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A REVIEW ON UPPER RESPIRATORY TRACT INFECTION

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Abstract

Upper respiratory tract infection (URI) is a general term for a heterogeneous group of illnesses caused by numerous etiologic agents that affect the mucosal lining of the upper respiratory tract, including the middle-ear cavity and par nasal sinuses. URIs are primarily caused by viruses, rhinoviruses being the most common etiological agents. Respiratory viruses transmit easily via direct contact or aerosols. The incidence of URI is highest in children who suffer 6–8 infections per year. The main symptoms of URI are nasal blockage and discharge, sneezing, sore throat, and cough. Fever occurs variably, most commonly in children. Viral URIs often predispose to bacterial complications. Acute otitis media is the most common complication in children, whereas sinusitis and pneumonia are more frequent in adults and the elderly. The treatment of URI is mainly symptomatic because specific antiviral are available only for influenza viruses. Antibiotics have no efficacy for viral URI but are commonly used for treating acute otitis media and sinusitis. Most URIs are self-limited illnesses with an average duration of 7–10 days and an excellent prognosis.

Keywords: Upper respiratory tract infection, par nasal sinuses, antiviral, influenza viruses.

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Introduction

Upper respiratory tract infection (URI), or 'common cold', is the most frequent illness in humans. The main symptoms of URI are nasal stuffiness and discharge, sneezing, sore throat, and cough. The presence of low-grade fever is variable and more common in children than in adults. In spite of the benign nature of the illness, URIs cause a substantial economic burden on society in terms of medications, visits to physicians and other healthcare providers, and absenteeism. Young children suffer on average 6–8 and adults 2–4 URIs per year. The occurrence of URI displays a clear seasonal variation. The highest incidence rates are observed in the autumn and winter in temperate regions of the northern hemisphere. In tropical countries, most URIs occurs during the rainy season [1]. URIs are usually self-limited illnesses confined to the upper respiratory tract, but occasionally the viral infection spreads to adjacent organs, resulting in different clinical

manifestations. Viral URIs may also predispose to bacterial complications. In children, the most common complication of URI is acute otitis media (AOM). The highest incidence of AOM occurs in children between 6 months and 2 years of age. By the age of 2 years, approximately 70% of children have experienced at least one episode of AOM. In adults and the elderly, the most frequent complications of URI are par nasal sinusitis and pneumonia.

Sinusitis has been estimated to occur as a complication in 0.5–2% of URIs. Recent studies have demonstrated, however, that par nasal sinuses are frequently affected during URI, and most sinus abnormalities are not evidence of a true bacterial complication but instead are part of the natural history of URI [2,3].

Etiology

URIs has probably tormented mankind for thousands of years, but it was not until the middle of the last century that viruses were demonstrated as the etiologic agents of these illnesses. Influenza A virus was the first virus to be isolated in 1933. Since then, intensive research into the etiology of URIs during the 1950s and 1960s led to the discovery of several other groups of respiratory viruses, for example,

adenoviruses, rhinoviruses, par influenza viruses, respiratory syncytial viruses, enteroviruses, and corona viruses. During the past few years, the application of molecular techniques to viral detection has resulted in the discovery of several respiratory viruses that had remained unknown before the polymerase chain reaction (PCR) era, for example, human metapneumovirus and new corona viruses. Although the viral etiology of URIs can be currently documented in over 90% of cases by the use of modern diagnostic techniques, it is probable that a number of viruses causing respiratory illnesses still remain to be identified [4].

Among all respiratory viruses, rhinoviruses are the most common etiologic agents in URI. On an annual level, rhinoviruses are estimated to account for approximately 30–50% of all respiratory illnesses, but this percentage may rise to 80% during the autumn peak season. Recent studies have disclosed that at least in children the relative role of enteroviruses is greater than previously known [5].



AOM is generally considered a bacterial complication of URI. However, bacterial pathogens – mainly *Streptococcus pneumoniae*, *Haemophilic influenza*, or *Moraxella catarrhalis* – can be isolated from the middle-ear fluid in only approximately 70% of cases. Intensive research into the etiology of AOM since the 1980s has produced strong evidence for a key role of viruses in the etiology of AOM. By the use of PCR-based techniques, viruses have been found in the middle-ear fluid in the majority of children with AOM, with or without bacteria [6].

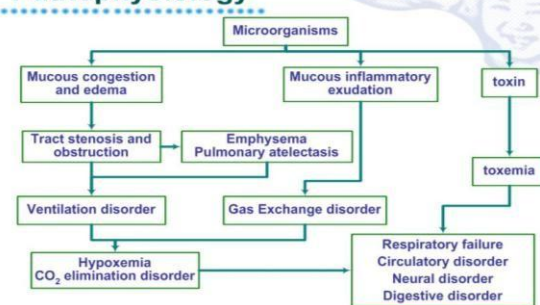
The bacterial pathogens found in sinusitis are much the same as those found in AOM. There is, however, growing evidence for an important role of viruses also in the etiology of sinusitis. Rhinovirus RNA has been detected in sinus aspirates even in the absence of bacteria. Rhinoviruses have also been detected by *in situ* hybridization in the epithelial cells of maxillary sinuses in adult patients with sinusitis. It is probable that with increasing interest in the etiology of sinusitis, our knowledge regarding the relative role of viruses in this condition will expand [7].

Pathology

Owing to the great number of different viruses causing URIs, it is probable that the histopathology changes during various viral infections will be markedly different. For example, influenza viruses are thought to have an extensive direct cytopathic effect on the respiratory epithelium,

which leads to degeneration of epithelial cells and pseudometaplastic changes in the epithelium. On the other hand, during rhinovirus infection the number of infected cells in the upper respiratory epithelium is limited, and no histopathology changes have been seen in nasal biopsy specimens from subjects infected with rhinoviruses. The absence of epithelial destruction during rhinovirus infections – the most frequent cause of URIs – suggests that the clinical symptoms of URI are not primarily caused by virus-induced epithelial injury but instead are caused by the inflammatory response of the host. [8].

Pathophysiology



Clinical Features

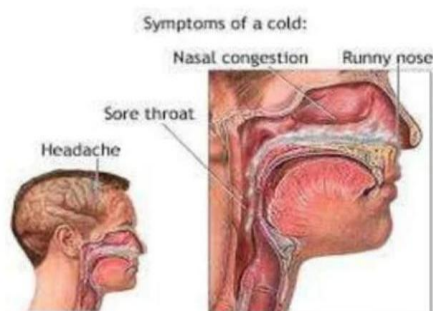
In most cases, the diagnosis of URI is obvious and the condition is usually self-diagnosed. The diagnosis may sometimes be delayed in infants and young children, especially when fever is the leading symptom during the early stage of the illness. The incubation period of URI varies considerably among different viruses, ranging from 12 h to 7 days. A typical illness starts with a sore throat that is shortly accompanied by nasal stuffiness, runny nose, sneezing, and cough. The soreness of the throat often disappears quickly, whereas the initial watery nasal discharge soon turns thicker and more purulent. Usually the severity of the symptoms increases rapidly and peaks within 2–3 days. The average duration of URI is 7–10 days, but in a number of patients some symptoms may still be present after 3 weeks [9].

When AOM develops as a complication of URI, it is most frequently diagnosed on days 3 or 4 after the onset of upper respiratory symptoms. Most symptoms that are generally listed as associated with AOM overlap significantly with those of an uncomplicated URI. In clinical practice, earache is the only symptom that can be considered specific for AOM. However, the value of this symptom in suspecting AOM is severely limited by the fact that almost half of infants and young children with AOM either do not have earache or they cannot express it to their parents. The ultimate diagnosis of AOM requires inspection of the tympanic membrane by otoscopy [10].

Analogous to symptoms of AOM, many symptoms that are conventionally thought to indicate sinusitis have been found to be as common in patients with radiologically normal sinuses. As sinuses are affected at least to some degree during most cases of URI, distinguishing between viral URI and bacterial sinusitis is a great challenge in

clinical practice. In the absence of sinus puncture, facial pain (especially if unilateral), maxillary toothache, postnasal drip, and nasal obstruction or thick nasal discharge for more than 7–10 days are usually thought to be indicative of bacterial sinusitis. The value of detecting mucosal thickening in sinus radiographs or by ultrasound is questionable because the finding correlates poorly with bacterial etiology of the condition [11, 12].

CLINICAL FEATURES



Pathogenesis

The transmission of viruses occurs most often by direct contact with virus-containing secretions, followed by self-inoculation of the viruses in the anterior nasal mucosa or in the eye. Other routes of transmission include small-particle aerosols lingering in the air and direct hit by large-particle aerosols from an infected person. The primary ways of transmission as well as the detailed pathogenetic mechanisms differ among various respiratory viruses. For example, the primary site of replication of influenza viruses is in the trachea, whereas rhinovirus replication starts predominantly in the nasopharynx. The currently available evidence does not lend support to the popular belief that chilling or exposure to a cold environment has a role in the pathogenesis of URI.

Respiratory viruses gain entrance to epithelial cells by binding to specific receptors on the cells. About 90% of rhinovirus serotypes use intercellular adhesion molecule-1 as their receptor. Viral replication starts rapidly inside the cells, and progeny viruses can be detected within 10 h of viral inoculation. However, not all infections lead to clinical illness. Viral infection of the nasal mucosa results in vasodilatation and increased vascular permeability, which, in turn, cause nasal obstruction and discharge that are the hallmark symptoms of URI. Cholinergic stimulation leads to increased mucous gland secretion and sneezing. There is increasing evidence that the clinical symptoms of the patient are primarily caused by the host's inflammatory response. Increased levels of several inflammatory mediators, for example, interleukin (IL)-1, IL-6, IL-8, tumor necrosis factor, leukotrienes, kinins, histamine, and RANTES (regulated upon activation normally T-cell expressed and secreted), have been found in nasal secretions from patients with URI. It has been reported that

the concentrations of IL-6 and IL-8 in nasal secretions correlate with the severity of symptoms. The host response mechanisms during respiratory viral infections are, however, very complicated, consisting of a network of factors affecting each other in a time-dependent manner, and it is probable that several essential factors still remain to be identified [13].

Viral infection in the nasopharynx results in congestion of the nasopharyngeal mucosa. Congestion in and around the eustachian tube leads to dysfunction of the tube, which is considered the most important factor in the development of AOM. Inflammatory mediators play a key role in disruption of normal eustachian tube function although certain viruses, for example, influenza viruses, can also cause direct damage to the epithelial cells in the eustachian tube. Dysfunction of the eustachian tube results in formation of under pressure in the middle-ear cavity, decreased drainage of middle-ear secretions into the nasopharynx, and loss of protection of the middle-ear from nasopharyngeal secretions. Eventually, these events lead to microbial invasion of the middle ear, host inflammatory response in the middle-ear mucosa, and clinical signs and symptoms of AOM.

Scarce data are available on the exact pathogenic mechanisms involved in the development of sinusitis. It is likely that mucosal swelling around the narrow orifice of paranasal sinuses and viral infection of the sinus mucosa interfere with the normal cleansing mechanisms, which increases the possibility for secondary bacterial infection [14].

Animal Models

Most of our knowledge about viral URIs is derived from extensive community follow-up studies and experimental infections in volunteers. However, animal studies have been of crucial importance for research into the role of viruses in the pathogenesis of AOM. Most experimental studies in this area have been performed in chinchillas. They are well suited for otitis media research because their middle-ear is easily accessible and otitis media can be produced by intranasal inoculation of different microbes, thus mimicking the sequence of events in humans.

Management and Current Therapy

The treatment of URI is largely symptomatic and aimed at relieving the most unpleasant symptoms of the illness. Nasal stuffiness can be effectively reduced with intranasal or orally administered decongestants. First-generation (but not second-generation) antihistamines reduce sneezing and nasal discharge. This effect is probably more likely due to the anticholinergic rather than the antihistamine features of these drugs. Locally administered ipratropium has also been shown to reduce nasal discharge. Nonsteroidal anti-inflammatory drugs reduce fever and soreness of the throat. Cough medications are commonly used but their efficacy has not been demonstrated convincingly. Despite corticosteroids being potent anti-inflammatory agents, their intranasal or oral

use has not resulted in any clinical benefits. The use of intranasal steroids in children during rhino- virus infection may even increase the risk of AOM. Data on the efficacy of zinc, vitamin C, or Echinacea extracts in the treatment of URI are inconclusive. Although it is well known that antibiotics are not effective against viruses and that unnecessary use of antibiotics increases bacterial resistance, antibiotics are frequently used in the treatment of uncomplicated URIs. Specific antiviral treatments for respiratory viruses are currently available only for influenza viruses (oseltamivir, zanamivir, amantadine, and rimantadine). However, antiviral drugs for some other respiratory viruses (e.g., RSV, rhinoviruses, and enteroviruses) are currently being developed.

Although viruses play a key role in the development of AOM, bacteria are often found in samples of middle-ear fluid, and so AOM is usually treated with antibiotics. However, spontaneous resolution of the middle-ear effusion usually occurs within a couple of weeks or months, which have initiated an intense de- bate on whether antibiotic treatment is necessary in all cases of AOM. Unfortunately, clinically useful indicators to help decide which patients would really benefit from antibiotics are not currently available. The same problem applies to the treatment of sinusi- tis, in which spontaneous resolution is also frequent and reliable diagnosis of bacterial sinusitis is ex- tremely difficult without sinus puncture [15].

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Conflict of Interest

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Informed Consent

Not applicable.

Ethical Statement

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Author Contribution

All authors are contributed equally.

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