has no contraindications to the live attenuated vaccine. When vaccine supply is limited, preference should be given to those at higher risk, including children age 6–59 months, adults >50 years of age, those with

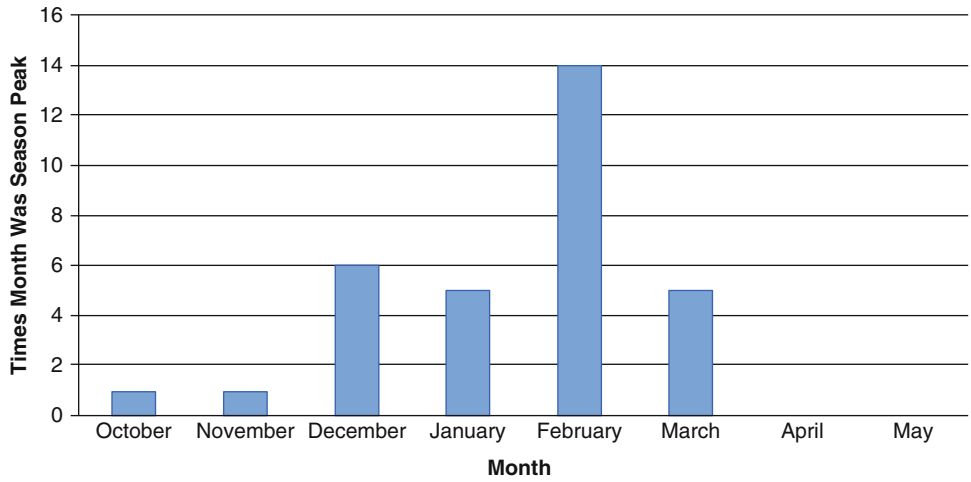

Fig. 2 Peak month of flu activity 1982–1983 through 2013–2014 [27]

immunosuppression or other severe chronic disease including morbid obesity, women who are or will become pregnant during the influenza season, residents of long-term care facilities, and Native Americans/Native Alaskans [32]. At this time, vaccination demonstrates a minimal effect on symptomatic influenza in otherwise healthy adults, with one case prevented for every 71 adults vaccinated [33]. However, universal vaccination is encouraged to improve herd immunity to influenza thus protecting high-risk individuals [34].

In certain situations, the antiviral medications oseltamivir or zanamivir can be used as an adjunct to vaccination for prevention of influenza. In a meta-analysis of prophylaxis trials, both medications demonstrated a significant reduction in the risk of symptomatic influenza in individuals and in households [35]. However, due to concern for increasing viral resistance, the CDC does not recommend the routine use of chemoprophylaxis for prevention of influenza, but rather recommends judicious use for those with known exposure who are at high risk for influenza complications or for whom the influenza vaccine is contraindicated [34].

Clinical Manifestations

Infection of the respiratory tract by influenza virus classically results in acute onset of systemic and respiratory symptoms such as fever, cough, sore throat, nasal congestion, headache, myalgias, or malaise [32]. However, infection by influenza virus can be asymptomatic or cause other syndromes such as the common cold, pharyngitis, or pneumonia. Other viruses such as respiratory syncytial virus, adenovirus, or coronavirus can also cause an influenza-like illness [30]. The majority of those who get influenza will recover within 3–7 days, but cough and fatigue may persist beyond 2 weeks. Some develop complications such as pneumonia (either viral or a secondary bacterial infection), which can be life threatening, particularly for those at high risk. Influenza infection can also exacerbate other underlying chronic diseases such as asthma, COPD, and congestive heart failure.

Diagnosis

If influenza is suspected clinically and the patient would benefit from antiviral treatment (see below), a presumptive clinical diagnosis of influenza should be sought. Reverse transcriptase polymerase chain reaction (RT-PCR) is the most sensitive and specific method of influenza diagnosis according to the Infectious Disease Society of America, however the test is slow and can often take several days for a definitive result. Rapid

Table 2 Persons at high risk for complications from influenza [34]

Children aged <5 years (especially those aged <2 years)
Adults aged ≥65 years
Persons aged ≤18 years who are receiving long-term aspirin therapy
Individuals with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematologic (including sickle cell disease), metabolic disorders (including diabetes mellitus) or neurologic and neurodevelopment conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy (seizure disorders), stroke, intellectual disability (mental retardation), moderate to severe developmental delay, muscular dystrophy, or spinal cord injury)
Immunosuppressed individuals, including that caused by medications or by HIV infection
Pregnant or postpartum women (within 2 weeks after delivery)
American Indians/Alaska Natives
Morbidly obese individuals (i.e., BMI ≥40)
Nursing home, or other chronic-care facility residents

influenza diagnostic tests (RIDTs) are antigen tests with results often available quickly enough to be clinically relevant. However, the results have poor sensitivity: in a meta-analysis of 159 studies of RIDT's compared to RT-PCR or viral culture, the RIDT's demonstrated a pooled sensitivity of 62.3 % (95 % CI 57.9–66.6 %) and a pooled specificity of 98.2 % (95 % CI 97.5–98.7 %) [36]. For this reason, a positive RIDT result can be considered adequate to make the diagnosis, but a negative RIDT result should not be used to exclude the diagnosis of influenza when clinically suspected.

Treatment

Four pharmacologic agents are available to treat influenza in the United States: the neuraminidase inhibitors zanamivir and oseltamivir, and the adamantanes amantadine and rimantadine. Amantadine and rimantadine are only effective against influenza A, and due to high rates of resistance (>99 % for influenza A H3N2 or H1N1) their use is not currently recommended [34]. Zanamivir (inhaled) and oseltamivir (oral) are effective against both influenza A and B and still demonstrate low rates of resistance [37]. Treatment with one of these agents is recommended as soon as possible for patients with known or suspected influenza who are hospitalized, manifest severe, complicated, or progressive illness, or are at high risk for complications, including adults >64 years of age, children <2 years of age, persons with severe underlying chronic illness or immunosuppression, or several other high risk groups (Table 2) [34]. One recent meta-analysis demonstrated small, non-specific effects on reducing the total duration of influenza symptoms without a demonstrated reduction in complications for otherwise healthy adults with influenza treated with oseltamivir or zanamivir [35]. The use of a neuraminidase inhibitor for treatment of proven or suspected influenza in an otherwise healthy adult without risk factors for severe disease should be determined by clinical judgment and shared decision making.

Acute Bronchitis

Definition/Background

Acute bronchitis is a self-limited infection of the epithelial cells of the bronchi characterized by the presence of cough, with or without sputum production. The symptoms of acute bronchitis can overlap with other clinical syndromes of upper and lower respiratory tract infections. Symptoms generally last for 2 weeks, but the associated cough may persist for up to 8 weeks [38]. In the USA, acute bronchitis is the ninth most commonly encountered diagnosis in the outpatient setting [39].

Causes

The majority (>90 %) of cases of uncomplicated acute bronchitis are due to a viral infection [40]. Influenza A and B viruses, parainfluenza virus, respiratory syncytial virus, coronavirus, adenovirus, rhinovirus, and human metapneumovirus have all been identified, though in the majority of cases no causative agent is isolated [41]. *Bordetella pertussis*, *Mycoplasma pneumoniae*, and *Chlamydophila (Chlamydia) pneumonia* cause acute bronchitis in approximately 5–10 % of adult cases [40]. Though pneumonia-causing pathogens such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis* are sometimes isolated from patients with acute bronchitis, their role is unclear and they do not appear to be etiologic agents of bronchitis in otherwise healthy adults [40, 41].

Diagnosis

The diagnosis of acute bronchitis is based on clinical evidence of a lower respiratory tract infection with a cough persisting at least 5 days without evidence of pneumonia [41]. In the absence of abnormal vital signs or physical exam findings consistent with pneumonia, a chest radiograph is not necessary unless the patient is elderly or otherwise immune suppressed [41]. Other alternative diagnoses such as asthma, pharyngitis, sinusitis, influenza, and pertussis should be ruled out when clinically appropriate.

Treatment

Antibiotic treatment of acute uncomplicated bronchitis is not recommended [40]. Systematic reviews of the available evidence have demonstrated that, though there may be a modest reduction in duration of cough-related symptoms, this is unlikely to be clinically significant [38]. Overall there is no benefit to using antibiotics for acute bronchitis in otherwise healthy individuals, unless there is clinical suspicion for pertussis as the etiologic agent [40]. Clinical judgment should guide the determination of antibiotic use for those who are elderly or who have chronic respiratory comorbidities.

In spite of this recommendation, approximately two thirds of patients with acute bronchitis are prescribed antibiotics in the United States [42]. Procalcitonin-guided therapy has been shown to safely reduce antibiotic use in lower respiratory tract infections (including pneumonia, asthma, COPD, and uncomplicated acute bronchitis) in the primary care setting and can help guide treatment if bacterial infection is a concern [43].

Special Populations: Children, Elderly, and the Immunocompromised

Children tend to have more episodes of respiratory infections than adults and, while many have 4–6 infections/year, 15 % of children may have up to 12 infections in a year. Children who attend daycare have a 50 % more respiratory infections than those who do not [44]. The majority of infections in children are self-limiting with supportive care the only treatment required.

Viral respiratory infections are particularly concerning in the elderly and the immunocompromised. Secondary infections including pneumonia and sepsis cause increased morbidity and mortality in these populations. All-cause mortality is also increased with influenza in this population [45]. Among the institutionalized elderly, respiratory syncytial virus (RSV), parainfluenza, and influenza are important causes of respiratory illness. Along with respiratory precautions and hand hygiene, increased efforts towards immunization of the elderly and their caregivers are important to decrease morbidity in this population.

New and Emergent Respiratory Infections

The ease of travel and the interdependency of markets have brought new challenges of spreading infectious pathogens. It is in this context that the practicing physician should be aware of the

growing threats of emergent respiratory infections and their pandemic potential. Severe acute respiratory syndrome-coronavirus (SARS-CoV), avian influenza viruses H5N1, H7N9, and H10N8, swine-origin influenza A H1N1, human adenovirus-14, and the Middle East respiratory syndrome-coronavirus (MERS-CoV) are a few of the viruses that are concerning for relatively high mortality rates and the potential to result in pandemics [46]. Some of these are zoonotic, affect the lower respiratory tract, and have high morbidity and mortality rates. The most effective methods of preventing these emerging viruses at this time include the scrupulous adherence to respiratory precautions and an awareness of regional spread and outbreaks [32].

Prevention

Respiratory viral infections are predominantly transmitted through infected droplets. Following general hygienic practices helps to decrease transmission. These include regular hand hygiene, minimizing contact with sick individuals, and avoiding the sharing of personal items. Following "cough etiquette," including covering the nose and mouth with a tissue while coughing, proper disposal of tissue, and prompt hand washing, is also shown to decrease spread of respiratory infections [47]. Currently, an effective vaccine is available only for influenza. Other measures of prevention include antivirals for close contacts of those with influenza and use of palivizumab, a monoclonal antibody, in high-risk individuals to prevent respiratory syncytial virus (RSV) infections.

Family and Community Issues

Antibiotic resistance in the healthcare setting is a growing threat to public health, and, as of 2013, two million people become infected and 23,000 people die each year from antibiotic-resistant infections [48]. In part, antibiotic-resistant infections stem from the prescribing of antibiotics when they are not needed, as in the case of viral respiratory tract infections. To avoid inappropriate use of antibiotics for viral infections, physicians should strive to adhere to clinical guidelines and decision-support tools combined with laboratory testing when indicated to determine risk for a bacterial infection.

Commonly, patients or parents will request antibiotics for viral infections, and physicians can feel pressured to prescribe antibiotics to address social stressors such as school or work absences. In this situation, family doctors need to clearly communicate that treating viral infections with antibiotics is ineffective and may be harmful. Additionally, pointing out negative or reassuring findings on exam and giving a specific diagnosis ("viral pharyngitis" or "viral upper respiratory infection" instead of "just a virus") can help with counseling patients. Lastly, it is important to acknowledge the suffering and discomfort caused by viral infections, to proactively offer treatment for symptoms, and to outline the normal course of the illness with clear indications for follow-up if symptoms do not resolve within an expected timeframe [49].

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