

Upper Respiratory Tract Infections

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ABSTRACT

Upper respiratory tract infections are the most common infections in the population. The term “upper respiratory tract” covers several mutually connected anatomical structures: nose, paranasal sinuses, middle ear, pharynx, larynx, and proximal part of trachea. Thus, infection in one part usually attacks the adjacent structures and may spread to the tracheobronchial tree and lungs.

Most of acute upper respiratory tract infections are caused by viruses. Bacterial pathogens can also be the primary causative agents of acute upper respiratory infections, but more frequently, they cause chronic infections.

Although most of the upper respiratory infections are self-limiting, some of them may cause severe complications. These includes intracranial spreading of suppurative infection, sudden airway obstruction due to epiglottitis and diphtheria, rheumatic fever after streptococcal tonsillitis, etc. In this chapter, we will describe clinical settings, diagnostic work-up, and treatment of upper respiratory infections, with special consideration to complications and life-threatening diseases occurring as a result of these infections.

INTRODUCTION

The upper respiratory system includes the nose, nasal cavity, pharynx, and larynx with subglottic area of trachea. In the normal circumstances, air enters the respiratory system through nostrils where it is filtered, humidified, and warmed inside the nasal cavity. Conditioned air passes through pharynx, larynx, and trachea and then enters in lower respiratory system. Dysfunction of any part of upper respiratory tract may change quality of inhaled air and consequently, may impair function of tracheobronchial tree and lung. Upper respiratory tract infections are the most common infections in the population. They are the leading cause for people missing work or school and, thus, have important social implications. They range from mild, self-limiting disease like common cold, syndrome of the nasopharynx to serious, life-threatening illnesses, such as epiglottitis.

Most of these infections are of viral origin, involving more or less all the parts of upper respiratory system and associated structures, such as paranasal sinuses and middle ear. Common upper respiratory tract infections include rhinitis (inflammation of the nasal mucosa), rhinosinusitis or sinusitis (inflammation of the nares and paranasal sinuses, including frontal, ethmoid, maxillary, and sphenoid), nasopharyngitis (rhinopharyngitis or the common cold—inflammation of the nares pharynx, hypopharynx, uvula, and tonsils), pharyngitis (inflammation of the pharynx, hypopharynx, uvula, and tonsils), epiglottitis (inflammation of the superior portion of the larynx and supraglottic area), laryngitis (inflammation of the larynx), laryngotracheitis (inflammation of the larynx, trachea, and subglottic area), and tracheitis (inflammation of the trachea and subglottic area).

In most cases, these diseases are self-limiting and can be managed at home. The more severe cases or those

with complications need to seek medical help. In general, symptomatic therapy is sufficient (analgesics, antipyretics, anticholinergic agents, antihistamines, antitussives, adrenergic agonists, corticosteroids, decongestants), in some instances antibiotics, or some traditional way of cure are also used. Rarely, surgical intervention or in most serious cases, care in the intensive care unit (ICU) is necessary.

NATURAL OCCURRENCE OF THE DISEASE

Most upper respiratory tract infections are caused by viruses and bacteria, which invade the mucosa. In most cases, the infection spreads from person-to-person, when touching the secretions by hand or directly by inhaling the respiratory droplets. Bacterial infections could be a prime cause of upper respiratory tract infection, but they may also be due to superinfection of a primarily viral infection.

Risk factors for the development of upper respiratory tract infections are close contact like close contact of small children who attend the kindergarten or school, travellers with exposure to numerous individuals, smoking (second-hand smoke too!), which may alter mucosal resistance, anatomic changes of respiratory tract, and nasal polyposis.

The respiratory tract is very well equipped to combat all kinds of invaders. The defense mechanisms include physical, mechanical, humoral, and cellular immune defenses. Mechanical barrier like hair in nose, which filter and trap some pathogens and mucus coats are very efficient. Ciliated cells with its escalator-like properties help transport all kinds of particles up to the pharynx; from there, they are swallowed into the stomach.

Humoral immunity, by means of locally secreted immunoglobulin A and other immunoglobulins and cellular immunity, acts to reduce the local infections. Inflammatory and immune cells (macrophages, monocytes, neutrophils, and eosinophils) coordinate by means of numerous cytokines and other mediators to engulf and destroy invaders. In case of diminished immune function (inherited or acquired), there is an increased risk for developing the upper respiratory tract infection or prolonged course of disease. Special attention is recommended in those with suboptimal immune defenses like those for instance, without a spleen, those with human immunodeficiency virus (HIV) infection, patients with cancer, patients receiving chemotherapy, dialysis, and those undergoing stem cell or organ transplantation. Adequate antimicrobial treatment and follow-up should be advocated, because a simple upper respiratory tract infection may rapidly

progress to a systemic illness in immunocompromised patients.

DIAGNOSIS

The diagnosis of upper respiratory tract infections in most cases rests only upon recognition of the symptoms and physical examination. The classification of those diseases is built upon the clinical manifestations, as already mentioned.

Some of these diseases can be treated at home. If the symptoms are severe, have unexpected prolonged duration, or in some other circumstances like in immunocompromised persons, or during epidemics, medical attention is necessary. The aim is to recognize or detect the causative agent and, thus, enable efficient therapy. In some instances, visualization and imaging techniques help in the management of these patients.

The armamentarium of investigations to reach the final diagnosis is huge.

Microbiology

As most of the upper respiratory tract infections are caused by viruses and as there are no targeted therapies for most viruses, viral testing usually is not indicated, except on several occasions like suspected influenza or in immunocompromised patients.

The search for the type of causative bacterial infection should be performed in some cases. Most frequent is a group A *Streptococcal* infection, especially with pharyngitis, colloquially known as a “strep throat”. Group A β -hemolytic streptococcus is the etiologic agent in approximately 10% of adult cases of pharyngitis. The clinical features¹ that can raise a suspicion are:

- Erythema, swelling, or exudates on tonsils or pharynx
- Fever with a temperature of at least 38.3°C for 24 hours
- Tender anterior cervical lymph nodes
- Absence of cough, rhinorrhea, and conjunctivitis (common in viral illness)
- Patient age 5–15 years
- Occurrence in the season with highest prevalence (winter-spring).

If clinical suspicion is high, no further testing is necessary and empirical antibiotic is given. When the diagnosis is inconclusive, further testing is recommended. The rapid antigen test for group A *Streptococcus* is fast, as it gives results in about half an hour, and its specificity is satisfactory. Throat cultures are not recommended for the routine primary evaluation of adults with pharyngitis or for the confirmation of negative rapid antigen tests. Throat cultures may be indicated as part of investigation of

outbreaks of group A β -hemolytic streptococcal disease, for monitoring the development and spread of antibiotic resistance, or when pathogens such as *Gonococcus* are being considered.

In most patients with suspected bacterial rhinosinusitis, the search for causative bacteria is not indicated. Sinus puncture aspiration may be performed by trained personnel in rare occasions like in a persistent disease, suppurative spread, and in immunocompromised patients or in nosocomial infections. The search for causative agent in rhinosinusitis may be necessary if the disease has an extended duration, or if influenza, mononucleosis, or herpes simplex is suspected. In rare occasions of laryngitis, the suspicion of diphtheria warrants specific tests.

The materials for microbiology analysis are collected by several procedures: throat swab, nasal wash, swabs, or aspirates for sinus puncture, and aspiration, or by the aid of endoscope.

Diagnostic tests for specific agents are helpful when targeted upper respiratory tract infection therapy follows the isolation of a specific microbe.

Imaging

Radiological studies, plain radiographic films, computed tomography (CT), ultrasound, and endoscopic inspection are not indicated in most cases, for instance, in common cold.²

Common plain radiographic findings of sinus include air-fluid levels and mucosal thickening, although all sinusitis patients do not show air-fluid levels (Figure 1).



FIGURE 1 Plain radiograph of sinuses shows polypoid edema predominantly on the left maxillary sinus, edema of the nasal conchae, and nasal septal deviation.

CT scanning can be helpful in the diagnosis of acute and chronic sinusitis, but it cannot distinguish between acute and chronic paranasal sinusitis. The CT findings have to be interpreted with respect to clinical features.³

CT findings of sinus opacification, air-fluid levels, and thickened localized mucosa are all features of acute sinusitis. Many nonspecific CT findings, including thickened turbinates and diffusely thickened sinus mucosa may be detected (Figure 2).

CT findings suggestive of chronic sinusitis include mucosal thickening, opacified air cells, bony remodeling, and bony thickening due to inflammatory osteitis of the sinus cavity walls. Bony erosion can occur in severe cases especially, if associated with massive polyps or mucocele.

If symptoms of rhinosinusitis extend despite therapy or if propagation of disease into adjacent tissue is suspected, sinus imaging is indicated. Signs or symptoms, which warrant intracranial extension of infection, request CT analysis to affirm the possibility of an intracranial abscess or other suppurative complications. Such symptoms may include proptosis, impaired intraocular movements, decreased vision, papilledema, changes in mental status, or other neurologic findings.

Sinus ultrasonography may also be useful in the intensive care or if radiation exposure is to be avoided. Recently, it has been reported⁴ that owing to a very good specificity and negative predictive value, bedside A-mode ultrasound may be a useful first-line examination for intubated and mechanically ventilated patients

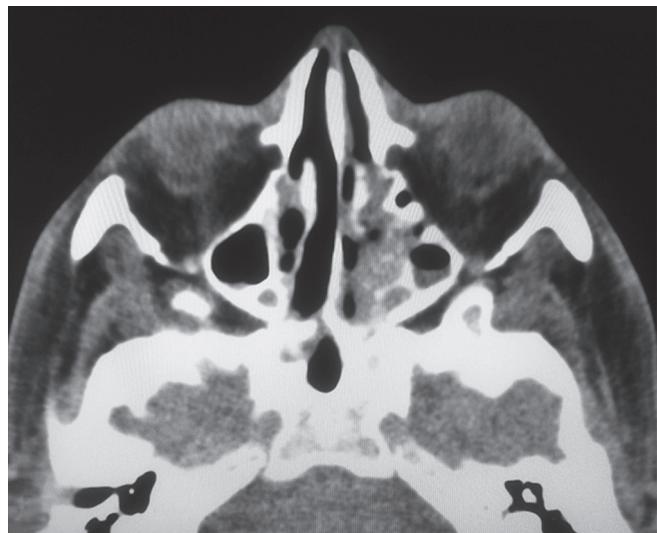


FIGURE 2 CT scan of paranasal sinuses shows thickening predominantly of the left maxillary sinus, almost diffuse opacification of ethmoid sinuses (especially left sinus) with partially resorbed intracellular septa. Marginal thickening of sphenoidal sinuses and thickening of the nasal passage is also detected.

in intensive care, especially to eliminate suspicion of maxillary sinusitis.

Nasal Endoscopy and Laryngoscopy

Nasal endoscopy has a definite role in the identification of sinonasal disease. But it has to be underlined that it does not apply to most of the patients with acute diseases who seek medical attention for the first time but only to those with prolonged course, severe symptoms, or when a suspicion of serious complications exists.

The indications for the procedure are the detection of disease in patients experiencing sinonasal symptoms (e.g., mucopurulent drainage, facial pain or pressure, nasal obstruction or congestion, or decreased sense of smell), evaluation of medical treatment (e.g., resolution of polyps, purulent secretions, convalescence of mucosal edema, and inflammation), evaluation of patients with complications or imminent complications of sinusitis, obtaining a culture of purulent secretions, evaluation of the nasopharynx for lymphoid hyperplasia, Eustachian tube problems, and nasal obstruction.

The laryngoscopy is performed in cases of suspected epiglottitis with great caution, only in well-equipped medical centers where the possible complications could be avoided. The instrumentation can provoke airway spasms and induce respiratory insufficiency.

RHINITIS AND RHINOSINUSITIS

Rhinitis is an inflammation and swelling of the mucous membranes of the nose, characterized by a runny nose, rhinorrhea, sneezing, congestion, obstruction of nasal breathing, and in some cases, pruritus. On the basis of duration of symptoms and changes of nasal mucosa, rhinitis may be acute or chronic. Etiology includes a number of causes, and infectious rhinitis is only one among many (Table 1). Each type of rhinitis may induce associated episode of sinusitis in a predisposed patient because of blockages in intranasal passages.

Acute Viral Rhinitis (Common Cold)

Acute infectious rhinitis and rhinosinusitis are usually the part of an upper respiratory infection, which involves pharynx known as common cold. Human rhinovirus is responsible for 50–80% of all common colds and the rest are caused by corona virus, adenovirus, parainfluenza virus, respiratory syncytial virus (RSV), or enterovirus.⁵

The incidence of the common cold varies by age. Children younger than 5 years tend to have 3–8 episodes of common cold per year on an average, while adolescents

TABLE 1

Classification and Etiology of Rhinitis

Type of rhinitis	Etiology
Infectious rhinitis	Viruses, bacteria, fungi
Vasomotor rhinitis	Disbalance of the parasympathetic and sympathetic system
Occupational rhinitis	Inhaled irritants
Hormonal rhinitis	Estrogen imbalance
Drug-induced rhinitis	ACEI, β -blockers, methyldopa, aspirin, NSAID, phentolamine, chlorpromazine, penicillamine, inhaled cocaine, estrogen, oral contraceptives
Gustatory rhinitis	Hot and spicy food
Allergic rhinitis	Various allergens
Nonallergic rhinitis with eosinophilia	Abnormal prostaglandin metabolism

ACEI, angiotensin-converting enzyme inhibitors; NSAID, nonsteroidal anti-inflammatory drugs.

and adults may have approximately 1–4 episodes in an year.⁶

Patients typically present with runny nose, sneezing, congestion, clear-to-mucopurulent nasal discharge, an altered sense of smell, postnasal drip with cough, and a low-grade fever. Facial pain and pressure may also be present. Occasionally, headache, rash (with group A streptococcal infections or enterovirus), gastrointestinal symptoms, myalgia, and fatigue are also present.

Substantial rhinorrhea is a distinctive feature of viral infection. During 2–3 days the nasal discharge turns from clear to mat, greenish and yellow. Fever is unusual in adults. These properties do not differentiate viral from bacterial infection. Due to pharyngeal involvement, the act of swallowing could be transiently disturbed and painful. Nasal blockage may cause mouth breathing and dry mouth.

Viral infections are generally self-limiting and resolve within 7–10 days. Therapy should be directed to symptomatic care, which includes analgesics, antipyretics, and saline irrigation. The use of topical or oral decongestants leads to rebound symptoms and should be avoided. Fluid intake should be encouraged to replace insensible losses and reduced oral intake. If symptoms like fever or cough are present, physical activities should be reduced, because rest is beneficial in the process of recovery.

Because of anatomical predisposition, acute viral rhinitis in young children may be accompanied by congestion of Eustachian tube, reducing air influx in the middle ear space, and resulting in otitis media. Since

1980s, there was controversy regarding antimicrobial therapy versus observation in children with a confirmed diagnosis of acute otitis media due to acute upper respiratory infection, presumably of viral origin. However, recent investigations showed that children recovered more quickly when they were treated with amoxicillin-clavulanate, initiated at the time of diagnosis.^{7,8}

Acute Bacterial Rhinosinusitis

Persistent symptoms of acute rhinosinusitis for longer than 10 days or worsening of symptoms after 5–7 days, purulent discharge, and moderate-to-high grade fever suggest a secondary bacterial infection (Figure 3). In children, the most common symptoms of bacterial rhinosinusitis are cough, nasal discharge, fever, and malodorous breath.

In patients with acute bacterial rhinosinusitis, nasal discharge is purulent and minimal, not responding to symptomatic medication and, occasionally, accompanied by sneezing. Hyposmia or anosmia is transitional. Usually, especially in adults, the pain is restricted to diseased sinus. The cough in rhinosinusitis is present all day around, but usually it is most striking in the morning, after waking up, as a reaction to the accumulated secretions in the posterior pharynx during the night.

The inspection reveals mucopurulent secretion, edema and erythema of mucosa, causes of nasal obstruction like polyps or septal deviation, periorbital swelling in ethmoid

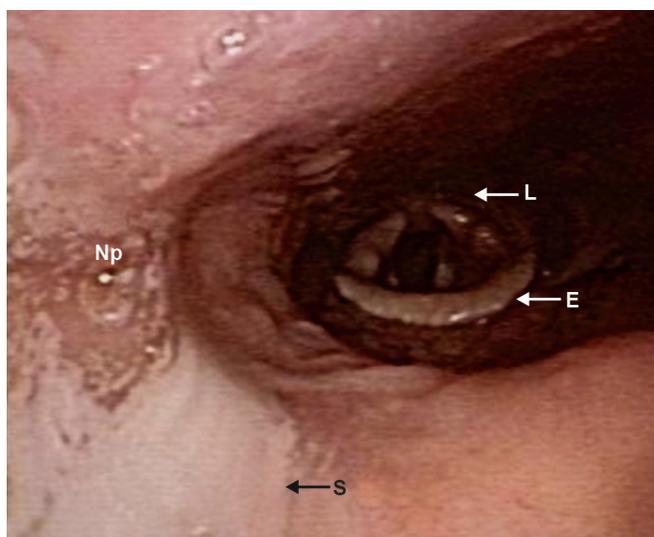


FIGURE 3 Bacterial rhinosinusitis and nasal drip (endoscopic view). Notice the leakage of purulent secretion from nasopharynx to oropharynx and larynx. Nasal drip induces laryngeal irritation and cough. L, larynx; E, epiglottis; Np, nasopharynx; s, secretion. (Courtesy of Professor Ranko Mladina, MD, PhD. Private Collection).

sinusitis, and facial tenderness in the projection of frontal and maxillary sinus.

Sinusitis is common in persons with viral upper respiratory tract infection, but it refers only to the transitional changes on CT. Yet, it is clinically explicit in only about 2–10% of persons with viral upper respiratory tract infection.⁹ The major pathogens of acute bacterial sinusitis are *Streptococcus pneumoniae* and *Hemophilus influenzae*, followed by α -hemolytic and β -hemolytic streptococci, *Staphylococcus aureus*, and anaerobes. In the past decade, *S. anginosus* and methicillin-resistant *S. aureus* (MRSA) has been increasingly recognized as a cause of bacterial sinusitis in children and adolescents.¹⁰ Plain radiograph of the sinuses may reveal complete sinus opacity, air-fluid level, or marked mucosal thickening. CT provides a detailed view of the paranasal sinuses, but this technique is not routinely indicated in evaluation of uncomplicated sinusitis. While nasopharyngeal swab is unreliable, microbiological cultures should be obtained by direct sinus aspiration. Endoscopically guided cultures of the middle meatus may be considered in adults, but their reliability in children has not been established. Due to lack of precision and practicality of current diagnostic methods, the clinical diagnosis of acute bacterial rhinosinusitis is made primarily on the basis of history and symptoms (Table 2).¹¹ Untreated bacterial rhinosinusitis may cause a number of severe complications: osteitis of the sinus bones, orbital cellulitis, and spread of bacteria to the central nervous system resulting in meningitis, brain abscess, or infection of intracranial cavernous sinus.¹² For this reason empirical antimicrobial therapy should be initiated immediately after the clinical diagnosis of bacterial infection is established. Amoxicillin-clavulanate is the first-choice antimicrobial agent, which is superior to amoxicillin in

TABLE 2

Viral and Bacterial Rhinosinusitis: Differential Diagnosis

Features	Viral rhinosinusitis	Bacterial rhinosinusitis
Duration of symptoms and signs compatible with acute rhinosinusitis	7–10 days	≥10 days
Fever ≥39°C	No	Yes
Purulent nasal discharge lasting for 3 or more consecutive days	No	Yes
Facial pain lasting for 3 or more consecutive days	No	Yes
New onset of symptoms after initial improvement	No	Yes

coverage of increasing β -lactamase-producing pathogens among upper respiratory tract isolates. Doxycycline is an alternative in adults with penicillin allergy. Children with non-type I penicillin allergy may be treated with combination of a third-generation oral cephalosporin and clindamycin. Fluoroquinolones are reserved for patients in whom first-line therapy has failed.⁶ Recommended duration of antimicrobial treatment is 5–7 days for uncomplicated bacterial rhinosinusitis in adults, and 10–14 days in children. Intranasal corticosteroids are recommended as an adjunct therapy in individuals with a history of allergic rhinitis. Over-the-counter drugs like decongestants and antihistamines should be avoided.⁶ The advantage of probiotics in preventing the antibiotic-associated diarrhea has been reported recently.¹³ The pooled evidence suggested that probiotics are associated with a reduction in antibiotic-associated diarrhea, but it was concluded that more research is needed to determine, which probiotics are associated with the greatest efficacy and for which patients should receive which specific antibiotics.

Chronic Rhinitis

Chronic rhinitis is usually a prolongation of subacute inflammatory or infectious viral rhinitis. Low humidity and airborne irritants may contribute to prolonged inflammation. It may also occur in chronic infective diseases, such as syphilis, tuberculosis, rhinosporidiosis, leishmaniasis, blastomycosis, histoplasmosis, and leprosy. All these diseases are characterized by the formation of granulomas, resulting in destruction of soft tissue, cartilage, and bone (Figure 4). The most common symptoms of chronic rhinitis are nasal obstruction, purulent discharge, and frequent bleeding.

A special form of chronic rhinitis is chronic atrophic rhinitis, which is characterized by progressive atrophy and sclerosis of nasal mucosa and underlying bone. The mucous membrane changes from ciliated pseudostratified columnar epithelium to stratified squamous epithelium, and the lamina propria is reduced in amount and vascularity. Atrophic rhinitis may be primary or secondary due to Wegener's granulomatosis or iatrogenically induced excessive nasal tissue extirpation.¹⁴ Primary atrophic rhinitis (also known as *ozena*) is a disease of unclear etiology that affects predominantly young and middle-aged adults, especially females, with racial preference amongst Asians, Hispanics, and African-Americans.¹⁵ Most of the patients are from rural or industrial environment with high predisposition to allergic or immunologic disorders.¹⁶ Familial etiology with dominant inheritance has also been described.¹⁷ Patients

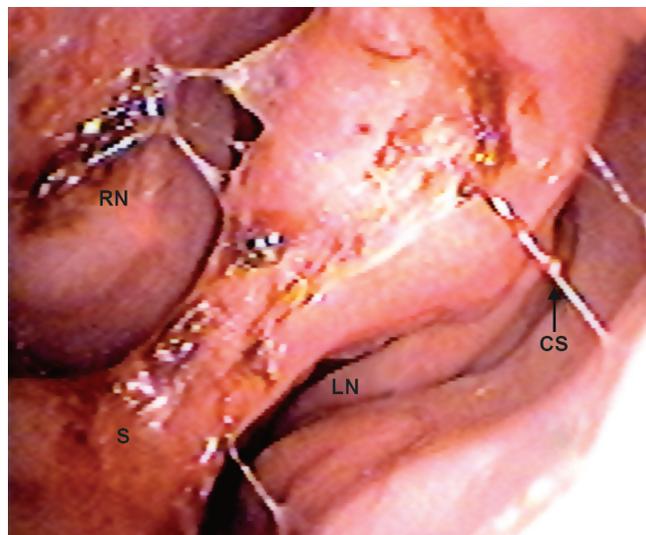


FIGURE 4 Chronic “cobweb” rhinitis (endoscopic view from the left nostril). Endoscopy reveals chronic rhinitis with multiple mucosal erosions and almost completely destroyed nasal septum. Cobweb secretion is consistent with colonization and invasion of molds (*Fusarium* spp.). RN, right nostril; LN, left nostril; S, destroyed septum; CS, cobweb pattern of secretion.

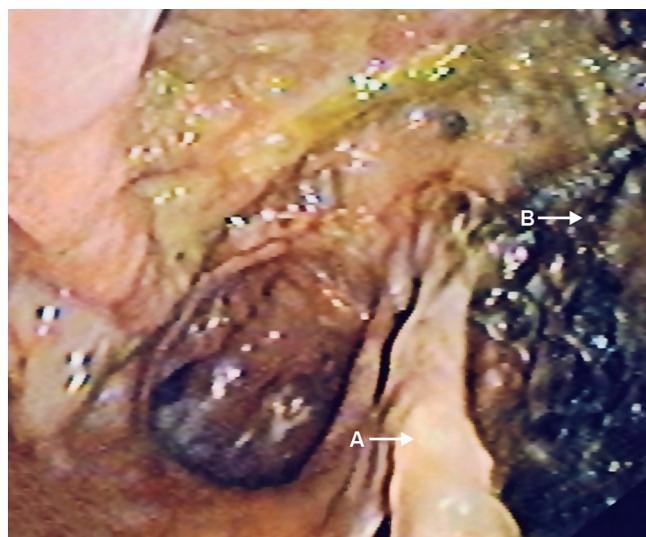


FIGURE 5 Chronic atrophic rhinitis (endoscopic view from the right nostril). Notice the remains of destroyed nasal septum (arrow A), and mucosal crusts in the contralateral nostril (arrow B).

have prolonged bacterial infection, mainly caused by *Klebsiella* species, especially *K. ozaen*. The common symptoms in both primary and secondary chronic atrophic rhinitis include fetor, crusting, nasal obstruction, epistaxis, anosmia, and sometimes, destruction of soft tissues and cartilages (Figure 5). Different treatment modalities have been described in the literature: nasal irrigation, nose drops (glucose-glycerin, liquid paraffin), topical and systemic antibiotics, vasodilators, estrogens,

vitamin A, and D sprayed into the nose or taken through mouth. Surgical treatment aims to decrease the size of the nasal cavities and improves lubrication of dry nasal mucosa. However, there is no evidence from randomized controlled trials concerning the long-term benefits of different treatment modalities for atrophic rhinitis.⁹

PHARYNGITIS

Acute Viral Pharyngitis

Pharyngitis is caused by inflammation and swelling of pharyngeal mucosa. The main symptom of acute pharyngitis is a sore throat. Other symptoms may include fever, headache, joint pain and muscle aches, skin rashes, and swollen lymph nodes in the neck. Inspection discloses pharyngeal erythema, exudates, sometimes mucosal erosions and vesicles, tonsillar hypertrophy, anterior cervical lymphadenopathy, conjunctivitis, and skin rash.

Similar to other upper respiratory infections, the most common cause of acute pharyngitis is a viral infection in settings of common cold or flu. The most common pathogens are rhinovirus, and influenza A and B. Some other viruses can cause specific forms of pharyngitis, such as enteroviruses, Epstein-Barr virus (EBV), and HIV.

Herpangina

Herpangina is a painful pharyngitis caused by various enteroviruses like Coxsackie virus A16, Coxsackie virus B, enterovirus 71, echovirus, parechovirus 1, adenovirus, and herpes simplex virus. Herpangina occurs worldwide, mainly during summer, and most commonly affects infants and young children aged 3–10 years.¹⁸ Clinical manifestation includes high fever, malaise, sore throat, painful swallowing, headache, anorexia, emesis, and sometimes, abdominal pain, which may mimic appendicitis. Enteroviral infections may be accompanied by various type of rash, which depends on viral subtype. In rare cases herpangina may be accompanied by aseptic meningitis and neurological symptoms. Herpangina is characterized by small (less than 5 mm in diameter) vesicular or ulcerative lesions that affect posterior pharyngeal wall, tonsils, soft palate, uvula, and sometimes tongue and buccal mucosa. Enlargement of cervical lymph nodes may also be present. Diagnosis is based upon clinical symptoms, characteristic physical signs, age, epidemiological data, and seasonal appearance. Microbiological standard for diagnosis is based on isolation of enterovirus in cell culture obtained from swabs of the nasopharynx. Other specimens include stool, urine, serum, and cerebrospinal fluid (CSF). However,

laboratory analyses are not necessary in most of cases, because herpangina is usually mild and self-limiting illness. Supportive therapy includes hydration, adequate caloric intake, limited activity, antipyretics, and topical analgesics.

Infectious Mononucleosis

EBV causes infectious mononucleosis, which is characterized by fever, tonsillar pharyngitis, lymphadenopathy, lymphocytosis, and atypical mononuclear cells in the blood. EBV spreads by a close contact between susceptible persons and EBV shedders. The majority of primary EBV infections are subclinical and inapparent. Antibodies to EBV have been demonstrated in 90–95% of adults worldwide. The incidence of symptomatic infection begins to rise from adolescence through adult years.¹⁹ Transmission of EBV requires intimate contact with the saliva of an infected person. The incubation period ranges from 4 to 6 weeks. The clinical diagnosis of infectious mononucleosis is suggested in adolescents or young adults with the symptoms of fever, sore throat, and swollen lymph glands. An enlargement of liver and spleen may also be present. Laboratory results include an elevated white blood cell count, an increased percentage of certain atypical white blood cells, and a positive reaction to a “monospot” test. Treatment strategy for infectious mononucleosis is supportive and symptomatic. The use of steroids has also been occasionally reported to decrease the overall prolongation and severity of illness, but there is no available randomized clinical studies to support such therapeutic approach. Persons with infectious mononucleosis may spread the infection for a period of weeks. However, no special precautions or isolation procedures are recommended, since the virus is also found in the saliva of healthy people who carry and spread the virus intermittently for life. These people are usually the primary reservoir of virus, and for this reason the transmission is impossible to prevent.²⁰

Acute HIV Infection

Primary or acute HIV infection (also known as acute retroviral syndrome) refers to the interval from initial infection to the time that antibody to HIV is detectable. During this stage of infection, patients are highly infectious due to enormous viral load in blood and genital secretion (>100,000 copies/mL), and negative or indeterminate HIV antibody test results.²¹ Approximately, 60% of recently infected persons develop primary acute infection 2–6 weeks after exposure to HIV.²² Symptoms include fever, fatigue, myalgia, mucocutaneous ulcerations,

pharyngitis, anorexia, generalized lymphadenopathy, rash, and sometimes neurologic symptoms. Pharyngitis, usually exudative, is accompanied with cervical lymphadenopathy resembling infectious mononucleosis (“mononucleosis-like” illness).²³ Common laboratory findings include leukopenia, thrombocytopenia, and mild transaminase elevations. Symptoms persist for less than 4 weeks, except lymphadenopathy that may last longer.

Acute Bacterial Pharyngitis

Acute bacterial pharyngitis and tonsillopharyngitis usually occur during the colder months. The most common cause is group A β -hemolytic *Streptococcus* (*S. pyogenes*), which is responsible for 15–30% of all cases of pharyngitis in children and for 10% in adults.²⁴ Antibiotic therapy is recommended to hasten the resolution of clinical symptoms, and to prevent the occurrence of nonsuppurative complications, such as rheumatic fever. A 10-day course of antibiotic therapy with penicillin is the standard of care for streptococcal tonsillopharyngitis. Alternatives to this “gold” standard are other β -lactams (e.g., amoxicillin, cephalosporins), macrolides, and clindamycin.

EPIGLOTTITIS

Epiglottitis is a part of oropharynx, and it forms the back wall of the vallecular space below the base of tongue. During the act of swallowing, it also protects larynx and trachea from aspiration. Infectious epiglottitis is a cellulitis of the epiglottis, aryepiglottic folds, and other adjacent tissues. Infection of epiglottitis is a consequence from bacteremia, or direct invasion of the epithelium by microbial pathogens. The primary source of bacteria is posterior wall of nasopharynx. The most frequent causative microorganisms are *H. influenzae*, *S. pneumoniae*, *S. aureus*, and β -hemolytic streptococci. Microscopic epithelial trauma by viral infection or mucosal damage from food during swallowing may predispose to bacterial invasion, inducing inflammation and edema. Swelling of tissue rapidly progresses, and involves aryepiglottic folds and arytenoids.²⁵ Thus, epiglottitis may cause life-threatening airway obstruction.

In children, symptoms develop abruptly within a few hours of onset. Symptoms and signs include sore throat, dysphagia, loss of voice, inspiratory stridor, fever, anxiety, dyspnea, tachypnea, and cyanosis. Dyspnea often causes the child to sit upright, lean forward, with hyperextended neck, and mouth open for enhancing the exchange of air (tripod position). Treatment of epiglottitis is based on the maintenance of airway. Patients should be monitored

continuously in the emergency department or intensive care unit by staff that is able to perform rapid resuscitation, stabilization of airway, and ventilation.²⁶ Orotracheal intubation or needle cricothyroidotomy should be performed in an emergency situation when respiratory arrest occurs. Antibiotic therapy is necessary but should be initiated after securing the airway. Before culture results, empirically administered antimicrobial therapy should cover the most likely causative pathogens, such as *S. aureus*, group A streptococci,²⁷ *H. influenzae*, and *Candida albicans* in immunocompromised patients.²⁸

Epiglottitis may be fatal due to sudden compromise of airways or complications like meningitis, empyema, or mediastinitis, with a mortality rate of around 1% in adults.

LARYNGITIS

Laryngitis is an acute or chronic inflammation of laryngeal structures. Etiology includes a number of infectious and noninfectious causes listed in table 3. The most common

TABLE 3
Classifications and Etiology of Laryngitis

Infectious laryngitis	
Viral	<ul style="list-style-type: none"> • Rhinovirus • Influenza A, B, C • Adenoviruses • Parainfluenza viruses • RSV • Measles • Varicella-zoster
Bacterial	<ul style="list-style-type: none"> • <i>Hemophilus influenzae</i> type B • β-hemolytic streptococci • <i>Moraxella catarrhalis</i> • <i>Streptococcus pneumoniae</i> • <i>Klebsiella pneumoniae</i> • <i>Staphylococcus aureus</i> • Diphtheria (<i>Corynebacterium diphtheriae</i>, <i>Corynebacterium ulcerans</i>) • Tuberculosis (<i>Mycobacterium tuberculosis</i>) • Syphilis (<i>Treponema pallidum</i>)
Fungal	<ul style="list-style-type: none"> • <i>Candida albicans</i> • <i>Blastomyces dermatitidis</i> • <i>Histoplasma capsulatum</i> • <i>Cryptococcus neoformans</i>
Noninfectious laryngitis	
Irritant laryngitis due to inhalation of toxic agents, alcoholism, smoking, drugs (crack), allergy, GERD, vocal abuse, laryngeal involvement of rheumatoid arthritis, SLE, hypothyroidism, angioneurotic edema	

RSV, respiratory syncytial virus; GERD, gastroesophageal reflux disease; SLE, systemic lupus erythematosus.



FIGURE 6 Chronic laryngitis (endoscopic view). The laryngeal mucosa appears hyperemic and swollen, forming inflammatory pseudotumors in the anterior part of both vocal folds.

causative agent of acute laryngitis is the rhinovirus. Others include influenza A and B, adenoviruses, parainfluenza viruses, *H. influenzae* type B, β -hemolytic streptococci, etc. Acute laryngitis may occur as an isolated infection or, more commonly, as a part of a generalized viral or bacterial upper respiratory tract infection. It begins with hoarseness (from mild-to-complete loss of voice), painful swallowing or speaking, dry cough, and laryngeal edema of varying degrees (Figure 6). Fever and malaise are common. Symptoms usually resolve in 7 days. In chronic laryngitis, hoarseness is usually the only symptom that persists for more than three weeks. When the clinical presentation lies between acute and chronic subtype, sometimes it may be of clinical utility to classify as subacute.

Diagnostic procedure begins with comprehensive history of disease that includes chronicity of the condition, epidemiologic data, exposure to environmental fumes and irritants, medication, and smoking habits. In acute laryngitis, indirect laryngoscopy reveals red, inflamed, and occasionally, hemorrhagic vocal cords with round swelling edges and exudates. Physical examination should also include the oropharynx, thyroid, and cervical lymph nodes. Chronic fungal laryngitis caused by *C. albicans* that is a common side effect of inhaled steroids, is characterized by multiple chalk-white mucosal patches spreading on epiglottis, and oropharynx.²⁹ Laboratory findings (white blood cell count, C-reactive protein) may be an aid in distinguishing viral from bacterial infection. If there is a suspicion on bacterial or fungal cause, laryngeal exudate and oropharyngeal swab should be

obtained for cultures. Rapid antigen detection test is also useful in detection of bacterial infection. Diagnosis of diphtheria requires positive culture from respiratory tract secretion, and positive toxin assay. Diagnosis of laryngeal tuberculosis that is usually a complication of extensive pulmonary tuberculosis is based on positive acid fast bacilli in sputum or oropharyngeal swab, and positive cultures for *Mycobacterium tuberculosis*.

Duration of hoarseness is important in differential diagnosis. Acute hoarseness is present in hay fever, acute inhalation of toxic fumes and irritants, aspiration of caustic chemicals, foreign body aspiration, and angioneurotic edema, besides acute infectious laryngitis. Differential diagnosis of chronic hoarseness includes numerous diseases, such as laryngeal cancer, lung cancer with mediastinal involvement, trauma of vocal cords, vocal abuse, gastroesophageal reflux disease (GERD), chronic rhinosinusitis with sinobronchial syndrome, laryngeal involvement in rheumatoid arthritis, systemic lupus erythematosus (SLE), and hypothyroidism.

Diphtheria

Diphtheria is caused by the Gram-positive bacillus *Corynebacterium diphtheriae* and in some cases by *C. ulcerans*. Infected individuals may develop respiratory disease, cutaneous disease, or become asymptomatic carrier. Infection spreads by close contact with infectious respiratory secretions or from skin lesions. The transmission of *C. ulcerans* via cow's milk has been described.³⁰ Diphtheria occurs throughout the year with peak incidence in winter. At the beginning patients suffer from malaise, sore throat, and low grade fever. Symptoms progress to hoarseness, barking cough, and stridor, also known as croup. Individuals with severe disease develop cervical lymph node enlargement and neck swelling ("bull-neck"). Physical examination reveals hyperemic pharyngeal and laryngeal mucosa with areas of white exudates forming the adherent grey pseudomembrane that bleeds with scraping.³¹ Extension of the pseudomembrane into larynx and trachea may lead to airway obstruction with subsequent suffocation and death. Definitive diagnosis requires positive cultures of *C. diphtheriae* from respiratory secretions or cutaneous lesions, and positive toxin assay. Specimens for cultures should be obtained from the throat and nose, including a portion of membrane.

C. diphtheriae was first identified in 1880. The first antitoxin against diphtheria was developed in the 1890s, with the first vaccine developed in the 1920s. With the administration of vaccine, the incidence of disease has decreased significantly, although it is still endemic in

many parts of the world. Furthermore, while diphtheria primarily affected young children in the prevaccination era, today an increasing proportion of cases occur in unvaccinated or inadequately immunized adolescents and adults.³²

Croup Illnesses

In prevaccination era the term “croup” was a synonym for diphtheria. Today, the word “croup” refers to a number of respiratory illnesses that are characterized by varying degrees of stridor, barking cough, and hoarseness due to obstruction in the region of the larynx.³³ “That group of illnesses affects infants and children younger than 6 years of age with a peak incidence between 7 and 36 months.³⁴ Host factors, especially allergic factors, seem to be important in the pathogenesis.³⁵ Croup illnesses are most commonly caused by parainfluenza viruses, following by influenza virus A, RSV, measles virus, adenovirus, and rhinovirus. In some instances, such as the laryngotracheal bronchopneumonitis and bacterial tracheitis, the croup feature is due to secondary bacterial infection, particularly from *S. aureus*. According to symptoms and signs, croup illnesses are divided in three clinical entities:

1. Spasmodic croup: sudden night time onset of stridor and barking cough, without fever, without inflammation, nontoxic presentation.
2. Acute laryngotracheobronchitis: hoarseness and barking cough, minimal-to-severe stridor, high fever, minimal toxic presentation.
3. Laryngotracheobronchitis, laryngotracheobronchopneumonitis, and bacterial tracheitis: hoarseness and barking cough, severe stridor, high fever, typically toxic presentation, and secondary bacterial infection is common.

Treatment of acute laryngitis depends on severity of illness and degree of airway compromise. The most common acute viral laryngitis is usually self-limiting, requiring only supportive treatment, such as analgesics, mucolytics,³⁶ voice rest, increased hydration, and limited caffeine intake. Antibiotics are needed only when a bacterial infection is suspected.³⁷ However, sometimes it is a challenge for the physician to recognize when antibiotics are required.

Patients with any degree of airway compromise, especially those suffering from diphtheria and other “croup” illnesses, require particular care. In addition, patients with an underlying risk factor that limits airway, such as subglottic stenosis or vocal cord paralysis, may develop severe airway obstruction even in settings of slight inflammation of laryngeal structures. Corticosteroids should be administered in all patients with possible

airway compromise, and airways should be monitored closely to assess the need for tracheotomy.³⁸

Patients who are suspected to have diphtheria, need to be hospitalized and should be given diphtheria antitoxin and antibiotic (penicillin or erythromycin). They must be isolated to avoid exposing others to the infection. Diphtheria antitoxin is a crucial step of treatment, and should be administered as early as possible, without waiting for culture results.³⁹ In severe cases of airway obstruction, when patient cannot breathe on their own, inserting breathing tube and tracheotomy may be necessary.⁴⁰

Treatment of croup illnesses other than diphtheria is based on corticosteroids (intramuscular dexamethasone 0.6 mg/kg). In severe cases, repeated treatments with epinephrine have been used and often decreased the need for intubation.⁴¹ Since the most severe types of croup illnesses are associated with secondary bacterial infection due to *S. aureus*, *S. pneumoniae*, *H. influenzae*, or *Moraxella catarrhalis*, antibiotics should be administered after cultures have been obtained. Most of the children with such severe form of croup require placement of mechanical airway and treatment in an intensive care unit.

Chronic tuberculous laryngitis is almost always a complication of active pulmonary tuberculosis and requires the same antituberculosis drug regimen as pulmonary tuberculosis. Since it is highly contagious, prompt diagnosis and adequate treatment are critical.

Fungal laryngitis commonly appears in immunocompromised patients, and treatment is based on systemic antifungal drugs. In immunocompetent individuals, fungal laryngitis is often associated with regular usage of inhaled corticosteroids for asthma control. Patients should be advised to rinse mouth before and after inhalation and the dose of corticosteroid should be reduced wherever it is possible.

TRACHEITIS

Tracheitis is an inflammatory process of the larynx, trachea, and bronchi. Most conditions that affect the trachea are bacterial or viral infections; however, irritants and dense smoke can injure the epithelium of the trachea and increase the likelihood of infections. Although infectious tracheitis may affect patients of any age, it presents a special problem in children because of the size and anatomic shape of the airway. The major site of disease is at the subglottic area, which is the narrowest part of the trachea. Airway obstruction may develop secondary to subglottic edema or accumulation of mucopurulent secretion within trachea. The most frequent causes of tracheitis are *S. aureus*’ group A

β -hemolytic streptococci, *M. catarrhalis*, *H. influenzae* type B, *Klebsiella* species, *Pseudomonas* species, anaerobes, *Mycoplasma pneumoniae*, and influenza A virus (H1N1).⁴² Rarely, bacterial tracheitis may develop as a complication of a preceding viral infection or an injury from endotracheal intubation. Bacterial tracheitis is uncommon, with the incidence of approximately 0.1 cases per 100 000 children per year.⁴³ However, it is the condition of high priority, because the mortality rate has been estimated at 4–20%.⁴⁴ Clinical presentation includes high fever, toxic appearance, inspiratory stridor, and bark like cough, hoarseness, dysphonia, and variable degree of respiratory distress. Diagnosis can be confirmed by direct laryngotracheobronchoscopy, which shows inflammation and purulent secretions in the subglottic area or by lateral neck X-ray, which reveals subglottic narrowing. Laryngotracheobronchoscopy enables obtaining specimens for cultures under direct visualization, and may also be therapeutic by performing tracheal toilet. Differential diagnosis includes angioedema, croup, diphtheria, epiglottitis, peritonsillar abscess, retropharyngeal abscess, and tuberculosis. Treatment is based on maintenance of an adequate airway, which implies endotracheal intubation in most of patients, and antibiotics. Initial antibiotics should cover the most common causative bacteria. Empirical antibiotic regimens include a third-generation cephalosporin and a penicillinase-resistant penicillin, or clindamycin administered intravenously. If there is a suspicion of MRSA in the community, vancomycin should be started. Once definitive microbiological diagnosis is made, appropriate antibiotic therapy should continue for more than 10 days. With appropriate airway support and antibiotics, patients improve within 5 days. However, up to 60% of patients may develop one or more complications that include bronchopneumonia, sepsis, toxic shock, adult respiratory distress syndrome (ARDS), post-extubation subglottic stenosis, anoxic encephalopathy, cardiorespiratory arrest, and retropharyngeal abscess or cellulitis.⁴⁵ Children with bacterial tracheitis should be admitted in the intensive care unit, with multidisciplinary medical support.

COMPLICATIONS

In most cases, respiratory tract infections resolve entirely but in a minor number of cases, complications may arise.

Otitis media may be a complication in some 5% of colds in children and around 2% in adults. It has recently been shown⁴⁶ in adjusted models controlling for the presence of key viruses, bacteria, and acute otitis media risk factors that acute otitis media risk was independently associated with high respiratory syncytial viral load with

S. pneumoniae and *H. influenzae*. The risk was higher for the presence of bocavirus and *H. influenzae* together. The conclusion was that acute otitis media risk differed with specific viruses and bacteria involved and that the preventive efforts should consider methods for reducing infections caused by RSV, bocavirus, and adenovirus in addition to acute otitis media bacterial pathogens.

The bronchial hyperreactivity may be enhanced or provoked by respiratory tract infections. Symptom-severity of asthma and the frequency of severe exacerbations were associated with previous exacerbations and susceptibility to upper respiratory tract infection, according to novel research on more than 7000 patients.⁴⁷

Patients with chronic obstructive pulmonary disease may also experience an exacerbation.

Patients who have persistent cough lasting for more than 3 weeks after they have got through acute symptoms of an upper respiratory tract infection, may have a post-infectious cough. In patients who have a cough lasting from 3 to 8 weeks with normal chest radiograph findings, the diagnosis of postinfectious cough has to be taken into consideration. In most patients, a specific etiologic agent will not be identified, and empiric therapy may be helpful. A high degree of suspicion for cough due to *Bordetella pertussis* infection will lead to earlier diagnosis, patient isolation, and antibiotic treatment.⁴⁸

Bacterial superinfection of viral infection may occur occasionally. The propagation of infection into adjacent tissues, or distant organs may ensue but such sequence of events is quite rare.

Possible complications of group A streptococcal pharyngitis are rheumatic fever, acute glomerulonephritis, scarlet fever, and streptococcal toxic shock syndrome.

Complications of influenza are numerous, and include bacterial superinfection, pneumonia, volume depletion, myositis, pericarditis, rhabdomyolysis, encephalitis, meningitis, myelitis, renal failure, and disseminated intravascular coagulation. Influenza also poses a risk of worsening underlying medical conditions, such as heart failure, asthma, or diabetes.

Complications of mononucleosis are splenic rupture, hepatitis, Guillain-Barré syndrome, encephalitis, hemolytic anemia, agranulocytosis, myocarditis, and Burkitt's lymphoma.

The complications of diphtherias may include airway obstruction, myocarditis, polyneuritis, thrombocytopenia, proteinuria, and hearing loss.⁴⁹

CONCLUSION

Upper respiratory tract infections are the most common infections in general population, with important social

implications like missed working hours. Most of acute upper respiratory tract infections are caused by viruses, especially rhinovirus, corona virus, adenovirus, para-influenza virus, RSV, and enterovirus, that are responsible for more than 80% of all common colds. Bacterial pathogens are more commonly causative agents of prolonged and/or chronic infection adhering to primary viral infections.

In most cases of acute infections, diagnostic work-up is based on recognition of symptoms and physical examination. Additional diagnostic procedure should be performed in prolonged and chronic course of infection and special circumstances such as streptococcal pharyngitis, diphtheria and croup disease, epiglottitis, and mononucleosis.

Immunocompromised persons have increased risk for developing the prolonged or complicated course of disease. Special attention is recommended in those with HIV infection, splenectomy, cancer, patients receiving chemotherapy, dialysis, and those undergoing stem cell or organ transplantation. Most of the acute upper respiratory infections are self-limiting, requiring no specific treatment. Antimicrobial therapy should be used for streptococcal pharyngitis, bacterial sinusitis and otitis media, pertussis, diphtheria, and chronic bacterial infections.

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